# Quantum Mechanical Modeling of Photochemistry in Complex Environments

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### Erklärung

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### Eidesstattliche Versicherung

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# Abstract

Quantum chemical and classical calculations have become an indispensable part of modern chemistry. A persistent challenge for computational methods is the description of weak molecular interactions as they occur in complex environments such as in solution, in catalystsubstrate assemblies, or in biomolecular contexts. This thesis presents a series of methods and applications where such environmental effects play a crucial role.

The first chapter focuses on organic photocatalysis with an emphasis on the formation of dispersive ground-state preassemblies between catalyst and substrate in condensed phase. By exploring the catalytic mechanisms through a series of high-level electronic structure calculations, preassemblies are found to open new pathways in two conceptually different types of chemical transformations. These reactions include on the one hand the electromediated photoredox conversion of phosphinated alcohols to carbanions by naphthalene monoimide type catalysts and on the other hand the photochemical C–H arylation of pyrroles *via* 3d-transition metal complexes.

The second chapter presents a multiscale workflow to include atomistic environmental effects in quantum dynamic wave packet simulations by sampling the potential energy surface over the course of a molecular dynamics trajectory. Using this method, the ultrafast  $S_2 \rightarrow S_1$  relaxation in uracil is found to be strongly affected by embedding the nucleobase in an RNA strand, with a trend towards slower relaxation times.

The third chapter of this thesis deals with the topic of artificial photosynthesis. First, the acid-strength dependent catalytic  $H_2$  generation *via* a cobalt-complex with the redox-active Mabiq ligand is investigated using high-level DFT/MRCI calculations. In the future,  $H_2$  evolving catalysts like Co(Mabiq) could be combined with natural photosystems, which would act as highly efficient photoactivated electron donors. This requires (a) a better understanding of the light-harvesting process and (b) an option to protect the photosystem against harsh environments while retaining or even enhancing its function. This work thus introduces a new computational model of the excitonic network in cyanobacterial photosystem I, which captures the molecular dynamics of the nanoscale system and describes the complex photophysics of chlorophyll in its natural environment at the DFT/MRCI level. This model is finally used to explore the structural and electronic effects of encapsulating photosystem I in the metal-organic framework ZIF-8.

Taken together, this thesis emphasizes the importance of including complex environmental effects in the computational description of molecular transformations. The presented case studies deepen our understanding of a broad range of photophysical and -chemical processes, introducing new photocatalytic strategies in organic synthesis, exploring the photostability of the genetic code, and paving the way toward artificial photosynthesis.

# List of Publications

This thesis is based on the following six publications listed in chronological order. They are reprinted in chapter 1 [2, 5], chapter 2 [1] and chapter 3 [3, 4, 6], respectively.

- S. Reiter, D. Keefer and R. de Vivie-Riedle, "RNA Environment Is Responsible for Decreased Photostability of Uracil", J. Am. Chem. Soc., 140, 8714–8720 (2018). DOI: 10.1021/jacs.8b02962
- [2] X. Tian, T. A. Karl, <u>S. Reiter</u>, S. Yakubov, R. de Vivie-Riedle, B. König and J. P. Barham, "Electro-Mediated PhotoRedox Catalysis for Selective C(sp<sup>3</sup>)–O Cleavages of Phosphinated Alcohols to Carbanions", *Angew. Chem. Int. Ed.*, **60**, 20817–20825 (2021). DOI: 10.1002/anie.202105895
- [3] C. G. Tok\*, <u>S. Reiter</u>\*, A. T. S. Freiberg, L. Reinschlüssel, H. A. Gasteiger, R. de Vivie-Riedle and C. R. Hess, "H<sub>2</sub> Evolution from Electrocatalysts with Redox-Active Ligands: Mechanistic Insights from Theory and Experiment Vis-à-Vis Co-Mabiq", *Inorg. Chem.*, **60**, 13888–13902 (2021). DOI: 10.1021/acs.inorgchem.1c01157
- [4] <u>S. Reiter</u>, F. L. Kiss, J. Hauer and R. de Vivie-Riedle, "Thermal Site Energy Fluctuations in Photosystem I: New Insights from MD/QM/MM Calculations", *Chem. Sci.*, 14, 3117–3131 (2023). DOI: 10.1039/d2sc06160k
- [5] J. Märsch, <u>S. Reiter</u>, T. Rittner, R. E. Rodriguez-Lugo, M. Whitfield, D. J. Scott, R. J. Kutta, P. Nuernberger, R. de Vivie-Riedle and R. Wolf, "Cobalt-Mediated Photochemical C-H Arylation of Pyrroles", *Angew. Chem. Int. Ed.*, **63**, e202405780 (2024). DOI: 10.1002/anie.202405780
- [6] <u>S. Reiter</u>, I. Gordiy, K. Kollmansberger, F. Liu, E. Thyrhaug, D. Leister, J. Warnan, J. Hauer and R. de Vivie-Riedle, "Molecular Interactions of Photosystem I and ZIF-8 in Bio-Nanohybrid Materials", *Phys. Chem. Chem. Phys.*, 26, 23228–23239 (2024). DOI: 10.1039/d4cp03021d

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Additional journal publications:

- M. K. Roos, <u>S. Reiter</u> and R. de Vivie-Riedle, "Ultrafast Relaxation from <sup>1</sup>L<sub>a</sub> to <sup>1</sup>L<sub>b</sub> in Pyrene: A Theoretical Study", *Chemical Physics*, **515**, 586–595 (2018).
   DOI: 10.1016/j.chemphys.2018.08.002.
- <u>S. Reiter</u>, M. K. Roos and R. de Vivie-Riedle, "Excited State Conformations of Bridged and Unbridged Pyrene Excimers", *ChemPhotoChem*, **3**, 881–888 (2019). DOI: 10.1002/cptc.201900096
- V. Piccinni<sup>\*</sup>, <u>S. Reiter</u><sup>\*</sup>, D. Keefer and R. de Vivie-Riedle, "Multiscale Conformational Sampling Reveals Excited-State Locality in DNA Self-Repair Mechanism", J. Phys. Chem. A, **124**, 9133–9140 (2020). DOI: 10.1021/acs.jpca.0c07207
- S. Felicetti, J. Fregoni, T. Schnappinger, <u>S. Reiter</u>, R. de Vivie-Riedle and J. Feist, "Photoprotecting Uracil by Coupling with Lossy Nanocavities", *J. Phys. Chem. Lett.* 11 (2020), 8810–8818. DOI: 10.1021/acs.jpclett.0c02236
- <u>S. Reiter</u>\*, L. Bäuml\*, J. Hauer and R. de Vivie-Riedle, "Q-Band Relaxation in Chlorophyll: New Insights from Multireference Quantum Dynamics", *Phys. Chem. Chem. Phys.*, 24, 27212–27223 (2022). DOI: 10.1039/d2cp02914f
- E. Keil, A. Kumar, L. Bäuml, <u>S. Reiter</u>, E. Thyrhaug, S. Moser, C. D. P. Duffy, R. de Vivie-Riedle and J. Hauer, "Reassessing the role and lifetime of Q<sub>x</sub> in the energy transfer dynamics of Chlorophyll a", *Chem. Sci.*, 16, 1684–1695 (2025). DOI: 10.1039/d4sc06441k

Textbook contributions:

<u>S. Reiter</u>, D. Keefer and R. de Vivie-Riedle, "Exact Quantum Dynamics (Wave Packets) in Reduced Dimensionality" in *Quantum Chemistry and Dynamics of Excited States* (Eds.: L. González, R. Lindh), Wiley, **2020**, pp. 357–382. DOI: 10.1002/9781119417774.ch11

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# Introduction

On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plains and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry and mankind is. And if in a distant future the supply of coal becomes completely exhausted, civilization will not be checked by that, for life and civilization will continue as long as the sun shines!

- Giacomo Ciamician, 1912<sup>[1]</sup>

The desire to control and harness the energy of the sun is as old as civilization itself. One of the earliest uses of photochemistry was the bleaching of linen in ancient Egypt,<sup>[2]</sup> but photochemistry as a scientific discipline began to emerge only in the 19<sup>th</sup> century.<sup>[3]</sup> At that time, the effects of sunlight on certain pigments were described on multiple occasions,<sup>[4–10]</sup> including the invention of photography.<sup>[11,12]</sup> These discoveries culminated in the seminal works of Giacomo Ciamician, who systematically explored the potential of photochemical reactions at the beginning of the 20<sup>th</sup> century.<sup>[1,13,14]</sup> Today, one hundred years after his visionary lecture on the future of photochemistry,<sup>[1]</sup> the scientific community is still trying to crack the "guarded secret of the plants" and harness light for chemical reactions.

As a molecule is promoted to an electronically excited state, a multitude of processes can follow: If the molecule remains in the excited state at least on a picosecond time scale, it can undergo chemical reactions which are governed by the topography of the excited state potential energy surface (PES). This can be exploited in the context of photocatalysis to bypass unfavorable thermodynamics or kinetics in the ground state PES.<sup>[15,16]</sup> Typical modes of operation for photocatalyzed reactions include single electron transfer,<sup>[17,18]</sup> halogen<sup>[19,20]</sup> or hydrogen atom transfer,<sup>[21–23]</sup> bond dissociations,<sup>[24–26]</sup> and isomerizations.<sup>[27–29]</sup> The absorbed energy can also be dissipated into the environment as heat *via* internal conversion (IC). This may involve multiple electronic states if they are connected by conical intersections (CoIns), crossing points between PESs of the same multiplicity where two electronic potentials become degenerate and the Born-Oppenheimer approximation breaks down.<sup>[30]</sup> Though controversial at the time of their discovery, it is now known that deactivation through CoIns is ubiquitous in nature, governing for example the photoisomerization of rhodopsin in the retina<sup>[31]</sup> or the exceptional photostability of the canonical nucleobases.<sup>[32]</sup> If the population crosses to a PES with different spin multiplicity, the process is called intersystem crossing (ISC). As the deactivation to the original ground state is spin forbidden, ISC typically leads to long-lived excited states. Radiative deactivation to the ground state occurs either via fluorescence if the ground and excited states are of the same multiplicity, or *via* phosphorescence if they are not. According to Kasha's rule,<sup>[33]</sup> such radiative decay generally occurs from the lowest-energy excited state. Apart from these intermolecular processes, the absorbed energy can be transferred radiationless to adjacent acceptor molecules, which plays an important role in photosensitized organic synthesis<sup>[34,35]</sup> and especially in photosynthetic light harvesting.<sup>[36–38]</sup> The mechanism of energy transfer depends on the distance between the interacting molecules: At long distances, the interaction is mainly dominated by the Coulomb force caused by the charge density rearrangement in the donor chromophore upon photoexcitation. According to the Förster model of energy transfer<sup>[39]</sup> adjacent acceptor chromophores can react to this change in the electric field by populating an excited state themselves while the donor returns to the ground state, thereby transferring the excitation energy. The resonant coupling is strongest when the energies of the interacting electronic states are similar and when their transition dipole moments are aligned in parallel. At short distances with sufficient wave function overlap between donor and acceptor, exchange interactions begin to dominate and give rise to Dexter energy transfer.<sup>[40]</sup> Here, the excited valence electron is transferred to the acceptor molecule, which in turn transfers an electron back to the donor, resulting in the acceptor molecule in the excited state and the donor in the ground state.

In all of these processes, the molecular environment plays a decisive role. Solvation effects tune the excited state landscape of molecules,<sup>[41–46]</sup> either enabling new deactivation pathways or trapping population in the excited state. Dispersive interactions between catalyst and substrate can decide the outcome of a reaction<sup>[17,47,48]</sup> and any kind of energy transfer process relies on the interaction between different chromophores and their electrostatic environment, which tunes both the respective spectra and the coupling.<sup>[49–51]</sup>

Because of their importance, the treatment of environmental effects in computational chemistry is an ever evolving field. Early attempts to determine the free energy of solvation go back to Born,<sup>[52]</sup> Kirkwood<sup>[53,54]</sup> and Onsager,<sup>[55]</sup> who laid the foundations for modern continuum models.<sup>[56]</sup> Here, a homogeneous solvent environment is modeled as a dielectric continuum acting as an effective potential on the molecular surface. By iteratively adjusting the effective electrostatic field of the solvent to the wave function and vice versa, the interaction energy is accessible without explicitly including any solvent molecules in the quantum mechanical problem. This significantly reduces the computational effort required for the

treatment of solvent effects and therefore has become the standard for comparing calculated properties to experiments. However, continuum models reach their limits whenever steric hindrance or energy/particle transfer plays a role or when the environment is highly heterogeneous like in biological systems. In these cases, at least some of the surrounding molecules must be modeled explicitly, either quantum mechanically or in multiscale hybrid approaches like the QM/MM or ONIOM frameworks.<sup>[57–62]</sup> In these, only a critical part of the system is treated quantum mechanically, while the rest of the environment is typically modeled in the *electrostatic embedding* approach as a set of classical point charges which polarize the wave function.<sup>[58,63–67]</sup> The interaction energy can be refined further by iteratively modeling the mutual polarization of the quantum and classical subsystems (*polarizable embedding*).<sup>[68–72]</sup> This is however associated with high computational cost and requires specialized force fields, which are not yet broadly adopted, though they might hold great potential.<sup>[73,74]</sup>

Any explicit model must address the challenge of sampling a vast conformational space, for which multiple strategies have evolved. One is to sample the phase space classically *via* molecular dynamics (MD) simulations, which is especially popular for biological systems with thousands to millions of atoms.<sup>[75]</sup> Smaller systems up to few thousand atoms can be sampled by iterative metadynamics with computationally efficient quantum mechanical, typically semiempirical, methods.<sup>[76–78]</sup> Such metadynamics simulations have the advantage of sampling a large portion of the phase space, giving a more complete overview of the relevant conformational degrees of freedom than conventional MD trajectories. Finally, geometry optimizations allow a more targeted prediction of energies and properties for singular structures, using high levels of theory at the expense of increased computational cost. As a result, geometry optimizations are often carried out from a set of manually preselected starting geometries or from a precalculated conformational ensemble.

This thesis will demonstrate six examples of photochemical and -physical processes, where the molecular environment takes on a critical role. The presented studies will traverse the spatial and temporal scales from single molecules to a complete photosynthetic lightharvesting apparatus, from femtosecond quantum dynamics to nanoscale MD simulations. The first chapter elucidates two photocatalytic reaction mechanisms with catalysts whose short excited state lifetimes should normally prevent diffusion-limited catalysis. Even so, dispersive ground state preassembly with the respective substrates successfully facilitates the reaction. The conformational space of preassemblies is explored *via* a series of structure optimizations and potential energy scans in the first study as well as iterative metadynamics in the second study. Multireference and double-hybrid DFT calculations provide in-depth insights into the photophysical properties that drive the reactions. Combined with experimental characterizations, a reaction mechanism could be formulated in both cases.

Continuing from a discussion of single critical points on the PES to excited state dynamics, the second chapter presents a new technique for performing wave packet quantum dynamics in an explicit environment. To test and demonstrate the new workflow, the ultrafast deactivation of the nucleobase uracil after photoexcitation was selected as a case study. Such femtosecond relaxation is responsible for the extraordinary photostability of all canonical nucleobases and, by extension, of the genetic code. Wave packet simulations inside a series of solvated RNA strands show how the natural environment of uracil affects the crucial  $S_2 \rightarrow S_1$  relaxation, accelerating or slowing down the deactivation process.

The theme of biological systems is carried on in the third chapter, which discusses three key steps towards artificial photosynthesis. Here, the overarching goal is to couple a fuelgenerating redox catalyst to a natural light-harvesting system, which converts sunlight into electrical current with high efficiency. Thus, the first study explores the mechanism of  $H_2$  evolution from the [Co(Mabiq)] transition metal complex. [Co(Mabiq)] catalyzes  $H_2$ evolution in acidic solution at two different potentials, depending on the acid strength. This suggests two intermediates in the H<sub>2</sub> evolution reaction, which are however challenging to characterize experimentally. Computational screening of the electronic structure and spectra of possible intermediates in an implicit solvation model fills this gap and allows to draw conclusions about a plausible reaction mechanism. The second study of chapter 3 focuses on the light-harvesting component of a prospective photosynthetic device, namely cyanobacterial photosystem I (PS I). An extensive new computational model of PS I is presented, which includes the dynamics of the full trimeric and membrane-embedded protein complex as well as the multireference character of chlorophyll excitations. The model is used to compute site energies and excitonic couplings in PS I with high precision and draw conclusions about energy traps and barriers upon photoexcitation. A discussion of the intermonomer coupling in PS I concludes the analysis of the natural light-harvesting system. Its prospective application in artificial photosynthesis is the subject of the final study in chapter 3, where protection of the photosystem by encapsulation in the metal organic framework (MOF) ZIF-8 is investigated through the microscopic lens of computational modeling. To this end, the model introduced in section 3.2 is extended to include the MOF, allowing the detailed analysis of interactions at the PS I/MOF interface. Modeling the excitonic network with and without the MOF suggests that these interactions give rise to spectral anomalies, which were hitherto unexplained.

# Synthetic Photoredox Catalysis: The Role of Preassemblies



**Chapter 1 Title Graphic:** Ground state preassembly between reaction partners can facilitate photocatalysis, despite short-lived excited states. The graphic illustrates the photoinduced charge transfer to and from a transition metal complex using earth-abundant 3d-metals (section 1.2).

Photoredox catalysis (PRC) is a transformative tool in synthetic chemistry which uses light to drive single electron transfer, thus opening new mechanistic pathways with remarkable efficiency and selectivity.<sup>[79–81]</sup> First reports on PRC date back to the 1970s, when the photocatalytic properties of  $[\text{Ru}(\text{bpy})_3]^{2+}$  (bpy = 2,2'-bipyridyl) were discovered.<sup>[82]</sup> Although a series of pioneering synthetic applications followed,<sup>[83–87]</sup> the use of PRC was largely confined to the field of artificial photosynthesis for the next few decades.<sup>[88,89]</sup> It was in 2008 and 2009 that the field experienced a renaissance in organic synthesis, when the groups of David MacMillan,<sup>[90]</sup> Tehshik Yoon,<sup>[91]</sup> and Corey Stephenson<sup>[92]</sup> independently presented three very different visible-light activated transformations, all catalyzed by  $[\text{Ru}(\text{bpy})_3]^{2+}$ . Since then, visible-light PRC has opened a plethora of novel reaction pathways, often shorter and cheaper than their ground state alternatives.<sup>[93]</sup>

Especially polypyridyl complexes of the precious metals Ru<sup>II</sup> and Ir<sup>III</sup> are prevalent as photocatalysts in both academic and industrial contexts,<sup>[94–97]</sup> due to their exceptional photophysical properties.<sup>[98,99]</sup> In particular, they absorb light at wavelengths longer than 400 nm, which enables their selective excitation without triggering unwanted side reactions of the organic substrates that typically absorb in the ultraviolet (UV) range. After excitation to an intramolecular charge-transfer (CT) state, they undergo ISC to the triplet domain. There the population is trapped for hundreds of nanoseconds up to multiple microseconds,<sup>[94,95]</sup> enabling diffusion-controlled reactions at typical substrate concentrations.<sup>[100]</sup> Once excited, the transition metal complexes can either accept an electron from or donate one to the substrate, enabling both reductive and oxidative activation. Finally, the catalyst is regenerated either by another substrate, sacrificial agent, co-catalyst or by an external current.<sup>[101]</sup> High absorption cross sections in the visible regime, chemical stability, the possibility to tune the photophysics by ligand substitution and most importantly the long excited state lifetimes represent significant advantages of Ru and Ir complexes in this mechanistic framework.<sup>[102]</sup>

Nevertheless, both Ru and Ir are among the rarest elements on Earth.<sup>[103]</sup> Besides being expensive, their mining and refinement come with a disproportionately high environmental and social impact, including freshwater and soil contamination, emission of greenhouse gases and high energy demands.<sup>[104]</sup> Thus, there is an increasing emphasis on the substitution of precious metal catalysts in PRC with either organic  $dyes^{[81,105]}$  or first-row transition metals.<sup>[106]</sup> However, the scope of suitable photocatalysts is limited by the need for long excited state lifetimes. This work introduces two photocatalyzed reactions, which circumvent this requirement by dispersive ground state preassemblies between the catalyst and the respective substrate or sacrificial electron donor. The presented studies were performed in close collaboration between synthetic (in)organic chemistry, spectroscopy, and theory to arrive at comprehensive mechanistic insights. In both cases, the catalysts' excited state lifetimes are much too short for diffusion-limited reactions, yet preassembly enables efficient single electron transfer. From a computational point of view, modeling the open-shell species with close to 100 atoms, while correctly describing the weak dispersive interactions in the preasembly is the main challenge to be addressed, for example by means of empirical corrections in DFT calculations<sup>[107–110]</sup> or high-level wave function based approaches.

Section 1.1 investigates the selective  $C(sp^3)$ -O cleavage of phosphinated alcohols via single-electron transfer from organic catalysts, based on the 2,6-diisopropylphenyl-containing naphthalenemonoimide (**NpMI**) scaffold. To this end, the reactivity of the substrates is rationalized by DFT and DLPNO-CCSD(T) simulations in the ground state, while the catalyst's excited states are explored via high-level DFT/MRCI and CASSCF calculations. Geometry optimizations and potential energy scans provide detailed insights into the formation and stability of dispersive preassemblies which enable the photoinduced single electron transfer from the catalyst to the substrate. The computational results provide a comprehensive explanation of the structure-activity relationship of differently substituted catalysts and elucidate the driving forces behind the reaction's selectivity. Next, section 1.2 discusses the C-H arylation of pyrroles catalyzed by earth-abundant first-row transition metal complexes. The conformational space of possible preassemblies is explored with metadynamics simulations, complemented by geometry optimizations. High-level CASSCF, NEVPT2, and double-hybrid TD-DFT calculations are used to characterize the electronic structure and excited state landscape of the involved open-shell species. These insights are supplemented by thermodynamics simulations of possible side reactions at the DLPNO-CCSD(T1) level. Based on the combined experimental and computational results, a mechanism for the full catalytic cycle is formulated. Both presented studies provide proof-of-concept that preassembly enables efficient PRC with simple catalysts made from earth-abundant elements, despite their short-lived excited states.

### 1.1 Selective C(sp<sup>3</sup>)–O Cleavages of Phosphinated Alcohols

While the benefits of PRC to organic synthesis are undeniable, some challenging reactions require higher potentials than those available from visible light catalysts. Common photocatalysts operate between -1.8 to +1.5 V vs. standard calomel electrode (V<sub>SCE</sub>).<sup>[94]</sup> Focusing on the reductive side of the scale, the popular [Ru(bpy)<sub>3</sub>]<sup>2+</sup> has an excited state reduction potential of  $-0.81 \text{ V}_{\text{SCE}}$ ,<sup>[98,111]</sup> while *fac*-Ir(ppy)<sub>3</sub> (ppy = 2-phenylpyridine) reaches up to  $-1.73 \text{ V}_{\text{SCE}}$ .<sup>[112,113]</sup> In contrast, the reduction of aromatic  $\pi$ -systems,<sup>[114]</sup> aryl halides<sup>[115]</sup> or esters<sup>[116]</sup> often requires potentials between  $-2.2 \text{ to} -3.4 \text{ V}_{\text{SCE}}$ . While electrochemistry can easily reach these potentials, it does so at the cost of reduced selectivity or even substrate decomposition. For this reason, reactions involving solutions of alkali metals<sup>[117,118]</sup> are still being used in organic synthesis, despite their harsh conditions, high cost and safety implications.<sup>[119]</sup>

Conventional PRC can reach higher potentials with two-photon strategies, inspired by the photosynthetic Z-scheme,<sup>[120]</sup> or *via* generation of solvated electrons from precious metal photocatalysts.<sup>[121,122]</sup> Here, energy is added to the system in two steps by photoreducing the catalyst to a reactive radical anion, which subsequently absorbs a second photon to reduce the substrate. Expanding on this idea and broadening the scope of suitable catalysts, the radical anion could also be created electrochemically before the photochemical step, giving rise to the emergent field of electro-mediated photoredox catalysis (e-PRC).<sup>[123–125]</sup>



Figure 1.1: Working mechanism of NpMI-based catalysts as elucidated in this work. (a) A radical anion is generated electrochemically and photoexcited to an intramolecular CT state, which transfers electron density to the aniline unit. (b) Exemplary structure of a dispersive ground state preassembly with <sup>n</sup>BuO-NpMI. Preassembly occurs preferentially at the aniline unit in a pincer-like conformation, enabling efficient single electron transfer upon photoexcitation.

e-PRC catalysts such as dicyanoanthracene<sup>[126]</sup> (DCA,  $E^{\circ} = -3.2 \,\mathrm{V_{SCE}}$ ) or NpMI ( $E^{\circ} < -3.4 \,\mathrm{V_{SCE}}$ )<sup>[127]</sup> can easily reach and even surpass the reductive potential of alkali metals, while retaining much milder reaction conditions. First introduced by Wickens *et al.*, NpMI (figure 1.1) has shown to activate aryl chlorides for radical coupled phosphorylations and arylations with remarkable selectivity, even in the presence of other reducible functional groups.<sup>[127]</sup>

This inspired the article presented below to expand the reaction scope of the NpMI scaffold to the selective generation of  $C(sp^3)$  carbanions from phosphinate esters of aliphatic alcohols. With a reduction potential between -2.2 to -2.6 V<sub>SCE</sub> this reaction is at the limit of conventional PRC but accessible *via* e-PRC. The newly developed catalyst <sup>n</sup>BuO-NpMI (figure 1.1) provides much higher product yields than NpMI, even though the two are alike in all relevant physicochemical properties. Extensive computational work will therefore help to explain the experimental characterizations and reveal the crucial role of preassemblies in the photocatalytic process.

The article "Electro-mediated PhotoRedox Catalysis for Selective  $C(sp^3)$ –O Cleavages of Phosphinated Alcohols to Carbanions" was published 2021 in Angew. Chem. Int. Ed. The most important points of the article are summarized below:

• A series of phosphinated aliphatic alcohols was reduced to carbanions *via* e-PRC. To this end, a new naphthalene monoimide-type catalyst, termed **<sup>n</sup>BuO-NpMI**, was synthesized, offering superior reactivity with a wider substrate scope, compared to previous catalysts with similar structural motifs. The mild conditions of the catalyzed reaction lead to high selectivity and tolerated even reductively labile aryl halides.

- In an attempt to rationalize the catalyst's selectivity for benzylic substrates, reduction potentials of the alkyl phosphinates were compared to the observed product yields. Reduction potentials calculated at the DFT level ( $\omega$ B97XD/6-311+G\*) were in good qualitative agreement with those obtained by cyclic voltammetry. However, there was no correlation with the observed product yields, indicating that the reduction of the substrate was not the decisive factor for the selectivity.
- In contrast, C(sp<sup>3</sup>)–O bond dissociation free energies, calculated at the DFT level (ωB97XD/6-311+G\*) and benchmarked against DLPNO-CCSD(T) calculations, correlated well with the product yields. The different reaction energies could be explained computationally by the favorable spin density delocalization in benzylic substrates. Thus the selectivity of the reaction is largely independent from the reduction potential of the substrate and rather rooted in the stability of the produced radicals.
- While these results explained the different reactivities within the substrate scope, they could not rationalize why <sup>n</sup>BuO-NpMI reacted with more substrates and gave higher yields than the structurally related NpMI. Both catalysts share the same reduction potential in the excited state (-3.7 to -3.8 V<sub>SCE</sub>) and their radical anions are generated with equal efficiency. Electron paramagnetic resonance (EPR) experiments were conducted with pregenerated NpMI<sup>•-</sup> and <sup>n</sup>BuO-NpMI<sup>•-</sup> radical anions in the presence and absence of a substrate that only reacted productively with <sup>n</sup>BuO-NpMI. The results showed that both catalysts are in principle able to reduce the substrate upon irradiation with blue light, further corroborating that the higher versatility of <sup>n</sup>BuO-NpMI was not rooted in its excited state redox potential.
- Excitation spectra of the electrochemically generated radical anions  $NpMI^{\bullet-}$  and  $^{n}BuO-NpMI^{\bullet-}$  indicated the existence of a long-lived species with an emission maximum at 540 nm and biexponential fluorescence decay ( $t_1 = 7 \text{ ns}, t_2 = 20 \text{ ns}$ ). This species was assigned to a lower-lying, long lived excited state, labeled ES<sub>1</sub>, that was not the initially excited state. Related studies have since demonstrated photocatalytic activity of a two-electron reduced and protonated  $NpMI^{-}$  singlet anion with an excited state lifetime of 20 ns.<sup>[128]</sup> However, as no quenching of the long-lived emission component was observed in the presence of a substrate, it is unlikely that this singlet species, formed under strongly reducing conditions, contributed to the reaction investigated here.
- To characterize ES<sub>1</sub>, CASSCF calculations were conducted using a  $C_{2v}$  symmetric model of <sup>n</sup>BuO-NpMI, where the butyl ether group was replaced by hydrogen. The energetic order of the excited states and their relative energies were in good agreement with high-level DFT/MRCI calculations and indicated the existence of a quartet state (Q<sub>1</sub>) 0.25 eV below the initially excited doublet state. Thus, ISC to the quartet domain was considered a plausible deactivation pathway for NpMI-type catalysts.

- Direct excitation of the lowest excited doublet state only lead to traces of the desired product, whereas excitation at 415 nm drove the reaction. Since ISC was ruled out as a possible reactive pathway, the involvement of a higher excited doublet state was proposed and labeled as "anti-Kasha"-photochemistry. The photophysics of the <sup>n</sup>BuO-NpMI<sup>•-</sup> radical anion was further characterized by DFT/MRCI calculations, whose results were in excellent agreement with the measured absorption spectrum. Two bright, intramolecular CT states were identified in the main absorption band, moving electron density from the naphthalene unit to the N-aniline moiety of the catalyst.
- The excited state lifetime of doublet states in similar species<sup>[129,130]</sup> had been measured to be in the picosecond range, presumably too short for diffusion limited photocatalysis.
- In light of these results, ground state preassembly between the catalyst radical anion and the substrate could explain the different reactivities between **NpMI** and <sup>n</sup>**BuO-NpMI**. Though such a preassembly was not directly accessible by spectroscopic methods, a structure-activity relationship study was performed with differently substituted catalysts that were increasingly shielded in the *ortho*-position of the Naniline unit. The product yield decreased with increasing steric hindrance, in line with the preassembly hypothesis.
- Further support for a preassembly-driven mechanism was provided computationally by means of structure optimizations at the DFT level ( $\omega$ B97XD/6-311+G\*). These resulted in 13 possible ground state preassemblies with the differently substituted catalysts. In all of them, the substrate coordinates to the N-aniline unit of the catalyst, which carries the unpaired electron density upon photoexcitation. Here, three of the substrate's aromatic groups encase the catalyst *via* attractive  $\pi$ - $\pi$  and T- $\pi$  interactions (figure 1.1b). Complexation with **nBuO-NpMI** was consistently associated with the largest gain in free energy, whereas preassembly with *ortho*-substituted catalysts was more unfavorable. Furthermore, potential energy scans along the catalyst-substrate dissociation coordinates illustrated that the energy barrier for the substrate to approach the catalyst is much higher when the N-aniline unit is sterically hindered. Thus, preassembly with **nBuO-NpMI** is more favorable both thermodynamically and kinetically, offering a viable explanation for its superior reactivity in e-PRC reactions.

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#### Photoelectrochemistry

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### Electro-mediated PhotoRedox Catalysis for Selective C(sp<sup>3</sup>)–O Cleavages of Phosphinated Alcohols to Carbanions

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**Abstract:** We report a novel example of electro-mediated photoredox catalysis (e-PRC) in the reductive cleavage of  $C(sp^3)$ —O bonds of phosphinated alcohols to alkyl carbanions. As well as deoxygenations, olefinations are reported which are *E*-selective and can be made *Z*-selective in a tandem reduction/photosensitization process where both steps are photoelectro-chemically promoted. Spectroscopy, computation, and catalyst structural variations reveal that our new naphthalene mono-imide-type catalyst allows for an intimate dispersive precomplexation of its radical anion form with the phosphinate substrate, facilitating a reactivity-determining  $C(sp^3)$ —O cleavage. Surprisingly and in contrast to previously reported photoexcited radical anion chemistries, our conditions tolerate aryl chlorides/bromides and do not give rise to Birch-type reductions.

#### Introduction

Synthetic methodologies involving single electron transfer (SET) are increasingly popular for the facile synthesis or modifications of important organic compounds. PhotoRedox Catalysis (PRC)<sup>[1]</sup> and Synthetic Organic Electrochemistry (SOE)<sup>[2]</sup> lead to easy SET processes, providing notable redox power for various organic transformations under mild conditions. Generally, visible-light PRC generates radical intermediates with good functional group tolerance in a mild manner. However, synthetic applications of PRC in terms of transformations needing highly oxidizing or reducing potentials are limited by the energetic limitations of visible light photons. One solution is to generate photoexcitable radical ions by multi-photon processes.<sup>[3]</sup> Such photoexcited radical ions are highly oxidizing<sup>[3a,b]</sup> or reducing species,<sup>[3c-h]</sup> leading

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© 2021 The Authors. Angewandte Chemie International Edition published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited. to a significantly expanded redox "window" for activating inert substrates. Sacrificial redox additives (e.g. DIPEA) are employed in stoichiometric excesses in consecutive Photoinduced Electron Transfer (conPET) processes to prime catalysts prior to excitation. Their excesses and organic byproducts can plague purification steps. In contrast, SOE allows direct access to high, user-controlled redox energy without involving photocatalysts or sacrificial redox additives, offering advantages to net-oxidative/reductive reactions. However, the applied constant current or voltage can cause uncontrollable over-reductions/oxidations to afford by-products. To address the aforementioned limitations in PRC and SOE, organic chemists have recently explored their combination (Scheme 1).<sup>[4]</sup>

Merging the advantages of these two important techniques has made photoelectrochemistry a tool for greener, more challenging and more selective molecular activations.<sup>[5]</sup> Pioneering reports by Xu,<sup>[5b-c,m]</sup> Lambert,<sup>[5g,h,i,k]</sup> Lin<sup>[5h,j]</sup> and



**Scheme 1.** Previous reductive e-PRC reports involving  $C(sp^2)-X$  cleavages to afford aryl radicals vs. this work involving  $C(sp^3)-O$  cleavages to afford alkyl radicals and carbanions. [a]  $E^p_{red}$ . [b]  $E_{1/2}$ . [c] Redox potential vs. SCE.

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Wickens<sup>[5f]</sup> have shown that introducing applied potential in photoredox catalysis is not only beneficial for accessing challenging redox reactions, but is also a green replacement for sacrificial redox additives.

Among the various strategies for combining photocatalysis and electrochemistry<sup>[4a]</sup> the sub-category coined electrochemically-mediated photoredox catalysis (e-PRC) is highly attractive. In addition to turning over "spent" closed-shell photocatalysts, e-PRC can also involve electrochemical generation of open-shell (radical ion) photocatalysts, followed by their photoexcitation to species with ultra-high redox potentials. A seminal report from the Lambert group demonstrated this strategy for super-oxidations of highly electron-poor arenes.<sup>[5k]</sup> In the reductive direction, photoexcited radical anions of dicyanoanthracene (DCA)[5h] and of 2,6-diisopropylphenyl-containing naphthalenemonoimide (NpMI)<sup>[5f]</sup> are highly reducing species ( $E^{\circ}_{red} < -3.0$  V vs. SCE) that reduce challenging aryl chlorides to their aryl radicals. Even pchloroanisole was reduced, beyond reach of the photon energy limit of monophotonic PRC and where SOE inevitably leads to dehalogenation via subsequent aryl radical reduction (Scheme 1 A).<sup>[6]</sup> Despite these elegant advances, reductive e-PRC and biphotonic strategies<sup>[3]</sup> are still heavily focused on the reductions of aryl halides/pseudohalides through  $C(sp^2)$ -X bond cleavages to generate any  $C(sp^2)$ radicals in an overall dehalogenation or functionalization with excesses of radical trapping agents.<sup>[5f,h]</sup>

Inspired by previous reports,<sup>[5]</sup> we envisioned that phosphinates of aliphatic alcohols ( $E^{p}_{red} = -2.2 \rightarrow -2.6$  V vs. SCE) could undergo e-PRC reduction to give carbanions (Scheme 1B). Thereby, an electroactivated-PhotoRedox Catalyst (e-PRCat) undergoes cathodic activation and photoexcitation to afford a potent reductant. SET reduction of 1 to its radical anion followed by C(sp<sup>3</sup>)-O bond cleavage delivers benzyl radical 1'. Its further reduction<sup>[7d]</sup> to carbanion intermediate 1" would enable either an olefination (X = Cl, Br) or a deoxygenation (X = H) process by a mechanism that does not depend on hydrogen atom transfer agents or decarboxylation.<sup>[7]</sup> Herein, we report the e-PRC reduction of alkyl phosphinates to alkyl(sp3) carbanions for olefination and deoxygenation reactions that i) proceeds under exceedingly mild conditions, ii) tolerates aryl halides/pseudohalides with similar or more accessible redox potentials than the target alkyl phosphinate moiety.

#### **Results and Discussion**

To assess the viability of our proposed e-PRC alkyl phosphinate reduction, we employed 2-chloro-1,2-diphenyl-phosphinate **1a** as a model substrate for the olefination reaction (Table 1). By using **DCA** as an e-PRCat and Zn(+)/RVC(-) as the electrodes in a divided H-cell, we examined the reduction of **1a** under blue light irradiation and with different applied constant potentials. A high constant voltage  $(U_{cell} = -3.2 \text{ V})$  as used previously<sup>[5h]</sup> for electron-priming **DCA** to its radical anion for photoexcitation gave notable decomposition, desired product *E*-stilbene (*E*-**2a**) in only 7% yield and a 25% yield of diphenylethane **3a**<sup>[8]</sup> (Table 1,

Table 1: Optimization of the reaction conditions.[a]



<b>F</b> .	<u> </u>	DDC i			
Entry	Substrate	e-PRCat	$U_{\text{cell}}[V]$	t [h]	Product: Yield
1	la	DCA	-3.2	12	<b>2a</b> : 7%, <i>E</i> -/ <i>Z</i> ->20:1 <sup>[b]</sup>
					<b>3a</b> : 25%
2	la	DCA	-1.6	12	<b>2a</b> : 70%, <i>E</i> -/ <i>Z</i> ->20:1 <sup>[b]</sup>
					3a: trace
3	la	DCA	-1.0	12	<b>2</b> a: 79%, <i>E</i> -/ <i>Z</i> ->20:1 <sup>[b]</sup>
					<b>3 a</b> : n.d.
4	4a	DCA	-1.0	24	<b>2a</b> : 79%, <i>E</i> -/ <i>Z</i> ->20:1 <sup>[b]</sup>
					<b>3 a</b> : n.d.
5 <sup>[c]</sup>	la	DCA	-1.0	12	<b>2a</b> : n.d.
					<b>3 a</b> : n.d.
6	1a	DCA	-	12	<b>2a</b> : n.d.
					<b>3 a</b> : n.d.
7	1a	-	-1.0	12	2a: trace
					<b>3a</b> : n.d.
8	la	NpMI	-1.6	12	<b>2a</b> : 80%, <i>E</i> -/ <i>Z</i> -=1:1.3 <sup>[0]</sup>
	_				<b>3a</b> : n.d.
9	1a	NpMI	-1.6	48	<b>2a</b> : 78%, <i>E</i> -/ <i>Z</i> -=1:10 <sup>[0]</sup>
z oldi					3a: n.d.
10 <sup>[0]</sup>	Id	DCA	-1.0	12	2d: n.d.
	ld		-1.6	12	2d: trace
			-1.6	12	2d: /5%
اغ <sup>رم</sup> ] ∎∡[c.d]	10		-	12	<b>2a</b> : n.a.
14 <sup>1-,3</sup>	10	виО-мрМІ	-1.6	12	<b>2a</b> : n.d.
12.4	Ia	-	-1.6	12	20: < 3%

[a] n.d. = not detected; yields determined by <sup>1</sup>H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [b] E/Z- ratios determined by <sup>1</sup>H NMR spectroscopy. [c] In the dark. [d] Fe cathode.

entry 1). A lower potential ( $U_{cell} = -1.6 \text{ V}$ ) led to a remarkable improvement in the reaction profile and yield of E-2a to 70% (Table 1, entry 2). The optimal yield of E-2a was obtained at an even lower potential ( $U_{cell} = -1.0$  V). Cyclic phosphate ester 4a was also a suitable substrate for preparing product E-2a (entry 4), offering an attractive Corey-Wintertype olefination that avoids explosive/toxic trimethylphosphite, harsh activating reagents or high temperature. Control reactions omitting light, constant potential or e-PRCat confirmed the photoelectrochemical nature of the olefination reaction (entries 5-7). In contrast to DCA, NpMI as catalyst delivered higher amounts of Z-2a (entry 8).<sup>[9]</sup> Allowing the reaction to proceed for 48 h (entry 9) increased the E-/Zratio to 1/10 (71% of Z-2a). Detailed investigations (see Supporting Information (SI)) revealed that light, constant potential and NpMI are all advantageous to the isomerization, representing a novel photoelectroisomerism of alkenes.

Reaction scope was expanded to other substrates including precursors to unsymmetrical stilbenes as well as cyclic, hindered and terminal olefins. Phosphinate precursors are readily synthesized from their ketones via  $\alpha$ -chlorination and

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one-pot NaBH<sub>4</sub> reduction/Cl-P(O)Ph<sub>2</sub> protection (see SI). Here we opted to use Fe instead of RVC as a cheaper, robust cathode material.<sup>[10]</sup> However, it was quickly identified that DCA and NpMI were ineffective e-PRCats for the majority of phosphinates. For example, cyclic substrate 1d underwent no reaction with these catalysts (entries 10-11). We synthesized "BuO-NpMI as a novel e-PRCat which afforded the desired product 2d in very good yield (entry 12). Control reactions confirmed operation of e-PRC (entries 13-15), while cathode materials greatly impacted the reaction (for detailed optimizations, see SI).<sup>[11]</sup> Optimal conditions were examined for a range of olefination reactions (Scheme 2). Unsymmetrical Z-stilbenes 2b, 2c were prepared in high yields from the tandem e-PRC reduction/photoelectroisomerism process. Cyclic olefins 2d-2h, rarely synthesized by the Wittig reaction due to the inconvenience of substrate preparations, were prepared in good to excellent (69-83%) yields. Terminal olefin 2i could not be prepared in high selectivity by dehydration of its corresponding tertiary alcohol as such a method inevitably leads to the most substituted olefin,<sup>[12]</sup> in this case, a tetrasubstituted instead of a terminal olefin.

After the successful preparations of a series of E-styrene derivatives (exclusive isomers) bearing divergent substituents including -Ph (2j), -OBz(2k), -OMe(2l) and -CF<sub>3</sub>(2n) at their arene rings, we questioned whether halogen substituents could be tolerated by our reaction. This is a highly challenging issue, since the reductions of aryl chlorides and bromides by photoexcited radical anions (either e-PRC or conPET-type) are highly efficient and heavily reported as discussed earlier (Scheme 1).<sup>[3c-g,5f,h]</sup> With this aim, we tested phosphinates bearing either a chloro- or bromo- substituent on their arene. To our delight, any chlorides 10-1q and any bromide 1r underwent olefination in moderate to good (39-69%) yields with high or exclusive selectivities for their *E*- or *Z*- isomers; only traces of dehalogenated styrenes were observed (>10:1 in favor of olefination for 2p). Compared with products 2o-**2p**, *p*-chlorostilbene **2q** has a more conjugated  $\pi$ -system and is easier to reduce, yet still gave only traces of dechlorinated product 2a. Substrate 1s, bearing both an alkyl and aryl phosphinate,<sup>[13]</sup> selectively underwent e-PRC reduction of the alkyl phosphinate leading only to C(sp<sup>3</sup>)-O cleavage to afford 2s in good yield. Our method retains reductively labile C(sp<sup>2</sup>)–O functionality, providing complementary selectivity to a recent report involving a phenothiazine photocatalyst.<sup>[13]</sup>

Styrene-forming substrates containing longer-chain aliphatic groups or a benzyl group retained high *E*-isomer selectivity, affording 2t-2v in good to high (62–79%) yields and high selectivities (>10:1 in favor of their *E*-isomers). Olefin geometry is not impacted by the diastereomeric ratio of phosphinate precursors, but by the reaction conditions. For example, although the diastereomeric ratios of phosphinate precursors to 2r, 2t and 2v were all >30:1, the *E*-/*Z*- ratios were 4:1, 10:1 and 20:1 respectively. Hindered olefins derived from carbocycles 1w-1x were formed in high (83–87%) yields. In the synthesis of 2x, our conditions offer an alternative to i) "BuLi or Grignard chemistry with expensive bromocyclobutane and ii) expensive Wittig reagents/cyclobutanone, instead starting from commercial, inexpensive



Scheme 2. e-PRC reductive olefination scope. [a] for compounds 2a-2q, 2t-2x, 2aa-2ad, X = CI; for compounds 2r-2s, 2y-2z, 2ae-2ag, X = Br. [b] Isolated yields. [c] *E-/Z*- ratios determined by <sup>1</sup>H NMR spectroscopy. [d] Yields in parentheses {} are <sup>1</sup>H NMR yields from NpMI as an e-PRCat.

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cyclobutyl phenyl ketone. Our e-PRC phosphinate reduction offers complementary selectivity to Birch-type photochemical reports involving SET,<sup>[14]</sup> or E<sub>n</sub>T.<sup>[15]</sup> Naphthalene-based substrate **1y** was well-tolerated, affording **2y** in good (62%) yield without Birch-type reduction products. Amide **1z** was also well-tolerated, in spite of its free proton and labile heterocycle that would react with strong bases. Although an alkyl phosphinate derived from a non-benzylic alcohol **1aa** did not react, alkyl phosphinates derived from allylic alcohols were feasible. Allylic substrates **1ab**, **1ac** derived from naturallyoccurring terpenes were found to be sluggish, but afforded dienes **2ab**, **2ac** in satisfactory (30–33%) yields in a complementary fashion to previous reports that require strong bases<sup>[16]</sup> or transition metal catalysis.<sup>[17]</sup>

Demonstrating the utility of our base-free approach, products 2ad-2ag were synthesized from their alkyl pacetylbenzoate precursors. Given the properties of Geraniol and Nootkatone as fragrance oils and cholesteryl benzoate as a liquid crystal, our reaction is a useful entry to terpeneloaded monomers for the synthesis of functional polymers.<sup>[18]</sup> Strategies involving strong base (for example i) Wittig reaction of an aldehyde or ii) ketone reduction, mesylation and  $E_2$ -elimination) lead to hydrolysis or  $E_2$  elimination of the benzoate,<sup>[19]</sup> while direct esterification suffers from the caveats that 4-vinylbenzoic is thermally sensitive and formulated with BHT stabilizer. Further exemplifying utility, substrate 1ah, readily prepared from its a-dichloroketone, underwent selective reduction to its unsymmetrical stilbene 2ah in good yield while leaving the olefinic Cl atom untouched (Scheme 3). This demonstrates the value of our method which retains reductively labile halides for further functionalizations. The method provides alternative access to unsymmetrical halogenated stilbenes that does not rely on transition metal catalysis.<sup>[20]</sup> While conPET photocatalysis and e-PRC are complementary approaches in the reductions of aryl halides/pseudohalides,<sup>[3d,g]</sup> conPET conditions did not effect the net-reductive transformation herein (Scheme 4).

At this juncture, we wondered if overall deoxygenation would be possible by removing the  $\alpha$ -Cl atom from **1a** (**1ai**) as the generated carbanion would be protonated. Photocatalytic deoxygenations of alcohols activated as their bis(trifluoromethyl)benzoates has been achieved with an iridium photo-



**Scheme 3.** e-PRC reduction of dichlorinated substrate **1 ah**. [a] Yield of isolated product. [b] *E-/Z-* ratio was determined by <sup>1</sup>H NMR spectroscopy.



Scheme 4. Attempted reduction of 1d under conPET conditions.

catalyst, but required stoichiometric Hantzsch ester, alkylamine and water at 40 °C.[21] Direct electrolytic reduction of alkyl phosphinates is known, and required a constant current of 600 mA at 60–110 °C where a constant potential ( $U_{cell} =$ -2.4 V vs. Ag/AgCl) was ineffective.<sup>[22]</sup> Reductive functionality (styrenes, aryl halides, dienes, benzoates) would not tolerate these conditions. e-PRC deoxygenation afforded desired product 1ai in good yield under standard conditions  $(U_{\text{cell}} = -1.6 \text{ V})$  with extended time (Scheme 5). Allylic substrate 1aj smoothly deoxygenated to 2aj (Limonene). When a Cl atom was present  $\beta$ - to the phosphinate (1ak), deoxygenation afforded 2ak and cyclopropane 2ak', confirming the intermediacy of a benzylic carbanion (see 1a', Scheme 1 c). An alkyl phosphinate derived from a nonbenzylic/allylic alcohol (1al) did not react. We sought explanations as to two questions: 1) why e-PRC conditions herein could not engage non-benzylic substrates (1aa and 1al, respectively) and 2) why "BuO-NpMI was a superior e-PRCat to NpMI; since NpMI as an e-PRCat gave no conversion of various substrates (1f, 1n, 1o, 1q, 1u) in olefinations (Scheme 2), and poor conversion of 1ai and 1aj in deoxygenations (Scheme 5).



**Scheme 5.** e-PRCreductive deoxygenation. [a] Isolated yields of products **2ai** and **2aj**. [b] Yields in parentheses {} are <sup>1</sup>H NMR yields from using **NpMI** as an e-PRCat. [c] Yields of **2ak** and **2ak'** are determined by <sup>1</sup>H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard, identified by literature comparisons and GC-MS traces.

Concerning the first question, measured reduction potentials ( $E^{p}_{red}$ ) of the alkyl phosphinates (in good agreement with those calculated by DFT) did not correlate with reactivity (Table 2). Instead, comparison of the C(sp<sup>3</sup>)–O bond-dissociation free energies (BDFEs) of phosphinate radical anions correlated well with reactivity. This corroborated C(sp<sup>3</sup>)–O cleavage as the rate-limiting step and rationalized i) the unique tolerance of our conditions to aryl halides due to their less exergonic C–X BDFEs (entries 4,5; 6,7) and ii) the lack of reactivity of phosphinates derived from non-benzylic/allylic alcohols that require higher temperatures<sup>[22]</sup> to assist C(sp<sup>3</sup>)– O cleavage (entries 9,10).

As to the second question, **NpMI** and **"BuO-NpMI** had identical redox potentials ( $E_{1/2} = -1.3$  V vs. SCE, Figure 1, left) by cyclic voltammetry. Their radical anions are electrogenerated with equal efficiency, which is entirely consistent with the spin densities of their radical anions (Figure 1, right) being localized on the naphthalene and being unaffected by substitution on the *N*-aniline. Spectroelectrochemistry of both e-PRCats gave identical UV-vis bands for their radical

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Entry	Radical anion	e-PRCat	Product yield [%] <sup>[a]</sup>	BDFE [kcal mol <sup>-1</sup> ] <sup>[b]</sup>	$E^{p}_{red}\left[V ight] \Delta E^{calc.[c]}$	$\Delta E^{\exp[d]}$
1	1 g	NpMI	78 ( <b>2</b> g)	-39.8 <sub>(C-O)</sub>	-2.55	-2.47
2	1a	NpMI	78 ( <b>2</b> a)	-39.2 <sub>(C-O)</sub>	-2.60	-2.23/ -2.34
3	1 ai	"BuO-NpMI	51 ( <b>2ai</b> )	-38.7 <sub>(C-O)</sub>	-2.62	ND
4	10	"BuO-NpMI	56 ( <b>2o</b> )	-38.1 (C-O)	-2.45	-2.60
5	10	<sup>n</sup> BuO-NpMI	5 (de-Cl)	-26.9 (C-CI)	-	-2.78 <sup>[f]</sup>
6	lr	"BuO-NpMI	39 ( <b>2 r</b> )	-38.2 (C-O)	-2.44	-2.33/ -2.46
7	lr	"BuO-NpMI	trace (de-Br)	-30.6 (C-Br)	-	$-2.44^{[f]}$
8	1 d	<sup>n</sup> BuO-NpMI	69 ( <b>2 d</b> )	-34.5 (C-O)	-2.44	-2.41
9	1 aa	"BuO-NpMI	n.d. ( <b>2 aa</b> )	-27.5 (C-O)	-2.40	-2.42
10	1 al	"BuO-NpMI	n.d. ( <b>2 al</b> )	-22.1 (C-O)	-2.56	-2.68

Table 2: Calculated properties of phosphinate radical anions vs. reactivity

[a] Product yields as defined in Scheme 2. [b] Bond dissociation free energies ( $\Delta G$ ) calculated at the  $\omega$ B97X-D/6–311 + G\*, IEFPCM (MeCN) theory level. [c] Calculated at the  $\omega$ B97X-D/6–311 + G\*, IEFPCM (MeCN) theory level and calibrated to an experimental set, see SI. [d] Measured at 10 mM [phosphinate] in 0.1 M <sup>n</sup>Bu<sub>4</sub>N-PF<sub>6</sub> in MeCN using Fc as an internal standard and calibrated vs. SCE, see SI. [f] Literature redox potentials of PhCl and PhBr are taken as surrogates.<sup>[6]</sup>



**Figure 1.** Cyclic voltammetry of e-PRCats (10 mM [e-PRCat] in 0.1 M  $^{n}Bu_4N\cdot PF_6$  in MeCN) vs. Ag/AgCl (left). DFT calculated spin densities (right) of **NpMI**<sup>-</sup> and **"BuO-NpMI**<sup>-</sup>, see SI for details.

anions (Figure 2, left and see SI). Taken together, these results indicate that their excited radical anions are equally potent reductants. To probe further, we electrochemically generated **NpMI**<sup>-</sup> and **"BuO-NpMI**<sup>-</sup> under inert conditions for analysis by EPR (Figure 2, right).<sup>[23]</sup> In both cases, a pentet was observed whose intensity was unchanged upon irradiation with blue LEDs. In both cases, in the presence of **1d** (10 equiv.), the EPR signal was identical in the dark (see SI), but upon irradiation by blue LEDs the EPR signal quenched,



**Figure 2.** Spectroelectrochemistry of **"BuO-NpMI** (2.5 mM in 0.1 M "Bu<sub>4</sub>N·PF<sub>6</sub> in MeCN) from 0 to -1.6 V vs. Ag/AgCl (left). EPR spectrum of electroreduced **"BuO-NpMI** (2.5 mM in 0.1 M "Bu<sub>4</sub>N·PF<sub>6</sub> in MeCN at U<sub>cell</sub> = -1.6 V for 1 h) in the presence of **1d** (10 equiv.) and signal quenching upon light irradiation (right).

corroborating successful SET from the doublet states  $(D_n)$  of both catalysts <sup>2</sup>[NpMI<sup>-\*</sup>] and <sup>2</sup>[<sup>n</sup>BuO-NpMI<sup>-\*</sup>] to 1d. Given that the reaction of 1d is only successful with <sup>n</sup>BuO-NpMI<sup>-</sup> and taken together with the discussion of  $E^p_{red}s$ and BDFEs in Table 2, this confirms SET is not the determining factor for the success of <sup>n</sup>BuO-NpMI<sup>-</sup>.

Neutral and electroreduced forms of **NpMI** and **"BuO-NpMI** were probed by luminescence spectroscopy (Table 3). For neutral e-PRCats, absorbance and emission (fluorescence) spectra corresponded with the literature.<sup>[24]</sup> Measured lifetimes were  $\tau \approx 3.0$  ns in both cases. Although some *N*-arylnaph-

thalimide derivatives have ultrashort-lived singlet states, due to rapid intersystem crossing to triplet states,<sup>[24]</sup> phosphorescence does not occur for the N-aryl-1,8-naphthalimides where N-aryl rotation becomes considerably hindered.<sup>[24]</sup> Electroreduction for 1 h and selective excitation of the radical anions at 452 nm led to a new emission band ( $\lambda_{max}$  ca. 540 nm) and a longer-lived species with biexponential decay ( $\tau_1 \approx 7$  ns and  $\tau_2 \approx 20$  ns) for both NpMI<sup>--</sup> and "BuO-NpMI<sup>--</sup>. The doublet (D<sub>1</sub>) states of similar radical anions (naphthalene diimide radical anions, perylene diimide radical anions) are picosecond-lived and do not luminesce,<sup>[25]</sup> and we confirmed by excitation spectra (see SI) that this emission was not deriving from the initially-formed excited state <sup>2</sup>[<sup>n</sup>BuO-NpMI<sup>.-\*</sup>] (Figure 2, left), but from a lower-lying, longer lived excited state, termed "ES1". Intersection of the longest wavelength excitation and shortest wavelength emission bands allows an estimation of  $E^{0-0}$  for photoexcited states.<sup>[26]</sup> For these emitting excited states, estimated  $E^{0-0}$  values ( $E^{ES}$ ) for both [NpMI<sup>-\*</sup>] and ["BuO-NpMI<sup>-\*</sup>] were ( $E^{ES}$  = 56.6 kcalmol<sup>-1</sup>) almost identical to the triplet energies  $(E^{T})$ of \*IrIII photosensitizers used in olefin photoisomerisms.[9a-c] It is therefore reasonable to propose E-/Z- photoisomerism occurs via energy transfer ( $E_nT$ ) from ES<sub>1</sub>.  $E_nT$  would be

exergonic to *E*-stilbene and less so to *Z*-stilbene ( $E^{T} = 51.0$  vs.  $E^{T} = 55.5$  kcal mol<sup>-1</sup>, respectively), rationalizing high *Z*-stilbene selectivity.<sup>[9b,c,27]</sup> However, the lifetime of ES<sub>1</sub> was unchanged in the presence of **1d** (10 equiv.), confirming its catalytic inactivity in the initial SET step.

In their study of photoexcited benzo-[ghi]perylenemonoamide (BPI) radical anions for Birch reductions, Miyake and coworkers made similar observations.<sup>[14]</sup> They assigned the long-lived excited state as the lowest-lying quartet excited state (<sup>4</sup>BPI<sup>--\*</sup>) arising from intersystem crossing (ISC) from the doublet state (<sup>2</sup>BPI<sup>--\*</sup>). Therefore, the lowest-lying quartet state <sup>4</sup>[**nBuO-NpMI**<sup>--\*</sup>]

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Entry	e-PRCat	Conditions	$\lambda_{\scriptscriptstyle max}$ (ex)/ $\lambda_{\scriptscriptstyle max}$ (em)	τ [ns]	E <sup>s/ES1</sup> [kcal mol <sup>-1</sup> ]
1	NpMI	-	375/412	$\tau = 3.2$	(S <sub>1</sub> ) 75.4
2	NpMI	—1.6 V, 1 h <sup>[a]</sup>	452/535	$\tau_1 = 5.4 \ \tau_2 = 21.7$	(ES <sub>1</sub> ) 56.6
3	"BuO-NpMI	-	375/412	$\tau = 3.2$	(S <sub>1</sub> ) 75.6
4	"BuO-NpMI	—1.6 V, 1 h <sup>[a]</sup>	452/548	$\tau_1 = 6.8 \ \tau_2 = 19.5$	(ES <sub>1</sub> ) 56.6
5	"BuO-NpMI	—1.6 V, 1 h <sup>[a]</sup>	452/548	$\tau_1 = 8.1 \ \tau_2 = 20.3$	_
	-	+10 equiv. <b>1 d</b>			

Table 3: Lifetimes of neutral and electroreduced<sup>[a]</sup> e-PRCats.

[a] Electroreduced e-PRCat (2.5 mM in MeCN (0.1 M  $^{n}Bu_{4}N \cdot PF_{6})$ , diluted 8×.

is a candidate for ES<sub>1</sub>, that allows E<sub>n</sub>T to be spin-conserved. We calculated the vertical excitation energy of this lowest quartet state with CASSCF (see SI) and found a reasonable agreement with the observed  $\lambda_{max}$  of luminescence. It is energetically close to the doublet states underlying the 415 nm absorption band so that ISC is plausible.

Miyake similarly found that the putative <sup>4</sup>BPI<sup>-+</sup> was not catalytically active in the Birch SET step. They hypothesized SET from a higher lying excited doublet state <sup>2</sup>BPI<sup>-+</sup> ( $D_n$ ) in an anti-Kasha fashion. Consistent with previously reported anti-Kasha photochemistry of doublet excited state photocatalysts,<sup>[5a,14]</sup> excitation of the broad absorption of <sup>2</sup>[<sup>n</sup>BuO-



**Figure 3.** Calculated DFT/MRCI absorption spectrum for **"BuO-NpMI**" (top). Dark states with oscillator strengths f < 0.01 are indicated by dotted orange lines. Leading electronic configurations for the bright excited states D<sub>1</sub>, D<sub>n</sub> and D<sub>n+1</sub> (bottom). Dotted red lines indicate single electron excitations from the ground state configuration.

**NpMI**<sup>·-\*</sup>] between 650–900 nm (D<sub>0</sub>→D<sub>1</sub>) with 740 nm or 850 nm LEDs gave only traces of **2d**.<sup>[28]</sup> Ruling out participation of the first excited state (D<sub>1</sub>), "effective minimum" potentials ( $E^{0}_{1/2}$ ) of **NpMI**<sup>--\*</sup> (D<sub>n</sub>) at -3.7 V vs. SCE and "**BuO-NpMI**<sup>·-\*</sup>(D<sub>n</sub>) at -3.8 V vs. SCE can be calculated by previously described methods,<sup>[29]</sup> easily reaching  $E^{p}_{red}$  of all phosphinates herein as well as aryl halides.<sup>[30,31]</sup> Partic-

ipation of a doublet excited state in SET is consistent with aforementioned quenching of the EPR signal (Figure 2).

High-level DFT/MRCI calculations were carried out for <sup>n</sup>**BuO-NpMI**<sup>-</sup> to characterize this  $D_n$  state. The computed spectrum (Figure 3, top) is in excellent agreement with the experimental absorption spectrum, especially at the band with  $\lambda_{max} = 415$  nm comprising two bright  $\pi - \pi^*$  states (D<sub>0</sub> $\rightarrow$  $D_n$  and  $D_0 \rightarrow D_{n+1}$ ). Contrary to the  $D_0 \rightarrow D_1$  transition around 870 nm, both these excitations transfer electron density from the naphthalene to the N-aniline unit of "BuO-NpMI-(Figure 3, bottom). Preassembly of ground state radical anion and substrate could explain (i) photochemistry of ultrashortlived doublet states<sup>[25]</sup> and (ii) faster than rates of diffusion.<sup>[5a]</sup> Preassembly of "BuO-NpMI-" with 1d being more favorable than that of NpMI- may explain the reactivity differences of the e-PRCats in effecting C(sp<sup>3</sup>)–O cleavage following SET, and may rationalize profound shift in the molecular site of reduction compared to previous reports.<sup>[32]</sup> However, like Miyake and co-workers, we were unable to find spectroscopic evidence of preassembly by UV-vis or EPR (see SI). While the absence of spectroscopic perturbations does not rule out a preassociation,<sup>[33]</sup> preassembly could occur at the N-aniline that is spin-disconnected from the naphthalene where the radical anion spin density is localized (Figure 1, right). Spin densities of favorable candidate preassemblies at the Naniline unit of "BuO-NpMI'- found by computational geometry optimizations do not differ from that of "BuO-NpMI" alone, while a favorable candidate preassembly at the naphthalene unit of "BuO-NpMI-" does differ (see SI). A preassembly at the N-aniline could also rationalize anti-Kasha photochemistry, since charge transfer to the N-aniline in the  $D_{n/n+1}$  states is proximal to the bound substrate and promotes intermolecular SET upon photoexcitation (Figure 3). In contrast, the charge density of the lowest excited doublet state D<sub>1</sub> remains localized on the naphthalene and is not close to the substrate.

Where spectroscopy offers little insight, a top-down approach varying catalyst structure and examining product yields has proven useful in investigating the mechanisms of reactions involving *in situ*-formed organic electron donors.<sup>[34]</sup> To probe the importance of a preassembly of **1d** at the *N*-aniline of the e-PRCat, we explored the influence of a series of e-PRCats with varying electronics and steric bulk (**5a**–**f**, Scheme 6). Compared to **NpMI**, catalysts with electron donating alkoxy or *p*-anisole substituents on the naphthalene unit (**5a**, **5b**) gave no reaction. Compared to **"BuO-NpMI**, a catalyst with additional alkoxy substituents on the *N*-aniline

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**Scheme 6.** e-PRC deoxygenation of 1d with various e-PRCats. Yields of 2d determined by <sup>1</sup>H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

(5c) gave a lower (41%) yield of 2d. The yield of 2d increased with decreasing steric hindrance at the *ortho*-positions of the *N*-aniline (NpMI  $\leq 5d < 5e$ ).<sup>[35]</sup> A decrease in "steric bulk" likely promotes preassociation of radical anion e-PRCat and 1d. In our computational investigations we found multiple stable ground state preassemblies. Geometry optimizations (see SI) converged to pincer-like conformations for all candidates, where two of the substrate's aryl groups coordinate to the *N*-aniline of the e-PRCat in a T- $\pi$  and  $\pi$ - $\pi$ orientation, respectively. The thermodynamics and kinetics of their formations (see SI) mirror reactivity trends in Scheme 6, corroborating a preassembly between e-PRCat and substrate before photoexcitation.

#### Conclusion

We report an electro-mediated photoredox catalytic reductions of phosphinates derived from a-chloroketones toward selective olefinations and deoxygenations. This study reports reductive formation of alkyl carbanions via photoexcited radical anions as super-reductants. The selective reduction of C(sp<sup>3</sup>)-O bonds in the presence of C(sp<sup>2</sup>)-X bonds was achieved. Reactivity differences of various radical anion photocatalysts and anti-Kasha photochemistry, backed by computational insights, suggest the importance of a close catalyst-substrate interaction for an effective, selective reaction. In this context, our calculations indicate that intramolecular charge transfer in the catalyst radical anion upon photoexcitation promotes SET to the substrate. Photocatalyst-substrate preassemblies such as EDA complexes,<sup>[36]</sup> noncovalent interactions,<sup>[5a, 37]</sup> hydrogen bonding<sup>[38]</sup> and ordering of solvent<sup>[39]</sup> are receiving increasing attention to unveil the next generation of photocatalytic transformations and offer new frontiers in selectivity and efficiency. Further studies into the nature of interactions and structure of preassemblies, as well as catalyst stability,<sup>[40]</sup> are ongoing.

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#### **Conflict of Interest**

The authors declare no conflict of interest.

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- Selected reviews on photochemistry: a) Q.-Q. Zhou, Y.-Q. Zou, L.-Q. Lu, W.-J. Xiao, Angew. Chem. Int. Ed. 2019, 58, 1586– 1604; Angew. Chem. 2019, 131, 1600–1619; b) L. Marzo, S. K. Pagire, O. Reiser, B. König, Angew. Chem. Int. Ed. 2018, 57, 10034–10072; Angew. Chem. 2018, 130, 10188–10228; c) J. Xie, H. Jin, A. S. K. Hashmi, Chem. Soc. Rev. 2017, 46, 5193–5203; d) N. A. Romero, D. A. Nicewicz, Chem. Rev. 2016, 116, 10075– 10166; e) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, Chem. Rev. 2013, 113, 5322–5363.
- [2] Selected general reviews on electrochemistry: a) T. H. Meyer, I. Choi, C. Tian, L. Ackermann, *Chem* 2020, *6*, 2484–2496; b) P. Xiong, H.-C. Xu, *Acc. Chem. Res.* 2019, *52*, 3339–3350; c) S. Tang, Y. Liu, A. Lei, *Chem* 2018, *4*, 27–45; d) A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* 2018, *57*, 5594–5619; *Angew. Chem.* 2018, *130*, 5694–5721; e) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* 2017, *117*, 13230–13319.
- [3] For selected representative examples, see: a) K. Targos, O. P. Williams, Z. K. Wickens, J. Am. Chem. Soc. 2021, 143, 4125–4132; b) D. Rombach, H.-A. Wagenknecht, Angew. Chem. Int. Ed. 2020, 59, 300–303; Angew. Chem. Int. Ed. 2020, 132, 306–310; c) J. I. Bardagi, I. Ghosh, M. Schmalzbauer, T. Ghosh, B. König, Eur. J. Org. Chem. 2018, 34–40; d) M. Neumeier, D. Sampedro, M. Májek, V. A. de la Peña O'Shea, A. Jacobi von Wangelin, R. Pérez-Ruiz, Chem. Eur. J. 2018, 24, 105–108; e) L. Zeng, T. Liu, C. He, D. Shi, F. Zhang, C. Duan, J. Am. Chem. Soc. 2016, 138, 3958–3961; f) I. Ghosh, B. König, Angew. Chem. Int. Ed. 2016, 55, 7676–7679; Angew. Chem. 2016, 128, 7806–7810; g) I. Ghosh, T. Ghosh, J. I. Bardagi, B. König, Science 2014, 346, 725–728; h) H. Li, X. Tang, J. H. Pang, X. Wu, E. K. L. Yeow, J. Wu, S. Chiba, J. Am. Chem. Soc. 2021, 143, 481–487; For full reviews, see: i) F. Glaser, C. Kerzig, O. S. Wenger, Angew. Chem.

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*Int. Ed.* **2020**, *59*, 10266–10284; *Angew. Chem.* **2020**, *132*, 10350–10370; j) M. Schmalzbauer, M. Marcon, B. König, *Angew. Chem. Int. Ed.* **2021**, *60*, 6270–6292; *Angew. Chem.* **2021**, *133*, 6338–6363.

- [4] For a full review on the combination of photoredox catalysis and organic electrochemistry: a) J. P. Barham, B. König, Angew. Chem. Int. Ed. 2020, 59, 11732-11747; Angew. Chem. 2020, 132, 11828-11844; For highlights, see: b) J. Liu, L. Lu, D. Wood, S. Lin, ACS Cent. Sci. 2020, 6, 1317-1340; c) L. Capaldo, L. L. Quadri, D. Ravelli, Angew. Chem. Int. Ed. 2019, 58, 17508-17510; Angew. Chem. 2019, 131, 17670-17672; d) Y. Yu, P. Guo, J.-S. Zhong, Y. Yuan, K.-Y. Ye, Org. Chem. Front. 2020, 7, 131-135.
- [5] For recent examples on homogeneous photoelectrochemistry, see: a) S. Wu, J. Žurauskas, M. Domański, P. S. Hitzfeld, V. Butera, D. J. Scott, J. Rehbein, A. Kumar, E. Thyrhaug, J. Hauer, J. P. Barham, Org. Chem. Front. 2021, 8, 1132-1142; b) P. Xu, P.-Y. Chen, H.-C. Xu, Angew. Chem. Int. Ed. 2020, 59, 14275-14280; Angew. Chem. 2020, 132, 14381-14386; c) X.-L. Lai, X.-M. Shu, J. Song, H.-C. Xu, Angew. Chem. Int. Ed. 2020, 59, 10626-10632; Angew. Chem. 2020, 132, 10713-10719; d) L. Niu, C. Jiang, Y. Liang, D. Liu, F. Bu, R. Shi, H. Chen, A. D. Chowdhury, A. Lei, J. Am. Chem. Soc. 2020, 142, 17693-17702; e) Y. Qiu, A. Scheremetjew, L. H. Finger, L. Ackermann, Chem. Eur. J. 2020, 26, 3241-3246; f) N. G. W. Cowper, C. P. Chernowsky, O. P. Williams, Z. K. Wickens, J. Am. Chem. Soc. 2020, 142, 2093-2099; g) H. Huang, Z. M. Strater, T. H. Lambert, J. Am. Chem. Soc. 2020, 142, 1698-1703; h) H. Kim, H. Kim, T. H. Lambert, S. Lin, J. Am. Chem. Soc. 2020, 142, 2087-2092; i) H. Huang, T. H. Lambert, Angew. Chem. Int. Ed. 2020, 59, 658-662; Angew. Chem. 2020, 132, 668-672; j) W. Zhang, K. L. Carpenter, S. Lin, Angew. Chem. Int. Ed. 2020, 59, 409-417; Angew. Chem. 2020, 132, 417-425; k) H. Huang, Z. M. Strater, M. Rauch, J. Shee, T. J. Sisto, C. Nuckolls, T. H. Lambert, Angew. Chem. Int. Ed. 2019, 58, 13318-13322; Angew. Chem. 2019, 131, 13452-13456; 1) F. Wang, S. S. Stahl, Angew. Chem. Int. Ed. 2019, 58, 6385-6390; Angew. Chem. 2019, 131, 6451-6456; m) H. Yan, Z. W. Hou, H.-C. Xu, Angew. Chem. Int. Ed. 2019, 58, 4592-4595; Angew. Chem. 2019, 131, 4640-4643.
- [6] L. Pause, M. Robert, J.-M. Savéant, J. Am. Chem. Soc. 1999, 121, 7158-7159.
- [7] For reductions of benzyl radicals to benzyl anions by PRC: a) K. Donabauer, B. König, Acc. Chem. Res. 2021, 54, 242–252; For examples of electrochemical reports: b) W. Zhang, S. Lin, J. Am. Chem. Soc. 2020, 142, 20661–20670; c) L. Lu, J. C. Siu, Y. Lai, S. Lin, J. Am. Chem. Soc. 2020, 142, 21272–21278; For the reduction potential of a benzyl radical: d) J. Grimshaw, Electrochemical Reactions and Mechanisms in Organic Chemistry, Elsevier, Amsterdam, 2000, pp. 89–157.
- [8] The alkane product likely forms via high-voltage-mediated C=C bond reduction, see: X. Liu, R. Liu, J. Qiu, X. Cheng, G. Li, *Angew. Chem. Int. Ed.* **2020**, *59*, 13962–13967; *Angew. Chem.* **2020**, *132*, 14066–14071.
- [9] For reviews on photosensitized TTET isomerizations of alkenes and its use in tandem strategies: a) J. J. Molloy, T. Morack, R. Gilmour, Angew. Chem. Int. Ed. 2019, 58, 13654-13664; Angew. Chem. 2019, 131, 13789-13800; b) S. Yakubov, J. P. Barham, Beilstein J. Org. Chem. 2020, 16, 2151-2192; c) D. C. Fabry, M. A. Ronge, M. Rueping, Chem. Eur. J. 2015, 21, 5350-5354; d) J. J. Molloy, M. Schäfer, M. Wienhold, T. Morack, C. D. Daniliuc, R. Gilmour, Science 2020, 369, 302-306.
- [10] We found that although RVC (foam) electrodes provided a large surface area to the reaction and were superior to graphite felt, mechanical shearing oftentimes occurred. Fe plate was more robust and gave a similar yield of 2a (see SI).
- [11] For relevant reviews on electrode materials, see: a) A. M. Couper, D. Pletcher, F. C. Walsh, *Chem. Rev.* 1990, 90, 837-

865; b) D. M. Heard, A. J. J. Lennox, Angew. Chem. Int. Ed. **2020**, 59, 18866–18884; Angew. Chem. **2020**, 132, 19026–19044.

- [12] a) J. Iqbal, R. R. Srivastava, J. Org. Chem. 1992, 57, 2001–2007; b) H. A. Dabbagh, M. Zamani, Appl. Catal. A 2011, 404, 141– 148; A method for selective elimination to terminal olefins was reported but requires triphosgene: c) M. O. Ganiu, A. H. Cleveland, J. L. Paul, R. Kartika, Org. Lett. 2019, 21, 5611–5615.
- [13] S. Jin, H. T. Dang, G. C. Haug, R. He, V. D. Nguyen, V. T. Nguyen, H. D. Arman, K. S. Schanze, O. V. Larionov, J. Am. Chem. Soc. 2020, 142, 1603–1613.
- [14] J. P. Cole, D.-F. Chen, M. Kudisch, R. M. Pearson, C.-H. Lim, G. M. Miyake, J. Am. Chem. Soc. 2020, 142, 13573-13581.
- [15] A. Chatterjee, B. König, Angew. Chem. Int. Ed. 2019, 58, 14289– 14294; Angew. Chem. 2019, 131, 14427–14432.
- [16] a) B. Harirchian, N. L. Bauld, J. Am. Chem. Soc. 1989, 111, 1826–1828; b) L. Liao, R. Guo, X. Zhao, Angew. Chem. Int. Ed. 2017, 56, 3201–3205; Angew. Chem. 2017, 129, 3249–3253.
- [17] a) H. Lebel, M. Davi, S. Díez-González, S. P. Nolan, J. Org. Chem. 2007, 72, 144–149; b) H. Level, V. Paquet, J. Am. Chem. Soc. 2004, 126, 320–328.
- [18] a) T. Ganicz, W. Stańczyk, *Materials* 2009, 2, 95–128; b) G. Mishra, A. K. Srivastava, *Polym. Bull.* 2007, 58, 351–358; c) G. Castruita, V. García, E. Arias, I. Moggio, R. Ziolo, A. Ponce, V. González, J. E. Haley, J. L. Flikkema, T. Cooper, *J. Mater. Chem.* 2012, 22, 3770–3780; d) G. Misra, A. K. Srivastava, *Colloid Polym. Sci.* 2008, 286, 445–451; K. Nilles, P. Theato, *Eur. Polym. J.* 2007, 43, 2901–2912.
- [19] Conversion of a *p*-acetylbenzoate to a *p*-vinylbenzoate has been reported only as a low-yielding side reaction: E. Tayama, K. Watanabe, S. Sotome, *Org. Biomol. Chem.* **2017**, *15*, 6668–6678.
- [20] For transition metal catalyzed approaches: a) A. Minato, K. Suzuki, K. Tamao, J. Am. Chem. Soc. 1987, 109, 1257–1258;
  b) T. Iwai, T. Fujihara, J. Terao, Y. Tsuji, J. Am. Chem. Soc. 2009, 131, 6668–6669.
- [21] D. Rackl, V. Kais, P. Kreitmeier, O. Reiser, *Beilstein J. Org. Chem.* 2014, 10, 2157–2165.
- [22] K. Lam, I. E. Markó, Org. Lett. 2011, 13, 406-409.
- [23] For full EPR investigations on NpMI<sup>--</sup>, see SI.
- [24] A. Demeter, T. Bercés, L. Biczók, V. Wintgens, P. Valat, J. Kossanyi, J. Phys. Chem. 1996, 100, 2001–2011.
- [25] a) D. Gosztola, M. P. Niemczyk, W. Svec, A. S. Lukas, M. R. Wasielewski, *J. Phys. Chem. A* 2000, *104*, 6545–6551; b) C. Lu, M. Fujitsuka, A. Sugimoto, T. Majima, *J. Phys. Chem. C* 2016, *120*, 12734–12741.
- [26] This can only be an estimation for measurements at rt. Cryogenic measurements are required for accurate E<sup>0-0</sup> determinations: F. Strieth-Kalthoff, M. J. James, M. Teders, L. Pitzer, F. Glorius, *Chem. Soc. Rev.* 2018, 47, 7190–7202.
- [27] SET reduction of the *E*-isomer by  $[NpMI^{-*}]$  cannot be ruled out, but redox potential differences between *E*-/*Z*- isomers are deemed insufficient to provide high (>10:1) *Z*-selectivities. Literature precedent for photoisomerism by closed-shell photocatalysts favors  $E_nT$ .
- [28] See the Supporting Information for full wavelength dependence experiments.
- [29] For a relevant example, see: C. J. Zeman IV, S. Kim, F. Zhang, K. S. Schanze, J. Am. Chem. Soc. **2020**, 142, 2204–2207. Calculated by the sums of ground state redox potentials ( $E_{1/2}$  vs. SCE) and the tail of the UV-vis band at 490 nm (525 nm = 2.45 eV) as  $E^{0.0}$ .
- [30] In Ref. [14], formation of solvated electrons is proposed. Herein, reactions take place in non-alcoholic solvents. Formation of solvated electrons cannot rationalize reactivity differences between catalysts. Substrate-catalyst preassociation could allow ultrashort lifetimes of excited doublet state photocatalysts to be circumvented.

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- [31] In Ref. [30a], an attempt to determine the lifetime of <sup>2</sup>[Narylnaphthalimide<sup>--</sup>\*] in MeCN by transient absorption spectroscopy led to rapid bleaching, suggesting solvent redox processes.
- [32] π-stacking interactions were implicated by DFT to explain selective reduction of arenes over aliphatic esters by photoexcited neutral electron donors: E. Doni, B. Mondal, S. O'Sullivan, T. Tuttle, J. A. Murphy, J. Am. Chem. Soc. 2013, 135, 10934–10937.
- [33] Hunter and Sanders claimed π-π stacking rarely leads to notable UV-vis perturbations, advocating the participation of σπ stacking in favorable edge-to-face binding: C. A. Hunter, J. K. M. Sanders, J. Am. Chem. Soc. 1990, 112, 5525-5534.
- [34] a) S. Zhao, E. Doni, G. M. Anderson, R. G. Kane, S. W. MacDougall, V. M. Ironmonger, T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc.* 2014, *136*, 17818–17826; b) J. P. Barham, G. Coulthard, R. G. Kane, N. Delgado, M. P. John, J. A. Murphy, *Angew. Chem. Int. Ed.* 2016, *55*, 4492–4496; *Angew. Chem.* 2016, *128*, 4568–4572; c) J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire, T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc.* 2016, *138*, 7402–7410.
- [35] When the reaction was attempted with the N-phenyl derivative (N-Ph NpMI, with no para- or ortho-substitution), no product was observed. We confirmed this was not due to solubility differences, both catalysts are fully soluble in reactions and solubility limits of N-Ph NpMI and "BuO-NpMI are 62.5 mM

and 250.0 mM in MeCN, respectively. Instead, we presume a certain degree of electron richness is required in the *N*-aniline moiety to render it sufficiently reductive in its higher order charge transfer excited doublet state.

- [36] Selected reviews: a) C. G. S. Lima, T. de M. Lima, M. Duarte,
  I. D. Jurberg, M. W. Paxião, ACS Catal. 2016, 6, 1389–1407;
  b) G. E. M. Crisenza, D. Mazzarella, P. Melchiorre, J. Am. Chem. Soc. 2020, 142, 5461–5476.
- [37] A. Bhattacharyya, S. De Sarkar, A. Das, ACS Catal. 2021, 11, 710–733.
- [38] Selected examples: a) N. Berg, S. Bergwinkl, P. Nuernberger, D. Horinek, R. M. Gschwind, J. Am. Chem. Soc. 2021, 143, 724– 735; b) F. Burg, T. Bach, J. Org. Chem. 2019, 84, 8815–8836.
- [39] Selected examples: a) M. Giedyk, R. Narobe, S. Weiß, D. Touraud, W. Kunz, B. König, *Nat. Catal.* **2020**, *3*, 40–47; b) J. Kaur, A. Shahin, J. P. Barham, *Org. Lett.* **2021**, *23*, 2002–2006.
- [40] While this manuscript was in press, a complementary e-PRC reductive cleavage of C(sp<sup>2</sup>)–O bonds was disclosed: C. P. Chernowsky, A. F. Chmiel, Z. K. Wickens, *Angew. Chem. Int. Ed.* 2021, DOI:10.1002/anie.202107169; *Angew. Chem.* 2021, DOI:10.1002/ange.202107169.

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### 1.2 C–H Arylation of Pyrroles Catalyzed by 3d-Metal Complexes

Transition metal catalysts have long been a fundamental component of the organic synthesis toolkit in the electronic ground state. Their ability to open shorter and often cheaper synthetic routes from readily available raw materials has paved the way for widespread industrial applications.<sup>[131,132]</sup> Complementary to purely organic catalysts like the one discussed in section 1.1, transition metal complexes also offer an attractive and versatile platform for PRC.<sup>[103,106,133]</sup> While Ru and Ir complexes are still prevalent, there are growing efforts to replace them with complexes of earth abundant and less environmentally damaging first-row transition metals.<sup>[103,106,134–144]</sup>

However, the application of 3d-metals in PRC introduces new challenges. The conventional photocatalytic process requires low-energy intramolecular CT states, below the d-d transitions, to set up the subsequent diffusion-controlled single electron transfer to or from the substrate while avoiding fast internal conversion. This is the case in strong ligand fields with sufficient overlap between ligand and d-orbitals. The 4d and 5d orbitals of Ru and Ir enable such overlap, as they extend well beyond the respective s- and p-shells (figure 1.2). In contrast, the radial distribution function of the 3d-orbitals in first-row transition metals has a maximum around the same distance from the nuclei as the 3s and 3p orbitals due to the lack of a radial node. This is known as the primogenic effect<sup>[145,146]</sup> and results in weaker metal-ligand bonds, as the bonding overlap with the 3d-orbitals is counteracted by electrostatic repulsion from the 3s and 3p orbitals.<sup>[138]</sup> As a result, the ligand-field splitting in 3d-metal complexes is much smaller than in their 4d and 5d homologues, such that the d-d transitions are now lower in energy than the photoexcited intramolecular CT states. This opens non-radiative decay channels and leads to short excited state lifetimes that hamper



Figure 1.2: Radial distribution function of the valence s-, p- and d-shells with increasing principal quantum number, visualizing the primogenic effect. The 4d and 5d shells extend further beyond the respective s- and p-shells, facilitating larger overlap with ligand orbitals and thereby lower-energy CT states in transition metal complexes than the 3d-shells. Figure inspired by ref. 138.

diffusion-controlled reactions. So far, strategies to navigate around this issue have focused on either suppressing the low-energy ligand-field transitions by employing d<sup>10</sup> metals or on increasing the excited state lifetimes with elaborate ligand design.<sup>[103]</sup>

The article "Cobalt-Mediated Photochemical C–H Arylation of Pyrroles", published 2024 in Angew. Chem. Int. Ed. follows a different route. Rather than enforcing certain excited state properties of the catalyst, thereby limiting its synthetic accessibility, single electron transfer is facilitated by the formation of a dispersive preassembly with the substrate before photoexcitation. This circumvents the need for long-lived excited states, as the photoinduced process is no longer controlled by diffusion. Moreover, the complex is readily accessible from a synthetic point of view, featuring two simple diiminopyridine ligands (figure 1.3). The catalytic cycle was characterized through close collaboration between synthesis, spectroscopy and theory, culminating in the formulation of a detailed reaction mechanism that is mediated by ground state preassemblies. Correctly describing the electronic structure of the large and weakly bound open-shell species posed the main challenge for the computational part of this work. The most important points of the article are summarized below:

- The C-H arylation of pyrroles was successfully photocatalyzed by a series of bis-(diiminopyridine) complexes with first-row transition metals (center of figure 1.3). While the reaction proceeded with Fe, Ni, and Zn, the highest yields were obtained using Co as the metal center of the complex, which will be further denoted as [1-Co]. Both the oxidized ([1-Co]<sup>2+</sup>) and one-electron reduced forms ([1-Co]<sup>+</sup>) of the complex were isolated.
- Steady-state absorption spectroscopy indicated a two-step mechanism for the photochemical reaction: In the first step, the complex [1-Co]<sup>2+</sup> is reduced to [1-Co]<sup>+</sup> upon photoexcitation with blue light in the presence of triethylamine NEt<sub>3</sub>. The reaction also proceeds with other amines, albeit with lower product yields. [1-Co]<sup>+</sup> was detected by a characteristic absorption at 340 nm and a broad band beyond 630 nm into the near infrared range. In the second step, [1-Co]<sup>+</sup> is converted back to [1-Co]<sup>2+</sup> in the presence of an aryl halide and an N-substituted pyrrole, forming the final product. The successful regeneration of [1-Co]<sup>2+</sup> and thus completion of the catalytic cycle was confirmed by <sup>1</sup>H-NMR spectroscopy.
- Transient absorption spectroscopy of **[1-Co]**<sup>2+</sup> established a very short excited state lifetime of only 8 ps, which is much too short for diffusion-controlled photocatalysis.<sup>[100]</sup> The ensuing questions about how the mechanism proceeds instead were investigated computationally.
- The ground state electronic structures of [1-Co]<sup>2+</sup> and [1-Co]<sup>+</sup> were studied at the DFT (r<sup>2</sup>SCAN-3c) and CASSCF levels of theory. [1-Co]<sup>2+</sup> is best described by a d<sup>7</sup> configuration on the metal and two neutral ligands [Co<sup>II</sup>L<sub>2</sub><sup>0</sup>]. In [1-Co]<sup>+</sup>, the additional electron is delocalized across the metal and ligands, resulting in a multiconfigurational mixture of [Co<sup>II</sup>L<sup>0</sup>L<sup>-</sup>] and [Co<sup>I</sup>L<sub>2</sub><sup>0</sup>].



Figure 1.3: Proposed mechanism for the C–H arylation of N-methylpyrrole, catalyzed by a cobaltdiiminopyridine complex.

• The possibility of a dispersive ground state preassembly between the catalyst and the substrates, amine and aryl halide, was explored *via* metadynamics simulations at the semiempirical GFN2-xTB<sup>[147]</sup> level. Structures representative of the sampled ensemble were additionally optimized at the DFT (r<sup>2</sup>SCAN-3c) level of theory. The formation of both preassemblies between [1-Co]<sup>2+</sup> and amine, and between [1-Co]<sup>+</sup> and the aryl halide were energetically favorable. Additionally, the metadynamics revealed that the binding sites of amine and aryl halide to the complex are complementary, such that the two substrates do not interfere with each other.

- Two representative preassembly structures of  $[1-Co]^{2+}$  with NEt<sub>3</sub> and of  $[1-Co]^+$  with 4-bromobenzonitrile were selected for the calculation of absorption spectra. The range-separated double-hybrid density functional SCS- $\omega$ PBEPP86<sup>[148]</sup> was used for its accuracy in the description of CT states. An automated wave function analysis was employed to characterize the transitions underlying the main absorption bands and to identify CT states, which are expected to drive the reaction. In both preassemblies, a CT state was found within the emission range of the blue photoreactor LED. The first one transfers electron density from NEt<sub>3</sub> to the pyridine unit of the ligand, while the second one moves an electron from there to the aryl halide.
- While these results already provided an outline of the catalytic mechanism, they could not explain the difference in yields when different amines were used. A radical chain side reaction,<sup>[149,150]</sup> initiated by α-aminoalkyl radicals was suspected to proceed in parallel to the main reaction. Indeed, the free energies of the deprotonation and subsequent oxidation of α-aminoalkyl radicals, calculated at the at the DFT (r<sup>2</sup>SCAN-3c) and DLPNO-CCSD(T1)/ma-ZORA-def2-QZVPP levels, correlated well with experimental yields. The role of the amine-initiated radical chain in the final product generation is not yet clear, however, the successful regeneration of [1-Co]<sup>+</sup> indicates that both mechanisms are at play.
- In combination, the experimental and computational results allowed to formulate the consecutive photoinduced electron transfer (conPET) reaction mechanism shown in figure 1.3. First, the complex  $[1-Co]^{2+}$  and the amine form a preassembly in the ground state *via* hydrogen bonds. Photoexcitation of the assembly triggers single electron transfer from the amine to the diiminopyridine ligand. As the complex relaxes to the ground state, the extra electron density is delocalized across the metal and ligand. The thus generated  $[1-Co]^+$  in turn forms a stable preassembly with the aryl halide, mainly *via*  $\pi$ -stacking interactions. In a second light-induced step, an electron is transferred from the partially occupied  $\pi^*$  orbital of the ligand to the aryl halide, regenerating  $[1-Co]^{2+}$  and forming an aryl radical. The latter can then react further with the N-substituted pyrrole, yielding the final product. As a side reaction, the same aryl radical can be formed *via* reductive dehalogenation by  $\alpha$ -aminoalkyl radicals.
- In summary, the results provide proof-of-concept that the need for long excited state lifetimes in transition metal PRC can be circumvented *via* ground state preassemblies.

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#### C-H functionalization

### **Cobalt-Mediated Photochemical C–H Arylation of Pyrroles**

Julia Märsch, Sebastian Reiter, Thomas Rittner, Rafael E. Rodriguez-Lugo, Maximilian Whitfield, Daniel J. Scott, Roger Jan Kutta, Patrick Nuernberger,\* Regina de Vivie-Riedle,\* and Robert Wolf\*

Abstract: Precious metal complexes remain ubiquitous in photoredox catalysis (PRC) despite concerted efforts to find more earth-abundant catalysts and replacements based on 3d metals in particular. Most otherwise plausible 3d metal complexes are assumed to be unsuitable due to short-lived excited states, which has led researchers to prioritize the pursuit of longer excited-state lifetimes through careful molecular design. However, we report herein that the C-H arylation of pyrroles and related substrates (which are benchmark reactions for assessing the efficacy of photoredox catalysts) can be achieved using a simple and readily accessible octahedral bis(diiminopyridine) cobalt complex,  $[1-Co](PF_6)_2$ . Notably,  $[1-Co]^{2+}$  efficiently functionalizes both chloro- and bromoarene substrates despite the short excited-state lifetime of the key photoexcited intermediate \*[1-Co]<sup>2+</sup> (8 ps). We present herein the scope of this C-H arylation protocol and provide mechanistic insights derived from detailed spectroscopic and computational studies. These indicate that, despite its transient existence, reduction of  $*[1-Co]^{2+}$  is facilitated via pre-assembly with the NEt<sub>3</sub> reductant, highlighting an alternative strategy for the future development of 3d metal-catalyzed PRC.

#### Introduction

Photoredox catalysis (PRC) is a relatively new but highly versatile technique that is becoming pervasive in organic synthesis.<sup>[1-4]</sup> While exact mechanisms can differ, all PRC processes involve single electron transfer to or from an excited state of the photocatalyst PC as a key step. The former option involves an electron transfer from a substrate to the excited state of the PC (Figure 1a), a process that is often termed "reductive quenching". Since its inception, PRC has relied heavily on second and third row transition metal complexes as PC, and especially complexes of the precious metals Ru and Ir.[5,6] Even though they remain probably the most frequently and widely-used family of catalysts for PRC, there are growing concerns around cost, scarcity, and security of supply. This has prompted extensive efforts to find alternative PC based on more earth-abundant elements.<sup>[7-20]</sup> Significant progress has been made in the use of organic dyes as **PC**;<sup>[5,6]</sup> however it has been argued that this approach is limited by the synthetic complexity of many organic PC, and corresponding difficulties in tuning their redox and other catalytically-relevant properties.[19]

In this context, an alternative solution would be to replace the currently employed Ru and Ir polypyridyl complexes with analogues based on their much cheaper 3d metal homologues Fe and Co. However, with a few notable exceptions (e.g. based on  $Cu^{1})^{[21-23]}$  3d metal **PC** remain significantly underdeveloped relative to their precious metal and organic counterparts. This can be attributed to the fact that, in practice, the photophysical and photochemical properties of 3d metal complexes tend to differ fundamentally from those of analogous 4d and 5d complexes.<sup>[12,14-19]</sup> In particular, for 3d complexes the prevailing excited states **\*PC** are typically short-lived, with lifetimes in the fs to ps range.<sup>[10,15,24]</sup> It has often been argued that these are too short to permit diffusion-limited, intermolecular interactions with

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**Figure 1.** (a) General mechanism of photoredox catalysis mediated by an electron transfer from a sacrificial electron donor (PC = photocatalyst, D = electron donor, A = electron acceptor); (b) previously reported Fe- and Co-based photocatalysts and their catalytic applications; (c) use of simple diiminopyridine complexes as photocatalysts in C–H arylations, as reported herein.

substrates,  $[^{12,25]}$  and that this precludes these complexes from being effective **PC**.

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This has led to significant efforts to develop Fe and Co complexes with longer \*PC excited-state lifetimes, and in recent years a number of breakthroughs have been achieved through sophisticated ligand design. Employed strategies include exploitation of the Marcus inverted region,<sup>[19]</sup> and the destabilization of metal-centered (MC) electronic states with simultaneous stabilization of metal-to-ligand (MLCT) or ligand-to-metal (LMCT) charge transfer states. This could be achieved through the incorporation of push-pull ligand sets, strong  $\pi$ -acceptor ligands,  $\sigma$ -donating N-heterocyclic carbenes (NHC) and by  $\sigma$ - and  $\pi$ -donation of cyclometalating ligands.<sup>[12,13,26-29]</sup> As a result, complexes with excited-state lifetimes well into the ns range have emerged (Figure 1b, top). At the same time, there have been significant advances in electronic structure and dynamics methods,<sup>[11,30]</sup> enabling a detailed theoretical description of photocatalytic processes.

These fundamental developments have been accompanied by pioneering reports describing early examples of PRC using Fe and Co photocatalysts, some relevant examples of which are shown in Figure 1b.<sup>[19,27,31-42]</sup> While these reports represent an important advance for the field of PRC, in many cases achieving these longer excited-state lifetimes demand elaborate ligand syntheses, and/or places significant restrictions on molecular design that need to be balanced with the optimization of other important properties such as \*PC redox potentials. In contrast, we report in this work successful PRC via a simple Co complex with an extremely short excited-state lifetime, demonstrating that long \*PC lifetimes are in fact not a strict requirement. Specifically, we show that the simple, octahedral, bis(diiminopyridine) cobalt complex  $[1-Co](PF_6)_2^{[43]}$  successfully mediates the C-H arylation of pyrrole with bromo- and chloroarenes (Figure 1c). Spectroscopic studies confirm the key photochemical reduction of  $[1-Co]^{2+}$  to  $[1-Co]^{+}$ . Highlevel quantum chemical calculations reveal the crucial role of preassembly in enabling this process and provide detailed mechanistic insights.

#### **Results and Discussion**

Despite the previous emphasis on excited-state lifetimes, we were motivated to investigate whether PRC might in fact be achievable using 3d-based PC even with very short-lived \*PC states. We were encouraged by recent reports from elsewhere in the field of PRC, specifically consecutive photoinduced electron transfer (conPET) and electro-mediated photoredox catalysis (e-PRC) reactions,[44-48] in which intramolecular electron transfer to the excited states of organic radical anions PC<sup>•-</sup> (or from the excited states of organic radical cations **PC**<sup>•+</sup>) has been proposed to be a viable and essential mechanistic step despite the short excited-state lifetimes of these \*PC<sup>•-</sup> (or \*PC<sup>•+</sup>) states.<sup>[49-52]</sup> As a proof of principle we therefore chose to investigate the catalytic behavior of the known complexes  $[1-M]^{2+}$  (M=Fe, Co) whose full structures are shown in Figure 1c.  $[1-M](PF_6)_2$  are easily synthesized, are based upon a highly tunable ligand scaffold, and their redox properties have

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previously been studied in detail being appropriate for PRC.  $^{\left[ 43\right] }$ 

#### Photoreduction of [1-Co](PF<sub>6</sub>)<sub>2</sub> by NEt<sub>3</sub>

The cobalt complex  $[1-Co](PF_6)_2$  was investigated by transient absorption spectroscopy, which, as expected, showed a short excited-state lifetime of just 8 ps upon excitation at 405 nm (see Figure S44, SI). Nevertheless, the photochemical reduction of  $[1-Co](PF_6)_2$  by the common sacrificial electron donor NEt<sub>3</sub> (Figure 2a) was monitored by electronic absorption spectroscopy in the UV/Vis-NIR spectral range. Irradiation at 405 nm of a solution of  $[1-Co](PF_6)_2$  (20 µM) and NEt<sub>3</sub> (200 µM, 10 equiv. with respect to  $[1-Co](PF_6)_2$  in MeCN (250 µL) induced clear absorption changes (Figure 2a). The one-electron reduced complex [1-Co]<sup>+</sup> (Figure 2b) was identified as the reaction product by its characteristic absorption at 340 nm and a broad band extending from 630 nm far into the NIR (see Figure S41, SI).<sup>[43]</sup> Isosbestic points at 365 nm and 624 nm corroborate direct reduction of  $[1-Co]^{2+}$  to  $[1-Co]^{+}$  and decomposition of the spectra into the individual contributions of both oxidation states (Figure 2a, inset) yields concentration profiles that can be described by the rate equation for a single photochemical step (Figure 2a, see fit



**Figure 2.** (a) Electronic absorption spectra in the UV/Vis-NIR spectral range of a mixture of **[1-Co]**(PF<sub>6</sub>)<sub>2</sub> (20  $\mu$ M) and NEt<sub>3</sub> (200  $\mu$ M) in MeCN (250  $\mu$ L) after different time intervals of irradiation at 405 nm. Inset: Concentration time profiles of **[1-Co]**<sup>2+</sup> (violet), **[1-Co]**<sup>+</sup> (red), and the sum of both profiles demonstrating the conservation of mass (black). (b) Reaction sequence of the photoreduction.

in the inset).<sup>[53]</sup> Since both light and NEt<sub>3</sub> are necessary to enable reduction of  $[1-Co]^{2+}$  (Figures S31–S33, SI),  $[1-Co]^{2+}$  is reduced in its excited state, \* $[1-Co]^{2+}$ , by NEt<sub>3</sub> yielding  $[1-Co]^+$  and the  $[NEt_3]^{++}$  radical cation. The latter cannot be detected because it is rapidly deprotonated due to excess of NEt<sub>3</sub> resulting in the formation of products that do not absorb in the spectral detection window (Figure 2b).<sup>[54]</sup>

The photochemical reduction of  $[1-Fe](PF_6)_2$  by NEt<sub>3</sub> was also investigated showing a significantly reduced efficiency (see Figure S19, SI). This is presumably a consequence of the more negative reduction potential of  $[1-Fe](PF_6)_2$ , influenced by the electronic structure of the reduced complex  $[1-Fe]^+$ , which retains a formal Fe<sup>II</sup> oxidation state by reducing one of its diiminopyridine ligands to the radical anion (see Figure S47, SI).<sup>[43]</sup> Furthermore,  $[1-Fe]^+$  is prone to disproportionation into  $[1-Fe](PF_6)_2$  and  $[1-Fe]^0$ , as also evident by a non-clean formation of  $[1-Fe](PF_6)$ , even after several days of irradiation.

#### Preassemblies between [1-Co](PF<sub>6</sub>)<sub>2</sub> and NEt<sub>3</sub>

Due to the extremely short excited-state lifetime of \*[1-Co] $^{2+}$  a diffusion-limited reaction between this excited state and NEt<sub>3</sub> at the concentrations employed experimentally seems unlikely. Instead, we speculated that the observed reactivity could be due to a ground-state preassembly of **[1-Co]**<sup>2+</sup> and NEt<sub>3</sub> prior to photoexcitation. Notably, similar explanations have been proposed for conPET and e-PRC reactions, and it has been demonstrated that such preassembly can exist even if it is not detectable by steadystate spectroscopic methods.<sup>[55,56]</sup> Indeed, while no significant change is observed in the UV/Vis-NIR absorption spectrum upon addition of NEt<sub>3</sub> to  $[1-Co]^{2+}$ , the excited-state lifetime of the  $*[1-Co]^{2+}$  is decreased from 8 ps to 5 ps in the presence of NEt<sub>3</sub> (109 mM), consistent with this proposal (see section S6 in the SI). This corresponds to a rate constant of 7.5.10<sup>10</sup> s<sup>-1</sup> for the PET process. Since no further intermediates were detected by transient absorption spectroscopy despite the reduction of the excited-state lifetime, we hypothesize that the geminate back electron transfer occurs significantly faster. This reduces the overall efficiency of the process (see also the discussion in section S6 in the SI).

The possibility of preassembly and potential chargetransfer pathways was also investigated computationally. First, the geometries of  $[1-Co]^{2+}$  and  $[1-Co]^+$  were optimized at the r<sup>2</sup>SCAN–3c level of theory<sup>[57]</sup> using the ORCA<sup>[58-60]</sup> software package and verified as minima by the absence of imaginary vibrational frequencies. The calculated geometries of  $[1-Co]^{2+}$  and  $[1-Co]^+$  agree well with crystal data,<sup>[43]</sup> and selected bond lengths and angles are compiled in Tables S13 and S14 in the SI. Conformations of possible ground state assemblies between the starting species  $[1-Co]^{2+}$  and NEt<sub>3</sub> were screened via metadynamics<sup>[61,62]</sup> at the semiempirical GFN2-xtb<sup>[63]</sup> level. 774 unique structures remained within an energy window of 2 kcal/mol above the lowest energy conformer, which will be considered as especially relevant in the following discussion of non-

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**Figure 3.** Visualization of the sampled (GFN2-xtb) preassemblies of **[1-Co]**<sup>2+</sup> with NEt<sub>3</sub> (purple) and **[1-Co]**<sup>+</sup> with 4-bromobenzonitrile (cyan) within an energy window of 2 kcal/mol of the lowest energy conformation. Colored spheres indicate the position of the coordinating N-atom (purple) or the center of the aryl unit (cyan) of the respective substrate. The coordination sites of the two substrates are complementary.

covalent preassemblies. Figure 3 reveals preferential coordination sites at the imine-bound methyl groups and at the pyridine units. In all cases, the bonding situation is best described as hydrogen bonds between the amine nitrogen and the ligand.

Six representative structures with NEt<sub>3</sub> coordinating to different positions of the complex were optimized with the higher-level r<sup>2</sup>SCAN-3c method<sup>[57]</sup> to assess their thermodynamic stability (Table 1). Initial conditions for the geometry optimizations were selected manually to cover a wide range of possible binding sites. The formation of all optimized assemblies from the isolated molecules comes with a

**Table 1:** Energies and enthalpies for the formation of preassemblies between [**1-Co**]<sup>*n*+</sup> and substrates, relative to the energies of the isolated molecules ( $r^2SCAN-3c$ ). Distances refer to the N-H distance for assemblies between [**1-Co**]<sup>2+</sup> and NEt<sub>3</sub>, and to the center-to-center distance of interacting aromatic units for assemblies between [**1-Co**]<sup>+</sup> and **2a**<sub>Br</sub> (see also Figures S54, S55, SI). Preassemblies with amines other than NEt<sub>3</sub> (g-k) are listed in Table S11, SI.

Cat.	Substr.	ID	$\Delta E$ [kcal/mol]	$\Delta H$ [kcal/mol]	Dist. [Å]
[1-Co] <sup>2+</sup>	NEt <sub>3</sub>	a b c d e f	-6.69 -4.67 -6.44 -6.99 -6.61 -4.56	-5.44 -3.52 -5.13 -5.59 -5.11 -3.35	2.29 2.38 2.37 2.59 2.30 2.32
[1-Co] <sup>+</sup>	2a <sub>Br</sub>	l n o p q	7.94 7.56 8.36 8.60 8.20 6.90	-6.64 -6.38 -7.40 -7.26 -7.06 -5.80	3.69 4.85 3.96 4.10 3.82 3.54

decrease in energy of 4.56–6.69 kcal/mol, which indicates that dispersive preassemblies are generally favorable in the ground state. Coordination at the axial positions of the pyridine units (b and f in Table 1), i.e., along the z-axis of the complex, is slightly less favorable than at other sites, which may be attributed to fewer possibilities for dispersive interactions between the amine and the catalyst at these positions. Apart from this, the energies of coordination to various positions around the complex are comparable.

Following the reduction of  $[1-Co]^{2+}$  to  $[1-Co]^{+}$ , the possibility of preassembly with a model substrate for catalysis, 4-bromobenzonitrile ( $2a_{Br}$ , Figure 3), revealed 826 conformations within 2 kcal/mol above the lowest energy structure. In this group, the dominant interaction among the lower-energy conformations is  $\pi$ -stacking between the 4methoxyaniline units and the aromatic substrate. Toward higher energies, hydrogen bonds between ligand protons and the negatively polarized bromide become more prevalent. In contrast to NEt<sub>3</sub> coordination, the pyridine units of the ligand are excluded from the favorable coordination sites, which is attributed to the higher steric hindrance of the 4-bromobenzonitrile preventing  $\pi$ -stacking on these sites. Six structures were optimized (r<sup>2</sup>SCAN-3c) and exhibit stabilization energies of 6.90-8.60 kcal/mol, compared to the isolated fragments. Out of these, three conformers (l, o and p in Table 1) are characterized by  $\pi$ -stacking interactions between one of the ligands and 2a<sub>Br</sub>. In two cases (n and q), the substrate rather coordinates to one of the peripheral methoxy groups of the ligand, which are sterically more accessible than the aromatic units. The conformers n, o, and p are the most stable out of the optimized structures. Additionally, in one case (m), a T- $\pi$ -interaction can be observed.

Comparing the two substrates, the favored coordination sites of NEt<sub>3</sub> and  $2a_{Br}$  appear complementary (Figure 3), indicating that both the amine and the substrate can in principle coordinate to the metal complex at the same time. To test this hypothesis, we sampled preassemblies with both NEt<sub>3</sub> and  $2a_{Br}$  coordinating simultaneously to either  $[1-Co]^{2+}$  or  $[1-Co]^{+}$ . The results confirm the idea that both substrates have their preferred binding sites which are separate from each other (Figure S46, SI). As will be shown in the following sections, the photocatalytic mechanism likely consists of two consecutive steps. Therefore, simultaneous binding of both substrates to the catalyst is not a strict requirement for the electron transfer to occur. However, the two substrates not blocking each other's binding site is beneficial to the reaction, as it is less limited by the diffusion of the substrates. Thus, we conclude that both NEt<sub>3</sub> and  $2a_{Br}$ forming a stable dispersive assembly with the catalyst in the ground state enables the catalyst to efficiently mediate the electron transfer between the amine and the substrate  $2a_{Br}$ .

#### Catalytic C–H arylation of N-methylpyrrole

The experimentally-proven feasibility of electron transfer from NEt<sub>3</sub> to \*[**1-M**]<sup>2+</sup> and appropriate redox properties of the resulting [**1-M**]<sup>+</sup> imply that the salts [**1-M**](PF<sub>6</sub>)<sub>2</sub> should

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be capable of mediating a full photocatalytic redox cycle. Thus, as a model reaction, the reductive coupling of aryl halides with pyrroles was investigated. This can be considered a "benchmark" reaction for the assessment of new **PC** candidates and has been studied for a variety of precious metal and organic catalysts.<sup>[64-77]</sup> However, to our knowledge there have been no previous reports of such C–H arylation reactions being successfully catalyzed by 3d metal complexes.

Initially, the coupling of 4-bromobenzonitrile  $2a_{Br}$  with *N*-methylpyrrole 3a was targeted, and the results of this preliminary analysis are summarized in Table 2. Low catalyst loadings of both complexes  $[1-M](PF_6)_2$  (M=Fe, Co) promote the formation of the targeted cross-coupling

**Table 2:** Photoreductive coupling of 4-bromobenzonitrile  $2a_{Br}$  with *N*-methylpyrrole **3 a** catalyzed by complexes  $[1-M](PF_6)_2$  (M=Fe, Co).



[a] Conversion of starting material  $2a_{Br}$  as well as the yields of 4a and the hydrodehalogenation product 5a were determined by GC-FID using hexamethylbenzene as internal standard.

product **4a** in good yield, alongside minor hydrodehalogenation of  $2a_{Br}$  to **5a** (for optimization studies, see SI). Control reactions confirmed that all reaction components are required.

Amines such as N,N-dimethylethylamine (DMEA), N,N-diisopropylethylamine (DIPEA) or diisopropylamine (DIPA) gave significantly lower yields of 4a (see SI). When using the isostructural Ni and Zn complexes [1-Ni](PF<sub>6</sub>)<sub>2</sub> and [1-Zn](PF<sub>6</sub>)<sub>2</sub> significantly inferior results were obtained (see SI).<sup>[43]</sup> Under the best found conditions, both [1-Fe](PF<sub>6</sub>)<sub>2</sub> and [1-Co](PF<sub>6</sub>)<sub>2</sub> provided very good conversions of  $2a_{Br}$ , but the highest yield of product 4a was achieved using the Co complex, which is consistent with the easier photoinduced reduction by NEt<sub>3</sub> discussed above (although other factors such as the propensity of  $[1-Fe](PF_6)$ for disproportionation may also be relevant). Accordingly, the reaction scope was explored employing  $[1-Co](PF_6)_2$ (Scheme 1; see the Supporting Information for the substrate scope of  $[1-Fe](PF_6)_2$ ). At optimized conditions, moderate to good yields of cross-coupling product can be obtained with electron-deficient aryl bromides. High yields up to 77% are obtained with p-CN, o-CN, o-Br, and p-CF<sub>3</sub> substituents (products 4a, 4b, 4d, and 4g). In contrast, the p-Cl substituted product 4f was obtained in a comparatively low yield of 36%. Substrates with more electron-donating substituents resulted in lower activity, in line with previous reports using organic dyes such as rhodamine 6G and 4CzIPN.<sup>[67-77]</sup> Interestingly, the methodology is also suitable for aryl chlorides (albeit less efficiently), although they are



**Scheme 1.** Products **4a** to **4s** obtained by the light-driven C–H arylation reaction of pyrroles. Yields were obtained by GC-FID using hexamethylbenzene as internal standard. See the Supporting Information for the substrate scope of the analogous  $[1-Fe](PF_6)_2$ .

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а

0.6

0.5

0.4

typically considered very challenging to reduce (products **4i** to **4l**). For dibromoarenes, disubstitution was preferred over monosubstitution (cf. **4m** vs. **4n** and **4o** vs. **4p**), likely because the product of the latter is activated towards further functionalization.

Variation of the pyrrole coupling partner was also tolerated, and unsubstituted pyrrole, *N*-benzylpyrrole, and *N*-phenylpyrrole could all also be used to efficiently access the corresponding cross-coupled products (**4q** to **4s**). The results for [**1-Co**](PF<sub>6</sub>)<sub>2</sub> are comparable to the performance of organic dyes such as Rh-6G and 4CzIPN, while allowing for relatively low catalyst loadings and a facile work-up procedure.

#### Photoreactivity of [1-Co](PF<sub>6</sub>)

Having already established the photoreactivity of [1-Co](PF<sub>6</sub>)<sub>2</sub> towards NEt<sub>3</sub>, and confirmed in control experiments that it does not react with model substrates 4bromobenzonitrile  $(2a_{Br})$  or N-methylpyrrole (3a) in the absence of NEt<sub>3</sub> either under irradiation or in the dark (see SI), we sought to interrogate the reactivity of the reduced intermediate [1-Co]<sup>+</sup> in a similar manner. Irradiation of a solution containing all the components of the catalytic reaction, i.e.,  $[1-Co](PF_6)_2$  (20 µM), NEt<sub>3</sub> (2 mM. 100 equiv.), 4-bromobenzonitrile (2a<sub>Br</sub>, 6 mM, 300 equiv.), and N-methylpyrrole (3a, 10 mM, 500 equiv. with respect to  $[1-Co](PF_6)_2$  in MeCN (250 µL) (Figure S33, SI), with 405 nm light and monitoring by UV/Vis-NIR absorption spectroscopy showed initial formation of [1-Co]<sup>+</sup> (similarly to the results when using  $[1-Co](PF_6)_2$  and NEt<sub>3</sub> only, shown in Figure 2). However, further irradiation resulted in the total consumption of the initially formed [1-Co]<sup>+</sup> confirming that **[1-Co]**<sup>+</sup> is involved in subsequent reaction steps. Interestingly, when authentic, independently-prepared [1-Co](PF<sub>6</sub>) was combined with 2a<sub>Br</sub>, at catalytically relevant concentrations in THF oxidation of  $[1-Co]^+$  to  $[1-Co]^{2+}$  was observed by UV/Vis-NIR absorption spectroscopy upon irradiation at 405 nm (Figure 4).<sup>[78]</sup> These results suggest that, like [1-Co]<sup>2+</sup>, [1-Co]<sup>+</sup> is also able to engage in electron transfer only upon photoexcitation, in this case being oxidized by  $2a_{Br}$ . It should be noted, however, that in contrast to the preceding reduction of  $[1-Co]^{2+}$  (Figure 2, see above), in this case no defined isosbestic points were observed and the final spectrum, although similar, is not completely identical with that of pure [1-Co]<sup>2+</sup> (black dashed line in Figure 4a), indicating additional side reactions. Nevertheless, increasing the concentration of the substrate  $2a_{Br}$  significantly accelerated the oxidation of [1-Co]<sup>+</sup> (Figures S37 and S38, SI), while in the absence of substrate only a minor decrease of the [1-Co]<sup>+</sup> concentration was observed (Figure S36, SI), which is in agreement with the corresponding redox potentials  $(E_{red} (2a_{Br}) =$ -1.85 V vs. SCE;<sup>[79]</sup>  $E_{1/2}([1-Co]^{2+}/[1-Co]^{+}) = -0.53$  V vs. SCE) and provides evidence for a PET reaction between **[1-Co]**<sup>+</sup> and **2a**<sub>Br</sub>.<sup>[43,79]</sup>

The PET reaction between  $[1-Co]^+$  and  $2a_{Br}$  was also monitored by <sup>1</sup>H NMR spectroscopy (Figure 5). After

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0 min

1 min

3 min

7 min 15 min

31 min

55 min

**Figure 4.** (a) Electronic absorption spectra in the UV/Vis-NIR spectral range of a mixture of [**1-Co**](PF<sub>6</sub>) (20  $\mu$ M) and 4-bromobenzonitrile (**2a**<sub>Br</sub>, 2000  $\mu$ M) in THF (250  $\mu$ L) after different intervals of irradiation at 405 nm. Black dashed line: Spectrum of [**1-Co**](PF<sub>6</sub>)<sub>2</sub> in THF for comparison. (b) Reaction equation for the observed photochemical reaction between [**1-Co**]<sup>+</sup> and **2a**<sub>Br</sub>.

irradiation of **[1-Co]**<sup>+</sup> in the presence of 4-bromobenzonitrile (**2a**<sub>Br</sub>, 1:1, 0.01 M in MeCN- $d_3$ ) for 2 h (450 nm, TAK120 AC photoreactor), the formation of **[1-Co]**<sup>2+</sup> is visible from the appearance of its characteristic, paramagnetically shifted <sup>1</sup>H NMR resonances (Figure 5d). An increase in the exposure time to 24 h results in partial decomposition of the complex, as indicated by new <sup>1</sup>H NMR signals at 36.7, 30.9, 26.4, 0.26, and -2.9 ppm (marked with an asterisk in Figure 5e, cf. a and d).

#### Electronic structure of [1-Co]<sup>2+</sup> and [1-Co]<sup>+</sup>

To elucidate the electronic structure of the catalytic species, open-shell calculations on [1-Co]<sup>2+</sup> and [1-Co]<sup>+</sup> were performed once in the spin-unrestricted framework, which was also used for geometry optimizations, and once in a restricted open-shell formalism to eliminate spin-contamination.  $[1-Co]^{2+}$  is best described as a low-spin  $Co^{2+}$  ion  $(d^7)$ coordinated by two neutral ligands,  $[Co^{\hat{I}}(L^0)_2]^{2+}$  (L=2,6bis[1-(4-methoxyphenylimino)ethyl]pyridine). The unpaired electron occupies the  $d_{x^2-y^2}$  orbital and no significant spin % f(x)=f(x)density is observed on the ligands, even in the spinunrestricted calculation (Figure S48, SI). Upon reduction to  $[1-Co]^+$ , the formerly unoccupied  $d_{z^2}$  orbital of the metal is populated, in agreement with previous experimental deductions.<sup>[43]</sup> However, a small amount of antiferromagnetic coupling between the metal ion and the ligand-based pyridine  $\pi$ -orbitals is observed for  $[1-Co]^+$  in the spinunrestricted calculation (S = 1.12, ideal: 1.00). Restricting the



*Figure 5.* <sup>1</sup>H NMR spectra in MeCN-*d*<sub>3</sub> from bottom to top: (a) isolated [**1-Co**](PF<sub>6</sub>)<sub>2</sub>, signals highlighted with  $\nabla$ ; (b) isolated [**1-Co**](PF<sub>6</sub>), signals highlighted with ; (c) isolated [**1-Co**](PF<sub>6</sub>) in presence of the substrate 4-bromobenzonitrile (**2a**<sub>Br</sub>, 0.01 mM scale) before illumination; (d) isolated [**1-Co**](PF<sub>6</sub>), in presence of the substrate 4-bromobenzonitrile (**2a**<sub>Br</sub>, 0.01 mM scale) before illumination; (d) isolated [**1-Co**](PF<sub>6</sub>), in presence of the substrate 4-bromobenzonitrile (**2a**<sub>Br</sub>, 0.01 mM scale) after 2 h of illumination (TAK120 AC photoreactor, 7 W, 450 nm, 40 C); (e) isolated [**1-Co**](PF<sub>6</sub>) in presence of the substrate 4-bromobenzonitrile (**2a**<sub>Br</sub>, 0.01 mM scale) after 24 h of illumination (TAK120 AC photoreactor, 7 W, 450 nm, 40 C); the signals of decomposition products are marked with an asterisk.

spin to a pure triplet leads to a rise in energy of 0.25 eV. The partial occupation of ligand orbitals in the ground state of **[1-Co]**<sup>+</sup> was further corroborated by CASSCF<sup>[80]</sup> and NEVPT2<sup>[81-83]</sup> calculations with the Molpro software package.<sup>[84-86]</sup> In particular, the d<sub>xz</sub> and d<sub>yz</sub> orbitals donate electron density into ligand-based  $\pi^*$  orbitals, resulting in four partially occupied shells (Figure 6). Nevertheless, the triplet is favored over the quintet by an adiabatic energy difference of 0.4 eV (Table S12, SI). Therefore, the ground state of **[1-Co]**<sup>+</sup> is best described as a mixture of a Co<sup>I</sup> ion coordinated by two neutral ligands ([Co<sup>I</sup>(L<sup>0</sup>)<sub>2</sub>]<sup>+</sup>) and a high-spin Co<sup>II</sup> ion, coordinated by one neutral and one anionic ligand ([Co<sup>II,HS</sup>L<sup>0</sup>L<sup>-</sup>]<sup>+</sup>), setting the stage for subsequent electron transfer from the partially occupied  $\pi^*$  orbitals.

#### Electron transfer mediated by [1-Co]<sup>2+</sup> and [1-Co]<sup>+</sup>

To gain microscopic insight into the electron transfer processes, the absorption spectra for both the isolated complexes and the optimized catalyst-substrate aggregates were calculated. In a first step, the absorption properties of all optimized catalyst-substrate preassemblies were calculated at the low-cost r<sup>2</sup>SCAN-3c level of theory in a TDA-DFT framework to assess the influence of the different

preassembly conformations on the spectra. However, the energy of charge-transfer (CT) excitations is routinely underestimated in TD-DFT due to self-interaction errors.[87-91] Thus, higher-level calculations were performed at the TDA-SCS-@PBEPP86/def2-TZVP(-f) level of theory for the complexes  $[1-Co]^{2+}$  and  $[1-Co]^{+}$  as well as for selected preassemblies. The range-separated double-hybrid density functional SCS-@PBEPP86<sup>[92]</sup> includes a perturbative doubles correction and, thus, allows to describe CT excitations qualitatively.<sup>[90]</sup> Its use was crucial to reproduce the most prominent bands of the [1-Co]<sup>2+</sup> absorption spectrum (Figure 7). In general, the calculated spectrum of  $[1-Co]^{2+}$  is blue-shifted with respect to the experimental spectrum. Therefore, an empirical correction of 0.65 eV was applied to all calculated energies in the following discussion. At low energies, the spectrum of [1-Co]<sup>2+</sup> is composed exclusively of dark d-d transitions. In the visible range, the spectrum features two distinct bands at 500 nm and 580 nm, calculated at 602 nm and 633 nm in Figure 7a, which arise from transitions to two MLCT states transferring electron density from the  $d_{x^2-v^2}$  orbitals of the metal center to the pyridine units of either ligand. The prominent band with a maximum at 360 nm is dominated by ligand-centered  $\pi \rightarrow \pi^*$ transitions, mixed with transitions to ligand-to-ligand charge transfer (LLCT) states. The density of LLCT states

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*Figure 6.* Leading configurations of the most stable ground-state wave function of  $[1-Co]^{2+}$  and  $[1-Co]^{+}$  at the CASSCF(12,9)/def2-TZVP level of theory. MO levels are plotted in energetic order but not to scale for clarity. Percentages indicate the weight of the respective configuration in the total CASSCF wave function. Split percentages refer to additional configurations, where the spins of the two electrons highlighted in red are reversed.



*Figure 7.* Calculated absorption spectra of representative preassemblies between (a)  $[1-Co]^{2+}$  and NEt<sub>3</sub> and (b)  $[1-Co]^{+}$  and **2a**<sub>Br</sub> (TDA-SCS-  $\omega$ PBEPP86/def2-TZVP(-f)), compared to experimental spectra of the complexes. A constant red-shift of 0.65 eV has been applied to the calculated spectrum (a); spectrum (b) has not been modified. In both cases, photoexcitation in the photoreactor occurs at  $\lambda_{max}$ =450 nm. In this spectral region a CT state can be excited and transfer electron density (a) from the amine to  $[1-Co]^{2+}$ , forming  $[1-Co]^{+}$ , and subsequently (b) from  $[1-Co]^{+}$  to **2a**<sub>Br</sub>. The inset in (b) illustrates excited states in the NIR region, which are red-shifted by the calculations compared to the experimental signal between 700 and 1000 nm.

increases towards higher energies. The dip in absorbance at 320 nm is explained by a higher density of excited states to which the transition from the ground state is of low probability.

Independent of the coordination site, aggregation of  $[1-Co]^{2+}$  with NEt<sub>3</sub> introduces no distinct new spectral

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Instead, in all of the investigated preassemblies a series of weak transitions to CT states is observed, in which electron density is transferred from the amine to the ligand. For one of the preassemblies (Figure 7a), the first such CT transition

features (Figure S51, SI), in accordance with experimental

observations (see the Supporting Information for details).

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(Figure 8a) appears at 422 nm, which is within the emission spectrum of the photoreactor LED, so that direct population of the NEt<sub>3</sub> $\rightarrow$ [**1-Co**]<sup>2+</sup> CT state is feasible, facilitating the reduction to [**1-Co**]<sup>+</sup>. The low oscillator strength of this CT transition (f=0.0144) is in qualitative accordance with the relatively long illumination times employed experimentally. Apart from direct excitation, the high density of states in this spectral region implies that the relevant CT state may also be populated via excited state dynamics, after excitation into a higher excited state.

The calculated spectrum for [1-Co]<sup>+</sup> agrees with the experimental data in the visible and UV range. The characteristic NIR band is shifted to lower energies by ~0.8 eV and consists of d-d transitions and intra-ligand  $\pi \rightarrow \pi^*$  or LLCT excitations. This energy shift can be attributed to a higher degree of spin contamination in the ground state calculated at the SCS- $\omega$ PBEPP86 level (<S<sup>2</sup>>= 3.18, ideal: 2.00) which leads to higher partial occupation of ligand  $\pi^*$  orbitals and thereby to lower excitation energies into these orbitals. This effect also compensates the previously observed blue-shift in the visible and UV range, such that no empirical correction is required for the calculated spectrum of [1-Co]<sup>+</sup>. There are two bright excited states in the emission range of the photoreactor LED, one appearing at 480 nm, the other at 428 nm. They correspond to quasi-symmetry equivalent  $\pi \rightarrow \pi^*$  excitations on one of the two pyridine units of the ligands. The absorption band at 340 nm is also dominated by ligand-centered  $\pi \rightarrow \pi^*$  transitions. Toward higher energies, the absorbance first drops due to a series of weakly absorbing  $\pi \rightarrow \pi^*$  and LLCT transitions, then rises again as the density of LLCT transitions increases. The spectrum of [1-Co]<sup>+</sup> remains largely unaffected by substrate coordination (Figure S51, SI), apart from additional UV bands due to substrate-based  $\pi \rightarrow \pi^*$  excitations. In analogy to the oxidized species, the preassembly spectrum exhibits a weakly absorbing CT excitation (f=0.0016) from the ligand to  $2a_{Br}$  at 486 nm (Figure 8b), within the LED emission range. Excitation of this state effectively photo-reduces the substrate and thus enables the desired cleavage of the C-Br bond. The resulting hole on the ligand is filled by an electron from the



**Figure 8.** Difference densities of the relevant CT states with respect to the ground state in preassemblies between (a)  $[1-Co]^{2+}$  and NEt<sub>3</sub> and (b)  $[1-Co]^{+}$  and 4-bromobenzonitrile  $(2a_{Br})$ . Upon excitation, electron density is transferred from blue to yellow regions (isovalue: 0.002).

metal upon returning to the ground state, restoring the original  $[1-Co]^{2+}$  and completing the photocatalytic cycle.

Conceptualizing these insights, the ligand acts as an electron bridge between the redox-active metal and the other reactants. In the first photoactivated step, the ligand initially accepts an electron from the amine and transfers it partially over to the cobalt as the complex relaxes back to the ground state. Subsequently, excitation of the reduced complex transfers an electron from the ligand to the substrate, which causes the reoxidation of the metal upon deactivation. The electron transfer through the  $\pi^*$  orbitals (cf. Figure 6) of the diimininopyridine ligand is visually apparent in the calculated difference densities of the relevant CT states with respect to the ground state in the preassemblies (Figure 8).

#### Mechanistic discussion

Based on the combined investigations described above, we propose the mechanism summarized in Scheme 2 for the [1-Co](PF<sub>6</sub>)<sub>2</sub>-catalyzed arylation of **3a** by **2a**<sub>Br</sub>. Interestingly, the presence of two separate PET steps implies that this can formally be considered as an example of conPET reactivity, which is more commonly associated with organic PC. This mechanism is initiated by preassembly between [1-Co]<sup>2+</sup> and the sacrificial electron donor NEt<sub>3</sub> (step i), which upon irradiation undergoes PET (step ii), yielding the one-electron reduction product [1-Co]<sup>+</sup>. This can then engage in a second preassembly with the bromoarene **2a**<sub>Br</sub>. After photoexcitation (step iii), **2a**<sub>Br</sub> is reduced to regenerate the initial [1-Co]<sup>2+</sup> (step iv). This PET process results in C–Br bond cleavage to afford the radical **2a**<sup>•</sup>, which can couple to



**Scheme 2.** Proposed mechanisms for the cobalt-catalyzed C- arylation of *N*-methylpyrrole.

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N-methylpyrrole (step v), ultimately yielding product 4a after further steps. For simplicity, these further steps are not shown in Scheme 2, but may include radical chain elements and/or re-reduction of  $[1-Co]^{2+}$  to  $[1-Co]^{+}$ , as reported for other PC.<sup>[93]</sup> Note that an alternative mechanism based on Br atom transfer between  $2a_{Br}$  and the  $\alpha$ -aminoalkyl radical **B** is also possible (Scheme 2, steps vi and vii; this has been proposed for organic PC such as 4CzIPN).<sup>[76,93]</sup> It is plausible that both pathways contribute to the C-H arylation reaction.<sup>[94]</sup> As illustrated in Scheme 2, NEt<sub>3</sub> fulfills several roles, acting as a reductant for photoexcited \*[1-Co](PF<sub>6</sub>)<sub>2</sub>, as a Brønsted base, and as a source of the radical B. Our quantum chemical calculations indicate that the preassembly of NEt<sub>3</sub> with  $[1-Co]^{2+}$  and the formation of radical **B** exhibit a favorable thermodynamic driving force (see Table S11 and Scheme S4, SI). This may explain the superior utility of NEt<sub>3</sub> over other amine bases (see above).

#### Conclusion

Despite a short excited-state lifetime, the readily accessible bis(diiminopyridine) cobalt complex [1-Co](PF<sub>6</sub>)<sub>2</sub> is an efficient photocatalyst for the C-H arylation of pyrroles using both chloro- and bromoarenes as substrates. The performance of  $[1-Co](PF_6)_2$  is comparable to that of precious metal-based complexes and organic dyes. Photoinduced electron transfer between the metal complex and the reactants is facilitated by preassembly processes and proceeds via the diiminopyridine ligands with intermediate metal oxidation. These results challenge the perception that the development of late 3d metal photocatalysts is dependent on the development of complexes with artificially extended excited-state lifetimes and suggests an alternative direction for the development of 3d-metal based PRC. While these results represent an important proof of concept, we believe that significant further improvements will be possible through ligand design, and that the insights reported herein will be applicable to a wide range of other PRC transformations. The application of  $[1-Co](PF_6)_2$  and related metal complexes for a wider array of photochemical arylations is currently under investigation.

#### Supporting Information

The authors have cited additional references within the Supporting Information.  $^{[95-129]}$ 

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#### Conflict of Interest

The authors declare no conflict of interest.

#### **Data Availability Statement**

The data that support the findings of this study are available in the supplementary material of this article. All optimized structures are provided as xyz files in a separate zip-Archive, available free of charge at https://doi.org/10.5281/zenodo. 10528904.

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- [1] M. H. Shaw, J. Twilton, D. W. C. MacMillan, J. Org. Chem. 2016, 81, 6898–6926.
- [2] L. Marzo, S. K. Pagire, O. Reiser, B. König, Angew. Chem. Int. Ed. 2018, 57, 10034–10072.
- [3] R. C. McAtee, E. J. McClain, C. R. J. Stephenson, *Trends Chem.* 2019, 1, 111–125.
- [4] P. Melchiorre, Chem. Rev. 2022, 122, 1483-1484.
- [5] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* 2013, 113, 5322–5363.
- [6] N. A. Romero, D. A. Nicewicz, Chem. Rev. 2016, 116, 10075– 10166.
- [7] T. Duchanois, T. Etienne, C. Cebrián, L. Liu, A. Monari, M. Beley, X. Assfeld, S. Haacke, P. C. Gros, *Eur. J. Inorg. Chem.* 2015, 2469–2477.
- [8] L. Liu, T. Duchanois, T. Etienne, A. Monari, M. Beley, X. Assfeld, S. Haacke, P. C. Gros, *Phys. Chem. Chem. Phys.* 2016, 18, 12550–12556.
- [9] A. Francés-Monerris, P. C. Gros, X. Assfeld, A. Monari, M. Pastore, *ChemPhotoChem* 2019, 3, 666–683.
- [10] J. P. Zobel, O. S. Bokareva, P. Zimmer, C. Wölper, M. Bauer, L. González, *Inorg. Chem.* **2020**, *59*, 14666–14678.
- [11] K. D. Vogiatzis, M. V. Polynski, J. K. Kirkland, J. Townsend, A. Hashemi, C. Liu, E. A. Pidko, *Chem. Rev.* 2019, 119, 2453– 2523.
- [12] D. M. Arias-Rotondo, J. K. McCusker, Chem. Soc. Rev. 2016, 45, 5803–5820.
- [13] C. B. Larsen, O. S. Wenger, Chem. Eur. J. 2018, 24, 2039– 2058.
- [14] O. S. Wenger, J. Am. Chem. Soc. 2018, 140, 13522-13533.
- [15] J. K. McCusker, Science 2019, 363, 484-488.
- [16] B. M. Hockin, C. Li, N. Robertson, E. Zysman-Colman, *Catal. Sci. Technol.* **2019**, *9*, 889–915.
- [17] S. Kaufhold, K. Wärnmark, Catalysts 2020, 10, 132.
- [18] S. H. Kyne, G. Lefèvre, C. Ollivier, M. Petit, V.-A. R. Cladera, L. Fensterbank, *Chem. Soc. Rev.* **2020**, *49*, 8501– 8542.
- [19] A. Y. Chan, A. Ghosh, J. T. Yarranton, J. Twilton, J. Jin, D. M. Arias-Rotondo, H. A. Sakai, J. K. McCusker, D. W. C. MacMillan, *Science* 2023, 382, 191–197.
- [20] R. Lauenstein, S. L. Mader, H. Derondeau, O. Z. Esezobor, M. Block, A. J. Römer, C. Jandl, E. Riedle, V. R. I. Kaila, J. Hauer, E. Thyrhaug, C. R. Hess, *Chem. Sci.* **2021**, *12*, 7521– 7532.
- [21] S. Paria, O. Reiser, ChemCatChem 2014, 6, 2477-2483.
- [22] A. Hossain, A. Bhattacharyya, O. Reiser, Science 2019, 364, eaav9713.
- [23] Y. Abderrazak, A. Bhattacharyya, O. Reiser, Angew. Chem. Int. Ed. 2021, 60, 21100–21115.

Angew. Chem. Int. Ed. 2024, 63, e202405780 (10 of 12)

- [24] M. Kaupp, J. Comput. Chem. 2007, 28, 320-325.
- [25] K. Gadde, D. D. Vos, B. U. W. Maes, Synthesis 2023, 55, 164– 192.
- [26] L. Lindh, P. Chábera, N. W. Rosemann, J. Uhlig, K. Wärnmark, A. Yartsev, V. Sundström, P. Persson, *Catalysts* 2020, 10, 315.
- [27] P. Chábera, Y. Liu, O. Prakash, E. Thyrhaug, A. E. Nahhas, A. Honarfar, S. Essén, L. A. Fredin, T. C. B. Harlang, K. S. Kjær, K. Handrup, F. Ericson, H. Tatsuno, K. Morgan, J. Schnadt, L. Häggström, T. Ericsson, A. Sobkowiak, S. Lidin, P. Huang, S. Styring, J. Uhlig, J. Bendix, R. Lomoth, V. Sundström, P. Persson, K. Wärnmark, *Nature* 2017, 543, 695– 699.
- [28] W. Leis, M. A. Argüello Cordero, S. Lochbrunner, H. Schubert, A. Berkefeld, J. Am. Chem. Soc. 2022, 144, 1169–1173.
- [29] J. Moll, R. Naumann, L. Sorge, C. Förster, N. Gessner, L. Burkhardt, N. Ugur, P. Nuernberger, W. Seidel, C. Ramanan, M. Bauer, K. Heinze, *Chem. Eur. J.* 2022, 28, e202201858.
- [30] J. P. Zobel, L. González, JACS Au 2021, 1, 1116–1140.
- [31] P. Chábera, K. S. Kjaer, O. Prakash, A. Honarfar, Y. Liu, L. A. Fredin, T. C. B. Harlang, S. Lidin, J. Uhlig, V. Sundström, R. Lomoth, P. Persson, K. Wärnmark, *J. Phys. Chem. Lett.* **2018**, *9*, 459–463.
- [32] A. Gualandi, M. Marchini, L. Mengozzi, M. Natali, M. Lucarini, P. Ceroni, P. G. Cozzi, ACS Catal. 2015, 5, 5927– 5931.
- [33] K. S. Kjær, N. Kaul, O. Prakash, P. Chábera, N. W. Rosemann, A. Honarfar, O. Gordivska, L. A. Fredin, K.-E. Bergquist, L. Häggström, T. Ericsson, L. Lindh, A. Yartsev, S. Styring, P. Huang, J. Uhlig, J. Bendix, D. Strand, V. Sundström, P. Persson, R. Lomoth, K. Wärnmark, *Science* 2018, eaau7160.
- [34] N. W. Rosemann, P. Chábera, O. Prakash, S. Kaufhold, K. Wärnmark, A. Yartsev, P. Persson, J. Am. Chem. Soc. 2020, 142, 8565–8569.
- [35] A. Aydogan, R. E. Bangle, A. Cadranel, M. D. Turlington, D. T. Conroy, E. Cauët, M. L. Singleton, G. J. Meyer, R. N. Sampaio, B. Elias, L. Troian-Gautier, J. Am. Chem. Soc. 2021, 143, 15661–15673.
- [36] A. Aydogan, R. E. Bangle, S. D. Kreijger, J. C. Dickenson, M. L. Singleton, E. Cauët, A. Cadranel, G. J. Meyer, B. Elias, R. N. Sampaio, L. Troian-Gautier, *Catal. Sci. Technol.* 2021, *11*, 8037–8051.
- [37] J. Schwarz, A. Ilic, C. Johnson, R. Lomoth, K. Wärnmark, *Chem. Commun.* 2022, 58, 5351–5354.
- [38] J. Steube, A. Kruse, O. S. Bokareva, T. Reuter, S. Demeshko, R. Schoch, M. A. Argüello Cordero, A. Krishna, S. Hohloch, F. Meyer, K. Heinze, O. Kühn, S. Lochbrunner, M. Bauer, *Nat. Chem.* 2023, 15, 468–474.
- [39] A. Ilic, J. Schwarz, C. Johnson, L. H. M. de Groot, S. Kaufhold, R. Lomoth, K. Wärnmark, *Chem. Sci.* 2022, 13, 9165–9175.
- [40] A. K. Pal, C. Li, G. S. Hanan, E. Zysman-Colman, Angew. Chem. Int. Ed. 2018, 57, 8027–8031.
- [41] S. Kaufhold, N. W. Rosemann, P. Chábera, L. Lindh, I. Bolaño Losada, J. Uhlig, T. Pascher, D. Strand, K. Wärnmark, A. Yartsev, P. Persson, J. Am. Chem. Soc. 2021, 143, 1307– 1312.
- [42] N. Sinha, B. Pfund, C. Wegeberg, A. Prescimone, O.S. Wenger, J. Am. Chem. Soc. 2022, 144, 9859–9873.
- [43] B. de Bruin, E. Bill, E. Bothe, T. Weyhermüller, K. Wieghardt, *Inorg. Chem.* 2000, 39, 2936–2947.
- [44] H. Huang, K. A. Steiniger, T. H. Lambert, J. Am. Chem. Soc. 2022, 144, 12567–12583.
- [45] S. Wu, J. Kaur, T. A. Karl, X. Tian, J. P. Barham, Angew. Chem. Int. Ed. 2022, 61, e202107811.

- [46] J. Castellanos-Soriano, J. C. Herrera-Luna, D. D. Díaz, M. C. Jiménez, R. Pérez-Ruiz, Org. Chem. Front. 2020, 7, 1709– 1716.
- [47] F. Glaser, C. Kerzig, O. S. Wenger, Angew. Chem. Int. Ed. 2020, 59, 10266–10284.
- [48] J. P. Barham, B. König, Angew. Chem. Int. Ed. 2020, 59, 11732–11747.
- [49] A.J. Rieth, M. I. Gonzalez, B. Kudisch, M. Nava, D.G. Nocera, J. Am. Chem. Soc. 2021, 143, 14352–14359.
- [50] Y. Baek, A. Reinhold, L. Tian, P. D. Jeffrey, G. D. Scholes, R. R. Knowles, J. Am. Chem. Soc. 2023, 145, 12499–12508.
- [51] S. J. Horsewill, G. Hierlmeier, Z. Farasat, J. P. Barham, D. J. Scott, ACS Catal. 2023, 13, 9392–9403.
- [52] S. J. Horsewill, C. Cao, N. Dabney, E. S. Yang, S. Faulkner, D. J. Scott, *Chem. Commun.* **2023**, *59*, 14665–14668.
- [53] M. H. Deniel, D. Lavabre, J. C. Micheau, in Org. Photochromic Thermochromic Compd. Vol. 2 Physicochem. Stud. Biol. Appl. Thermochromism (Eds.: J. C. Crano, R. J. Guglielmetti), Springer US, Boston, MA, 2002, pp. 167–209.
- [54] F. Brandl, S. Bergwinkl, C. Allacher, B. Dick, *Chem. Eur. J.* 2020, 26, 7946–7954.
- [55] S. Wu, J. Žurauskas, M. Domański, P. S. Hitzfeld, V. Butera, D. J. Scott, J. Rehbein, A. Kumar, E. Thyrhaug, J. Hauer, J. P. Barham, Org. Chem. Front. 2021, 8, 1132–1142.
- [56] A. Kumar, P. Malevich, L. Mewes, S. Wu, J. P. Barham, J. Hauer, J. Chem. Phys. 2023, 158, 144201.
- [57] S. Grimme, A. Hansen, S. Ehlert, J.-M. Mewes, J. Chem. Phys. 2021, 154, 064103.
- [58] F. Neese, WIREs Comput. Mol. Sci. 2012, 2, 73-78.
- [59] F. Neese, F. Wennmohs, U. Becker, C. Riplinger, J. Chem. Phys. 2020, 152, 224108.
- [60] F. Neese, WIREs Comput. Mol. Sci. 2022, e1606.
- [61] P. Pracht, F. Bohle, S. Grimme, Phys. Chem. Chem. Phys. 2020, 22, 7169–7192.
- [62] S. Grimme, J. Chem. Theory Comput. 2019, 15, 2847-2862.
- [63] C. Bannwarth, S. Ehlert, S. Grimme, J. Chem. Theory Comput. 2019, 15, 1652–1671.
- [64] D. Alberico, M. E. Scott, M. Lautens, Chem. Rev. 2007, 107, 174–238.
- [65] D. T. Gryko, O. Vakuliuk, D. Gryko, B. Koszarna, J. Org. Chem. 2009, 74, 9517–9520.
- [66] M. Miura, T. Satoh, in *Modern Arylation Methods*, John Wiley & Sons, Ltd, 2009, pp. 335–361.
- [67] I. Ghosh, T. Ghosh, J. I. Bardagi, B. König, Science 2014, 346, 725–728.
- [68] I. Ghosh, L. Marzo, A. Das, R. Shaikh, B. König, Acc. Chem. Res. 2016, 49, 1566–1577.
- [69] I. Ghosh, B. König, Angew. Chem. Int. Ed. 2016, 55, 7676– 7679.
- [70] A. U. Meyer, T. Slanina, C.-J. Yao, B. König, ACS Catal. 2016, 6, 369–375.
- [71] L. Marzo, I. Ghosh, F. Esteban, B. König, ACS Catal. 2016, 6, 6780–6784.
- [72] I. Ghosh, R. S. Shaikh, B. König, Angew. Chem. Int. Ed. 2017, 56, 8544–8549.
- [73] J. I. Bardagi, I. Ghosh, M. Schmalzbauer, T. Ghosh, B. König, *Eur. J. Org. Chem.* **2018**, 34–40.
- [74] M. Neumeier, D. Sampedro, M. Májek, V. A. de la Peña O'Shea, A. Jacobi von Wangelin, R. Pérez-Ruiz, *Chem. Eur. J.* 2018, 24, 105–108.
- [75] N. G. W. Cowper, C. P. Chernowsky, O. P. Williams, Z. K. Wickens, J. Am. Chem. Soc. 2020, 142, 2093–2099.
- [76] T. Constantin, F. Juliá, N. S. Sheikh, D. Leonori, *Chem. Sci.* 2020, 11, 12822–12828.
- [77] J. Wang, K. Schwedtmann, K. Liu, S. Schulz, J. Haberstroh, G. Schaper, A. Wenke, J. Naumann, T. Wenke, S. Wanke, J. J. Weigand, *Green Chem.* 2021, 23, 881–888.

Angew. Chem. Int. Ed. 2024, 63, e202405780 (11 of 12)

- [78] The experiments were performed in THF due to the higher photostability of [1-Co]<sup>+</sup> in that solvent. See the Supporting Information for further details (Figures S17, S18, S37 and S40).
- [79] A. A. Isse, P. R. Mussini, A. Gennaro, J. Phys. Chem. C 2009, 113, 14983–14992.
- [80] D. A. Kreplin, P. J. Knowles, H.-J. Werner, J. Chem. Phys. 2020, 152, 074102.
- [81] C. Angeli, R. Cimiraglia, S. Evangelisti, T. Leininger, J.-P. Malrieu, J. Chem. Phys. 2001, 114, 10252–10264.
- [82] C. Angeli, R. Cimiraglia, J.-P. Malrieu, J. Chem. Phys. 2002, 117, 9138–9153.
- [83] C. Angeli, M. Pastore, R. Cimiraglia, Theor. Chem. Acc. 2007, 117, 743–754.
- [84] H.-J. Werner, P. J. Knowles, G. Knizia, F. R. Manby, M. Schütz, WIREs Comput. Mol. Sci. 2012, 2, 242–253.
- [85] H.-J. Werner, P. J. Knowles, F. R. Manby, J. A. Black, K. Doll, A. Heßelmann, D. Kats, A. Köhn, T. Korona, D. A. Kreplin, Q. Ma, T. F. Miller, A. Mitrushchenkov, K. A. Peterson, I. Polyak, G. Rauhut, M. Sibaev, J. Chem. Phys. 2020, 152, 144107.
- [86] H.-J. Werner, P.J. Knowles, P. Celani, W. Györffy, A. Hesselmann, D. Kats, G. Knizia, A. Köhn, T. Korona, D. Kreplin, R. Lindh, Q. Ma, F. R. Manby, A. Mitrushenkov, G. Rauhut, M. Schütz, K. R. Shamasundar, T. B. Adler, R. D. Amos, S. J. Bennie, A. Bernhardsson, A. Berning, J. A. Black, P. J. Bygrave, R. Cimiraglia, D. L. Cooper, D. Coughtrie, M. J. O. Deegan, A. J. Dobbyn, K. Doll, M. Dornbach, F. Eckert, S. Erfort, E. Goll, C. Hampel, G. Hetzer, J. G. Hill, M. Hodges, T. Hrenar, G. Jansen, C. Köppl, C. Kollmar, S. J. R. Lee, Y. Liu, A. W. Lloyd, R. A. Mata, A. J. May, B. Mussard, S. J. McNicholas, W. Meyer, T. F. Miller III, M. E. Mura, A. Nicklass, D. P. O'Neill, P. Palmieri, D. Peng, K. A. Peterson, K. Pflüger, R. Pitzer, I. Polyak, M. Reiher, J. O. Richardson, J. B. Robinson, B. Schröder, M. Schwilk, T. Shiozaki, M. Sibaev, H. Stoll, A. J. Stone, R. Tarroni, T. Thorsteinsson, J. Toulouse, M. Wang, M. Welborn, B. Ziegler, MOLPRO, Version 2023.2,a Package of Ab Initio Programs, 2023.
- [87] S. Grimme, M. Parac, ChemPhysChem 2003, 4, 292-295.
- [88] A. Dreuw, M. Head-Gordon, J. Am. Chem. Soc. 2004, 126, 4007–4016.
- [89] M. Campetella, F. Maschietto, M. J. Frisch, G. Scalmani, I. Ciofini, C. Adamo, J. Comput. Chem. 2017, 38, 2151–2156.
- [90] D. Mester, M. Kállay, J. Chem. Theory Comput. 2022, 18, 1646–1662.
- [91] J. P. Zobel, A. Kruse, O. Baig, S. Lochbrunner, S. I. Bokarev, O. Kühn, L. González, O. S. Bokareva, *Chem. Sci.* 2023, 14, 1491–1502.
- [92] M. Casanova-Páez, L. Goerigk, J. Chem. Theory Comput. 2021, 17, 5165–5186.
- [93] T. Constantin, M. Zanini, A. Regni, N. S. Sheikh, F. Juliá, D. Leonori, *Science* **2020**, *367*, 1021–1026.
- [94] This mechanism is consistent with the calculated thermodynamics for the deprotonation of the triethylamine radical cation **A** (Scheme, step vi) to generate **B** and the subsequent oxidation of **B** by  $2_{aBr}$  (step vii; see the Supporting Information for details).
- [95] B. L. Small, M. Brookhart, A. M. A. Bennett, J. Am. Chem. Soc. 1998, 120, 4049–4050.
- [96] A. L. Vance, N. W. Alcock, J. A. Heppert, D. H. Busch, *Inorg. Chem.* **1998**, *37*, 6912–6920.

- [97] G. M. Duarte, J. D. Braun, P. K. Giesbrecht, D. E. Herbert, *Dalton Trans.* 2017, 46, 16439–16445.
- [98] Z.-J. Li, S. Li, E. Hofman, A. H. Davis, G. Leem, W. Zheng, *Green Chem.* 2020, 22, 1911–1918.
- [99] R. J. Kutta, N. Archipowa, N. S. Scrutton, *Phys. Chem. Chem. Phys.* 2018, 20, 28767–28776.
- [100] T. Pavlovska, D. Král Lesný, E. Svobodová, I. Hoskovcová, N. Archipowa, R. J. Kutta, R. Cibulka, *Chem. Eur. J.* 2022, 28, e202200768.
- [101] E. Caldeweyher, S. Ehlert, A. Hansen, H. Neugebauer, S. Spicher, C. Bannwarth, S. Grimme, J. Chem. Phys. 2019, 150, 154122.
- [102] H. Kruse, S. Grimme, J. Chem. Phys. 2012, 136, 154101.
- [103] M. Cossi, N. Rega, G. Scalmani, V. Barone, J. Comput. Chem. 2003, 24, 669–681.
- [104] S. Grimme, Chem. Eur. J. 2012, 18, 9955-9964.
- [105] Y. Guo, C. Riplinger, U. Becker, D. G. Liakos, Y. Minenkov, L. Cavallo, F. Neese, *J. Chem. Phys.* 2018, 148, 011101.
- [106] Y. Guo, C. Riplinger, D. G. Liakos, U. Becker, M. Saitow, F. Neese, J. Chem. Phys. 2020, 152, 024116.
- [107] D. G. Liakos, Y. Guo, F. Neese, J. Phys. Chem. A 2020, 124, 90–100.
- [108] E. van Lenthe, E. J. Baerends, J. G. Snijders, J. Chem. Phys. 1993, 99, 4597–4610.
- [109] C. van Wüllen, J. Chem. Phys. 1998, 109, 392–399.
- [110] F. Weigend, R. Ahlrichs, Phys. Chem. Chem. Phys. 2005, 7, 3297–3305.
- [111] J. Zheng, X. Xu, D. G. Truhlar, Theor. Chem. Acc. 2011, 128, 295–305.
- [112] F. Neese, F. Wennmohs, A. Hansen, U. Becker, *Chem. Phys.* 2009, 356, 98–109.
- [113] R. Izsák, F. Neese, J. Chem. Phys. 2011, 135, 144105.
- [114] S. Kossmann, F. Neese, Chem. Phys. Lett. 2009, 481, 240-243.
- [115] A. Hellweg, C. Hättig, S. Höfener, W. Klopper, *Theor. Chem. Acc.* 2007, 117, 587–597.
- [116] F. Weigend, Phys. Chem. Chem. Phys. 2006, 8, 1057-1065.
- [117] W. Humphrey, A. Dalke, K. Schulten, J. Mol. Graphics 1996, 14, 33–38.
- [118] F. Neese, J. Phys. Chem. Solids 2004, 65, 781-785.
- [119] F. Weigend, J. Comput. Chem. 2008, 29, 167-175.
- [120] J. P. Perdew, Phys. Rev. B 1986, 33, 8822-8824.
- [121] J. P. Perdew, Phys. Rev. B 1986, 34, 7406-7406.
- [122] A. D. Becke, Phys. Rev. A 1988, 38, 3098–3100.
- [123] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, J. Chem. Phys. 2010, 132, 154104.
- [124] S. Grimme, S. Ehrlich, L. Goerigk, J. Comput. Chem. 2011, 32, 1456–1465.
- [125] S. Hirata, M. Head-Gordon, Chem. Phys. Lett. 1999, 314, 291– 299.
- [126] F. Plasser, J. Chem. Phys. 2020, 152, 084108.
- [127] F. Plasser, M. Wormit, A. Dreuw, J. Chem. Phys. 2014, 141, 024106.
- [128] F. Plasser, H. Lischka, J. Chem. Theory Comput. 2012, 8, 2777–2789.
- [129] T. J. Lee, P. R. Taylor, Int. J. Quantum Chem. 1989, 36, 199– 207.

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# 2

## Multiscale Quantum Dynamics



**Chapter 2 Title Graphic:** Multiscale quantum dynamics simulations unravel the ultrafast relaxation of the nucleobase uracil in its natural environment after photoexcitation.

The previous chapter examined photochemical reactions, focusing on selected critical points in the reaction mechanism. Going beyond this steady-state picture, we shall now shine a light on the ultrafast dynamics of the photoexcited nucleobase uracil, taking into account interactions with its natural RNA environment.

Excited state dynamics often break the framework of the Born-Oppenheimer approximation, as the system evolves non-adiabatically from one electronic state to another through CoIns.<sup>[30,151]</sup> In such cases, nuclear quantum effects begin to play a role, meaning that the nuclei should no longer be treated as point masses but rather as quantum objects. There are multiple ways to simulate non-adiabatic excited state dynamics.<sup>[152]</sup> One of the most widely used methods is to approximate the nuclear wave packet statistically by a swarm of independent trajectories.<sup>[153–157]</sup> Here, each trajectory treats the nuclei as classical particles and only an ensemble of many trajectories approximates the probability distribution of the quantum system. Environmental effects can be incorporated either implicitly via continuum models<sup>[56]</sup> or explicitly in QM/MM or ONIOM frameworks.<sup>[45,158–160]</sup> Reviews on environmental effects in trajectory based methods are available in refs. 161–164. Despite their merits, trajectory based approaches by design can not describe quantum effects like tunneling, wave packet interference or coherent control by laser pulses. Thus, in this work, we shall focus on solving the time-dependent Schrödinger equation (TDSE) by propagating a nuclear wave packet on electronic PESs.<sup>[165,166]</sup> The underlying theory is outlined in the following, before introducing a new approach to include environmental interactions in the wave packet dynamics. This approach is then applied to model the ultrafast  $S_2 \rightarrow S_1$ relaxation of the nucleobase uracil in an RNA strand.

#### Wave Packet Dynamics

The time evolution of a quantum system is described by the  $TDSE^{[167-170]}$ 

$$i\hbar \frac{\partial}{\partial t}\Psi(\boldsymbol{x},t) = \hat{\mathcal{H}}\Psi(\boldsymbol{x},t)$$
 (2.1)

where *i* is the imaginary unit,  $\hbar$  is the reduced Planck constant,  $\hat{\mathcal{H}}(\boldsymbol{x}, t)$  denotes the Hamiltonian and  $\Psi(\boldsymbol{x}, t)$  the wave function. For a two-state system in the adiabatic picture, the Hamiltonian in matrix form is defined as

$$\mathbf{H} = \begin{pmatrix} V_1 & 0\\ 0 & V_2 \end{pmatrix} + \begin{pmatrix} T_{11} & f_{12}\\ f_{21} & T_{22} \end{pmatrix}$$
(2.2)

where  $V_1$  and  $V_2$  are the potential energies of the two electronic states,  $T_{11} = T_{22}$  is the kinetic energy of the wave packet and  $f_{12}$  and  $f_{21}$  denote the non-adiabatic coupling elements (NAC) that facilitate population transfer at the CoIn. Optionally, the interaction between the molecular system with dipole moment  $\mu$  and an external electric field  $\epsilon(t)$  can be included by an additional term  $\mu \varepsilon(t)$ . By separating the spatial ( $\boldsymbol{x}$ ) and temporal coordinates (t) of the wave function, a general solution to the TDSE reads

$$\Psi(\boldsymbol{x},t) = \sum_{n=1}^{\infty} c_n e^{-\frac{i}{\hbar}E_n t} \psi(\boldsymbol{x}).$$
(2.3)

Here  $\psi(\boldsymbol{x})$  is a solution of the time-independent Schrödinger equation (TISE), obtained in the Born-Oppenheimer approximation with standard quantum chemistry methods, while the time-dependence is fully contained in the exponential term.  $E_n$  denotes a discrete set of eigenvalues to the electronic potential, thus the solution of the TDSE at any point in time is a superposition of eigenstates, weighted with the coefficients  $c_n$ . This superposition is called a wave packet. As a complete set of eigenstates is usually not available for molecular systems, the TDSE must be solved numerically by propagating the wave packet in small time increments  $\Delta t$  with respect to an initial condition  $\Psi(\boldsymbol{x}, t_0)$ :

$$\Psi(\boldsymbol{x}, t_0 + \Delta t) = \underbrace{e^{-\frac{i}{\hbar}\hat{\mathcal{H}}\Delta t}}_{\hat{\mathcal{U}}(\Delta t)} \Psi(\boldsymbol{x}, t_0).$$
(2.4)

In practice, the evolution operator  $\hat{\mathcal{U}}(\Delta t)$  is expanded to arrive at a propagation scheme.<sup>[171]</sup> Here, one possibility is to approximate the exponential by a finite Chebyshev series

$$\hat{\mathcal{U}}(\Delta t) = e^{-\frac{i}{\hbar}\hat{\mathcal{H}}\Delta t} \approx \sum_{k=0}^{N} a_k \varphi_k \left(-\frac{i}{\hbar}\hat{\mathcal{H}}\Delta t\right),\tag{2.5}$$

with the complex Chebyshev polynomials  $\varphi_k$  and expansion coefficients  $a_k$ .<sup>[172]</sup> Compared to other propagation schemes, the Chebyshev expansion offers higher accuracy and numerical stability over long simulation times,<sup>[171]</sup> which is the reason it was used in this work. The propagation was performed with the software QDng.<sup>[173]</sup>

#### Hamiltonian in Reduced Dimensionality

As the TDSE is solved numerically on a spatial and temporal grid, the computational effort of wave packet simulations scales exponentially with the number of molecular degrees of freedom. Therefore, the coordinate space is reduced to few, typically two, active dimensions that represent the molecular process in question.<sup>[174–176]</sup> The Hamiltonian  $\hat{\mathcal{H}}$  is generally defined as the sum of kinetic ( $\hat{\mathcal{T}}$ ) and potential ( $\hat{\mathcal{V}}$ ) energy operators. While the potential operator is multiplicative and translates directly into the reduced dimensional coordinate space, the kinetic energy operator

$$\hat{\mathcal{T}}_x = -\frac{\hbar^2}{2} \sum_{i=1}^{3N} \frac{1}{m_i} \frac{\partial^2}{\partial x_i^2}$$
(2.6)

in Cartesian coordinates x with masses m requires prior transformations, which can be achieved in the Wilson G-matrix formalism.<sup>[177–181]</sup> Here, the transformed operator in a

two-dimensional space of internal coordinates q is approximated as

$$\hat{\mathcal{T}}_q \simeq -\frac{\hbar^2}{2} \sum_{r=1}^M \sum_{s=1}^M \frac{\partial}{\partial q_r} \left[ G_{rs} \frac{\partial}{\partial q_s} \right].$$
(2.7)

The G-matrix elements  $G_{rs}$  are readily accessible via their inverse<sup>[178]</sup>

$$G_{rs}^{-1} = \sum_{i=1}^{3N} m_i \frac{\partial x_i}{\partial q_r} \frac{\partial x_i}{\partial q_s}$$
(2.8)

using finite differencing. Comparing eq. (2.7) and eq. (2.8), the G-matrix takes the role of a reciprocal mass in the kinetic energy operator. To obtain pure internal coordinates, translations and rotations are removed by applying the Eckart conditions<sup>[182]</sup> to the initial Cartesian geometries. In this work, the PES was spanned by two orthogonalized Cartesian difference vectors originating at the Franck-Condon point and ending at the S<sub>2</sub> minimum and at the S<sub>2</sub>/S<sub>1</sub> CoIn, respectively.<sup>[183]</sup> The coordinates and consequently the G-matrix were adopted from the gas phase simulation of uracil.<sup>[183]</sup>

#### Including Environmental Effects

While there are numerous examples of wave packet simulations being performed on isolated molecules,<sup>[24,174,180,183–189]</sup> the simulation of environmental effects remains challenging. Assuming that the molecular process is fast enough that its timescale can be separated from that of the environmental dynamics, the environmental influence  $\hat{\mathcal{V}}_{env}$  is entirely contained in a time-independent potential energy term of the Hamiltonian

$$\hat{\mathcal{V}} = \hat{\mathcal{V}}_{\rm mol} + \hat{\mathcal{V}}_{\rm env} \tag{2.9}$$

where  $\hat{\mathcal{V}}_{mol}$  corresponds to the PES of the isolated molecule. This assumption is valid as long as the process takes less than a few hundred femtoseconds. At longer timescales, the wave packet dynamics need to be coupled to the environmental motion, for example in an Ehrenfest approach as described elsewhere.<sup>[190]</sup> At short timescales, previous works have introduced the dynamic continuum ansatz to model  $\hat{\mathcal{V}}_{env}$  implicitly as a custom fitted potential which decelerates the wave packet.<sup>[191]</sup>

Moving from an implicit to an atomistic representation of the solvent cage, the next step was to parameterize the interaction potential for a large set of relative solvent-solute orientations sampled by MD simulations.<sup>[192]</sup>  $\hat{\mathcal{V}}_{env}$  could then be approximated from the library of precalculated parameters. The atomistic description of the solvent cage allowed to distinguish multiple reaction channels in a photochemical bond dissociation depending on the solvent orientation, which was not possible with the dynamic continuum ansatz.<sup>[192]</sup> However, the parameterization routine requires a large amount of preparatory work and



Figure 2.1: Multiscale quantum dynamics workflow to include atomistic environments in grid-based wave packet dynamics simulations.

its complexity only increases for heterogeneous environments as they occur in biological systems.

The present work therefore introduces an extension to the atomistic approach, where the interaction potential is evaluated explicitly at each point of the PES, without the need for precalculated parameters (figure 2.1). To this end, environment configurations are sampled from classical MD simulations. The quantum system, in this case uracil, is constrained at its ground state minimum geometry during the MD to ensure reproducible starting points for the setup of the PES. At each grid point of the PES, the geometry of the quantum system is inserted into the MD snapshot and aligned by satisfying the Eckart conditions<sup>[182]</sup> with respect to the frozen geometry from the snapshot. Next, the potential energy of the full system is evaluated at each point of the PES in a QM/MM ansatz. By subtracting the energy of the isolated quantum system at the same quantum mechanical (QM) level of theory from the QM/MM energy, only the interaction potential  $\hat{\mathcal{V}}_{env}$  remains. The final PES is then obtained by adding  $\hat{\mathcal{V}}_{env}$  to the precalculated excited state potential  $\hat{\mathcal{V}}_{mol}$  of the

quantum system. As  $\hat{\mathcal{V}}_{env}$  is unique to the MD snapshot chosen for the QM/MM calculation, this procedure is repeated many times to model different environment configurations. Along with the also precalculated kinetic energy operator of the quantum system, the TDSE can be solved for each snapshot.

Compared to the library approach,<sup>[192]</sup> this procedure requires less preparatory work and is easily transferable to any kind of environment, homo- or heterogeneous. Moreover,  $\hat{\mathcal{V}}_{mol}$ as well as the NACs can be calculated once at a high but expensive level of theory for the isolated molecule, while a different and computationally faster level can be used for the repeated evaluation of the interaction potential. In this work,  $\hat{\mathcal{V}}_{env}$  was calculated in the ground state, which saved computational effort and could be justified by similar charge distributions in the ground and excited state of uracil. The same workflow is easily adapted to evaluate  $\hat{\mathcal{V}}_{env}$  for an excited state by using an excited state method in the QM/MM calculation.

#### Photorelaxation of Uracil

The workflow described above was applied to model the  $S_2 \rightarrow S_1$  relaxation of uracil in an RNA environment. Like the other canonical nucleobases, uracil dissipates absorbed UV radiation in the form of heat on a timescale of few hundred femtoseconds.<sup>[193]</sup> This ultrafast relaxation protects the genetic code against photodamage and has been proposed as an evolutionary selection criterion under high UV pressure in the early Earth history.<sup>[194–196]</sup> Yet, photodamage occurs frequently enough *in vivo* that sophisticated repair mechanisms have evolved,<sup>[197–201]</sup> prompting the research question of the article below: Does a natural RNA environment affect the ultrafast relaxation to the ground state?

After photoexcitation around 250 nm to a bright  $\pi\pi^*$  excited state  $(S_2)$ ,<sup>[202]</sup> uracil can relax to a dark  $n\pi^*$  state  $(S_1)$  and from there back to the ground state *via* CoIns.<sup>[203]</sup> The first step of this relaxation has been modeled previously for the isolated nucleobase,<sup>[183]</sup> whereby the wave packet evolved from the Franck-Condon point to the potential energy minimum on the S<sub>2</sub> PES before crossing a barrier to the S<sub>2</sub>/S<sub>1</sub> CoIn seam. The simulated decay had a half-life of 186 fs after excitation with a Gaussian laser pulse and could be accelerated or delayed by custom shaped pump laser pulses.<sup>[183]</sup>

The article "RNA Environment Is Responsible for Decreased Photostability of Uracil", published 2018 in *J. Am. Chem. Soc.* investigates to what extent the natural environment of uracil affects the relaxation process on the  $S_2$  PES. The most important results are summarized below:

• PESs for uracil were calculated using 250 MD snapshots containing a 7-base RNA single-strand solvated in water. The environmental potential was explicitly calculated in a QM/MM framework for each snapshot, according to the scheme illustrated in figure 2.1. Subsequently, the nuclear wave packet dynamics after photoexcitation to  $S_2$  were simulated with a focus on the ultrafast  $S_2 \rightarrow S_1$  relaxation through a CoIn seam.

- The timescale of the relaxation process in isolated uracil is on the order of 200 fs and dominated by the movement of the wave packet over an energy barrier towards the CoIn seam.<sup>[183]</sup> Inclusion of an environmental potential resulted in part in strong modifications to the PES topography, such as higher or lower energy barriers and in few cases even additional minima. However, even seemingly minor changes to the topography were shown to steer the wave packet towards or away from the CoIn, leading to decreased or increased relaxation times.
- Out of the 250 sampled population dynamics, 82% decayed on a timescale similar to that of the isolated nucleobase. Faster relaxation was observed in 5% and slower relaxation in 13%. This distribution was found to be independent from the base sequence surrounding uracil. In the case of slower dynamics, decay times on the order of several picoseconds were observed, which is long enough for the nucleobase to undergo harmful chemical reactions in the excited state. In that sense, the environmental influence on the PES topography can be considered directly responsible for decreased photostability of the nucleobase in RNA under physiological conditions.

The article "RNA Environment Is Responsible for Decreased Photostability of Uracil" was published 2018 in *Journal of the American Chemical Society*. It is reprinted hereafter with permission from *J. Am. Chem. Soc.*, **140**, 8714–8720 (2018). The supporting information is available at https://doi.org/10.1021/jacs.8b02962 and reprinted in appendix B. Copyright 2018, American Chemical Society.



# RNA Environment Is Responsible for Decreased Photostability of Uracil

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**S** Supporting Information

**ABSTRACT:** UV light can induce chemical reactions in nucleic acids and thereby damage the genetic code. Like all of the five primary nucleobases, the isolated RNA base uracil exhibits ultrafast, nonradiative relaxation after photoexcitation, which helps to avoid photodamage most of the time. Nevertheless, within RNA and DNA strands, commonly occurring photolesions have been reported and are often ascribed to long-lived and delocalized excited states. Our quantum dynamical study now shows that excited-state longevity can also occur on a single nucleobase, without the



need for delocalization. We include the effects of an atomistic RNA surrounding in wave packet simulations and explore the photorelaxation of uracil in its native biological environment. This reveals that steric hindrance through embedding in an RNA strand can inhibit the ultrafast relaxation mechanism of uracil, promoting excited-state longevity and potential photodamage. This process is nearly independent from the specific combination of neighboring bases.

#### INTRODUCTION

UV radiation can cause severe damage to the genetic information by chemically altering the nucleobases of DNA and RNA. All five canonical nucleobases found today are extraordinarily stable toward photodamage, which is also seen as the reason why they survived the evolutionary selection pressure in the early days of life, when solar radiation on the surface of the earth was more intense than today.<sup>1,2</sup> This high photostability is usually attributed to ultrafast relaxation channels from electronically excited states back to the initial ground state, which have been reported both theoretically and experimentally for all five isolated bases.<sup>3–9</sup> Obstruction of these relaxation channels can be directly linked to the formation of photodamage.<sup>10–12</sup>

One of the most common photolesions, the cyclobutane pyrimidine dimer (CPD) has been extensively investigated for thymine,<sup>13–19</sup> which is structurally closely related to the subject of this paper, uracil. It has been shown that CPD formation originates mainly from excitation to a singlet <sup>1</sup> $\pi\pi^*$  state<sup>15</sup> and can happen within just 1 ps after excitation for favorable initial molecular geometries.<sup>13</sup> Triplet channels leading to CPD damage are also known but generally produce much lower yields.<sup>14,16–18</sup> Experimentally, the singlet <sup>1</sup> $\pi\pi^*$  state is usually excited with UVC radiation (200–290 nm) because of the strong absorption in this range.<sup>3,4,6–9</sup> Although the UVC wavelengths are filtered by the atmosphere, lower energy UVB radiation (290–320 nm) that does reach the surface of the earth can also induce harmful yields of photolesions in RNA under physiological conditions.<sup>20</sup>

Transferring these results to uracil, we will focus on the first relaxation step out of the bright  ${}^{1}\pi\pi^{*}$  S<sub>2</sub> state in our

investigation. In isolated uracil, this relaxation takes place within the ultrafast femtosecond regime, which is regarded as one of the main reasons for photostability. A recent quantum dynamical study on isolated uracil uncovered the possibility of inhibiting this ultrafast relaxation and preparing a long-living nuclear wave packet (WP) in the S<sub>2</sub> state with a tailored laser pulse, which might pave the way for experiments related to the formation of photodamage.<sup>21</sup>

However, the factor that induces excited-state longevity and therefore enables photochemical reactions in nature is not a laser field but the molecular environment of the nucleobases.<sup>22,23</sup> In our present theoretical study, we show that embedding of uracil in its natural nucleic acid environment may directly inhibit the ultrafast relaxation process responsible for photostability. Long-lived excited states in oligo- and polynucleotides are often ascribed to delocalization events in base stacks, such as excimer or exciton formation, where the extent of excited-state delocalization has long been subject to debate.<sup>24-33</sup> While this undoubtedly constitutes an important photochemical pathway in nucleic acids, we report that prevention of ultrafast photorelaxation can also occur on single nucleobases, without the need for delocalization events. For adenine, this was suggested previously by correlating quantum mechanics/molecular mechanics (QM/MM) energy profiles with experimental lifetimes.<sup>34</sup> In the present study, we can directly extract excited-state lifetimes from quantum dynamical simulations of uracil under atomistic consideration of the natural RNA environment. Moreover, we shed light on

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Figure 1. Flowchart for the combined QD/MD approach. Environmental conformations are sampled with classical MD trajectories and are used to compute an environmental potential  $\hat{V}_{env}$  on a QM/MM level of theory.  $\hat{V}_{env}$  is subsequently added to a precomputed high-level excited-state PES of the isolated base in order to perform wave packet dynamics under explicit consideration of the atomistic surrounding.

whether specific combinations of neighboring bases are more or less beneficial for this process and, thus, for the potential formation of photodamage.

#### COMPUTATION OF ENVIRONMENTAL INFLUENCES

We performed quantum dynamical WP propagations on multiscale QM/MM potential energy surfaces (PESs)<sup>35</sup> as described in detail hereafter. As a reference for our calculations, we used a previously published, two-dimensional (2D) PES of isolated uracil in its bright S<sub>2</sub> state ( ${}^{1}\pi\pi^{*}$ ) on the MRCI(12,9)/cc-pVDZ level of theory.<sup>21</sup> Containing the optimized molecular geometries of uracil at the Franck–Condon (FC) point, the S<sub>2</sub>-minimum, and a conical intersection (CoIn) seam between S<sub>2</sub> and S<sub>1</sub> ( ${}^{1}n\pi^{*}$ ), it has proven to reproduce experimental relaxation times well in quantum dynamical simulations.<sup>21</sup>

To include the effects of a biological environment, we employed a modified version of the quantum dynamics/ molecular dynamics (QD/MD) approach,<sup>36</sup> which is schematically drawn in Figure 1.

Here, the temporal evolution of the WP is described by the time-dependent Schrödinger equation (TDSE)

$$i\hbar\frac{\partial}{\partial t}\Psi = (\hat{T}_{\rm nuc} + \hat{V}_{\rm mol} + \hat{V}_{\rm env})\Psi$$
(1)

with the nuclear kinetic energy  $\hat{T}_{nuc}$ , the potential energy of the solute  $\hat{V}_{mol}$ , and the environment potential  $\hat{V}_{env}$ . In our case,  $\hat{V}_{mol}$  represents the high-level  $S_2$ -PES of isolated uracil, while  $\hat{V}_{env}$  contains the environmental influence and was computed as follows: In a first step, the conformations of 10 different uracil-containing RNA sequences in water were sampled by running MD trajectories and extracting 25 geometry snapshots per sequence at random times (total: 250 snapshots). We tested doubling the number of snapshots for the base sequence

5'-GAGUAGG-3' from 25 to 50 but observed no changes in the distribution of slower and faster relaxation times out of  $S_2$ . Since this study focuses on the rare occurrence of delayed relaxation rather than on the computation of average values, we concluded that 25 random snapshots per base sequence were an adequate number of samples for the purposes of this investigation.

Next, we used QM/MM calculations (DFT-D3/M06-2X/6-31G\*//Amber14Sb) with a QM region comprised of uracil, two neighboring bases, and the connecting sugar phosphate backbone (see also top right of Figure 1) to raster the 2D-PES of uracil and to obtain an atomistic evaluation of environmental influence for each snapshot. With around 100 atoms in the QM region and 250 PESs to be calculated, this is highly demanding in terms of computational effort, which is why we performed these calculations at the Leibniz Supercomputing Center in Munich. We also tested the effects of including water molecules in a 5 Å radius around the central uracil moiety in the QM region for several snapshots (~200 QM atoms) but found that the statistical results presented in the next section were not influenced by this. Moreover, Roßbach and Ochsenfeld showed that QM/MM energies of DNA strands converge beyond the first layer of adjacent nucleobases. Testing one snapshot, we observed similar convergence for the PES topography and excited-state lifetime. To avoid doublecounting of  $\hat{V}_{mol}$ , the PES of isolated uracil on the DFT-D3/ M06-2X/6-31G\* level of theory was subtracted from the QM/ MM potential, yielding  $\tilde{V}_{env}$ .

This interaction potential was finally added to the excitedstate PES of isolated uracil,  $\hat{V}_{mob}^{S_2}$  and WP simulations were performed on the obtained PES for every snapshot by launching a nuclear WP from the FC point, where it enters the  $S_2$  state after excitation. Adding the environmental influence on the ground state to the excited-state potential is a justifiable approximation in our case since the charge distribution of uracil after excitation to the  $\pi\pi^*$   $S_2$  state is in



Figure 2. Examples for strong environmental influence on the  $S_2$ -PES of uracil. The PESs were constructed by adding  $\hat{V}_{env}$  (see Figure 1) to the  $S_2$ -PES (MRCI(12,9)/cc-pVDZ) of the isolated base. Note that these are extreme cases and for most conformational snapshots the PES closely resembles the one of the isolated base.



Figure 3. Exemplary nuclear WPs on the  $S_2$ -PES of uracil at 0 fs (black), 50 fs gray, and 500 fs (white). Snapshots from the RNA sequence (a, b) 5'-GACUCGG-3', (c) 5'-GAGUUGG-3', and (d) 5'-GAAUAGG-3'. The WPs start at the FC point, evolve toward the  $S_2$ -minimum, and decay through the CoIn seam with vastly different relaxation times. In (a), the WP has already completely decayed before 500 fs. Animations of these quantum dynamical propagations are available in the online version of this article.

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DOI: 10.1021/jacs.8b02962 J. Am. Chem. Soc. 2018, 140, 8714–8720 close agreement with that in the ground state (see Supporting Information for details). The electrostatic interaction of this excited state with the environment will therefore be very similar to the ground-state interaction.

For the isolated base, it has been shown that the inclusion of a third dimension in the coordinate space does not change the lifetimes extracted from these WP simulations.<sup>21</sup> Moreover, we tested the inclusion of five normal modes, covering a wide range of molecular degrees of freedom, in the 2D coordinate space for five different MD snapshots but did not find any relevant new pathways in the third dimension (see Supporting Information for details).

#### RESULTS AND DISCUSSION

The influence of a biological environment can drastically alter the PES of isolated uracil. Examples for this are drawn in Figure 2b–d with the PES of the isolated nucleobase as a reference in Figure 2a. We observed several stabilizing and destabilizing effects, such as lowering of the barrier between  $S_2$ minimum and CoIn seam (Figure 2b), the relative stabilization of one of the two minima (Figure 2c), and even the formation of a new minimum on the PES (Figure 2d).

Nevertheless, the examples depicted in Figure 2 are extreme cases, and the majority of the 250 calculated PESs closely resemble the one of the isolated nucleobase. Linking the molecular structure to the PES topography, we noted stabilizing effects by hydrogen bonds from uracil to the sugar phosphate backbone. A similar interaction occurs when positively polarized hydrogen atoms of the uracil moiety are located favorably in the Coulomb field of the more electronegative nitrogen atoms in neighboring bases. Rises in energy could mostly be attributed to steric hindrances in the environment that impede the out-of-plane movement of uracil along the coordinate vectors of the PES.

As could be expected, such environmentally induced changes in the excited-state PES topography can have a strong effect on the path of a nuclear WP and, therefore, the relaxation time back to the ground state. In the isolated base, the WP undergoes two oscillations between the FC point and S<sub>2</sub>-minimum, before decaying through the CoIn to S<sub>1</sub> with a lifetime of  $t_{1/2} = 192$  fs. We define the excited-state lifetime  $t_{1/2}$  as the time where half of the population has decayed from S<sub>2</sub>.

The environmental influence on the WP behavior is illustrated in Figure 3. In Figure 3a and b, two different snapshots of the base sequence 5'-GACUCGG-3' are drawn, where the WPs are launched from the FC point and exhibit significantly different time evolution. The WP in Figure 3a reaches the CoIn after a very short time ( $t_{1/2}$  = 76 fs) and only one oscillation through the S2-minimum, whereas the WP in Figure 3b remains trapped in the  $S_2$  state for several picoseconds ( $t_{1/2}$  = 3.5 ps). Despite this trap, we observe that after a long amount of time, even the lower energetic parts of the WP eventually decay to S1, which can be explained by tunneling through the barrier to the CoIn. Another notable quantum effect is that even in cases where the PES closely resembles the one of isolated uracil (Figure 3c), minor topographical changes in critical areas of the PES, especially in the regions around the FC point and S<sub>2</sub>-minimum, can strongly decelerate the relaxation. This can also be observed in snapshots where the barrier between S2-minimum and CoIn is lowered (Figure 3d). Usually, a reduced barrier height leads to the assumption of faster relaxation times, which is not true in some of our cases. We attribute this counterintuitive behavior to a lack of initial momentum in the direction of the CoIn because of changed potential energy gradients in the FC region and at the turning point beyond the  $S_2$ -minimum. In such cases, the coherence of the WP hinders its evolution toward the CoIn and, thus, over the barrier. The extracted relaxation time is, therefore, insensitive to the height of the barrier. This observation emphasizes the need for true quantum dynamical simulations to obtain an accurate picture of photophysical relaxation processes, additional to comparing single-point energies.

The discussed effects can occur in all of the base sequences we tested. In this context, Figure 4 compiles the population



Figure 4. Temporal evolution of the population in the electronic  $S_2$  state of uracil in 250 different environmental snapshots compared to the reference population for the isolated base (black). The color of the curves indicates how much the half-life differs from the reference of 192 fs. While most snapshots exhibit lifetimes similar to that of the isolated base, about 13% decay slower and might promote photodamage.

decay curves of all 250 quantum dynamical simulations with the color encoding the respective half-life in  $S_2$ . The majority of snapshots (82%) decay with a half-life in the range of ±50 fs around the reference of 192 fs, while 5% exhibit significantly accelerated relaxation. This is in line with the high photostability of uracil, even inside an RNA strand. Nonetheless, 13% of the 250 sampled environmental conformations cause delayed relaxation and sometimes even increase the lifetime in  $S_2$  more than 10-fold. For the closely related thymine, it has been demonstrated that this might already be enough for harmful photochemical reactions to take place.<sup>13</sup> Since our PESs only include the monomer-like decay channel of uracil, these results indicate that steric influences of the environment alone can account for long excited state lifetimes and, therefore, can potentially enable the formation of photolesions.

To find out whether there are neighboring bases that favor this behavior, we considered 10 RNA sequences in our simulations, each with a different combination of uraciladjacent nucleobases. For each possible neighboring base A, C, G, and U, we extracted the percentage of faster  $(t_{1/2} < 142 \text{ fs})$ , similar  $(t_{1/2} = (192 \pm 50)\text{fs})$ , and slower  $(t_{1/2} > 242 \text{ fs})$ relaxation times as compared to the reference in all snapshots containing the respective base next to uracil. The obtained results are visualized in Figure 5 for each neighboring base. In all cases, the majority of samples exhibit lifetimes in S<sub>2</sub> that are very similar to the one in isolated uracil. Snapshots that induce faster or slower population decay occur for all four possible neighboring bases, with a clear trend toward the latter. There are no pronounced differences between the individual bases, and thus, we conclude that no single neighboring base is



**Figure 5.** Relative abundance (in percent) of slower, similar, and faster relaxation times  $t_{1/2}$  for each neighboring base in a total of 10 different RNA sequences of the type 5'-GAXUYGG-3', as compared to isolated uracil (192 fs). As the percentages are very similar for all four possible neighbors, we conclude that no particular base promotes delayed relaxation in uracil by sterical hindrance.

distinctly responsible for the promotion of excited-state longevity and thereby photodamage in uracil.

#### CONCLUSIONS

To summarize, our present study illustrates that the ultrafast photorelaxation of the RNA-base uracil can be strongly impeded by the steric influence of its biological surrounding. By modeling an atomistic environment with multiscale QM/ MM calculations and investigating the relaxation process of photoexcited uracil with quantum dynamical simulations, we demonstrated that long relaxation times of several picoseconds can occur in the monomer-like decay channel without the need for excited-state delocalization. With ultrafast relaxation being regarded as the main reason for photostability, it is conceivable that this long excited state lifetime is one of the mechanisms which enable the formation of photolesions in nucleic acid strands. Sampling a total of 250 environmental conformations in 10 different uracil-containing base sequences, we found longer relaxation times in about 13% of cases, while only 5% decayed significantly faster than in the isolated base. We noted that even small changes in the PES topography can dramatically influence the excited-state lifetime as compared to the isolated nucleobase. A majority of 82% showed very similar relaxation times to the one in isolated uracil, which is in line with the fact that photodamage is a rare event in nature, especially if we assume that only a small share of these 13% might actually lead to harmful photochemical reactions. There is no particular neighboring base that promotes trapping in the excited state and, therefore, photodamage, so we conclude that this is rather a general effect of steric hindrance in the RNA environment.

#### COMPUTATIONAL DETAILS

The optimized molecular structures of  $uracil^{38,39}$  (MRCI-(12,9)/cc-pVDZ), used to construct the 2D coordinate space, as well as the excited-state PES of isolated  $uracil^{21}$  and the coordinate vectors<sup>21</sup> for PES construction have been adopted from previous works as cited earlier. For convenience, they are also included in the Supporting Information of this article.

The structures of 10 RNA single strand A-type helices with the seven-base sequences outlined in Figure 6 were generated with the web-application Make-NA.<sup>40</sup> In every strand, the fourth base (uracil) was replaced with the optimized ground state geometry of uracil.

		base on 5' end					
		G	А	С	U		
base on 3' end	G	GUG	AUG	CUG	UUG		
	А	GUA	AUA	CUA	UUA		
	С	GUC	AUC	CUC	υυς		
	U	GUU	AUU	CUU	UUU	1	

**Figure 6.** Overview of the possible combinations of nucleobases in direct vicinity of uracil. The ones chosen for this study are highlighted in a darker shade and were complemented by a leading 5'-GA segment and a GG-3'-tail (e.g., 5'-GA-GUA-GG-3').

The prepared RNA strands were placed in a cubic box with 5.2 nm edge length and were solvated in TIP3P<sup>41</sup> water before neutralizing the system with sodium ions. Using the Gromacs 5.1.2<sup>42,43</sup> software in combination with the Amber14SB<sup>44-47</sup> force field, integration of Newton's equations was carried out with the Velocity Verlet integrator<sup>48</sup> over a period of 100 ps with a time step of 1 fs and using five different starting conditions per RNA sequence. Temperature control was achieved with the Berendsen thermostat<sup>49</sup> at 298.15 K. The system was equilibrated by propagating for 10 ps before extracting snapshots. To separate quantum from classical movement, the internal motion of uracil was frozen with the Rattle<sup>50</sup> algorithm during the simulations. This approximation might slightly influence the MD but enables a better comparison of the quantum dynamical simulations as all WPs start at the same FC point.

Multiscale QM/MM calculations were performed with the ChemShell 3.6.0<sup>51-53</sup> environment on the CooLMUC-2 infrastructure of the Leibniz Supercomputing Center. Here, the QM part of the calculations was carried out at the DFT- $D3/M06-2X/6-31G^*$  level of theory<sup>54</sup> with the Gaussian09<sup>55</sup> package, while the energy of the MM subsystem was evaluated with the DL POLY 2 module<sup>56</sup> using the TIP3P<sup>41</sup> and Amber14SB<sup>44-47</sup> force fields for water and RNA, respectively. An electrostatic embedding scheme<sup>57</sup> was used to couple the two subsystems via the link-atom<sup>52,58</sup> approach. Overpolarization of the QM region in the vicinity of the link atom was avoided by shifting classical charges away from the boundary region.<sup>52</sup> The QM subsystem was chosen to contain uracil with two neighboring bases and the interconnecting sugarphosphate backbone (see also top right of Figure 1). Specifically, the cuts between QM and MM regions went through the P-5'O and 3'O-P bonds. PESs were constructed in the 2D coordinate space described by Keefer et al.<sup>21</sup> and using the approach explained in the methodology section.

Using these PESs, the TDSE (eq 1) was solved on a spatial grid with  $128 \times 128$  points using the Chebyshev<sup>59</sup> propagation scheme for WP simulations. To represent the kinetic energy

operator in reduced coordinates, we employed the Wilson Gmatrix formalism.<sup>36,60,61</sup> Nonadiabatic couplings between S<sub>2</sub> and S<sub>1</sub> were adopted from previous works and can be found there along with the G-matrix elements.<sup>21</sup> The WP was absorbed by a masking function after crossing the CoIn to the S<sub>1</sub> state.

#### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b02962.

Optimized molecular geometries and coordinate vectors spanning the potential energy surfaces; electric dipole moments and electrostatic potentials for the first few excited states of uracil QM/MM potential energy scans in three dimensions

(PDF)

Animation of the quantum dynamical propagations for the isolated base

(AVI)

Animation of the quantum dynamical propagations shown in Figure 3a

(AVI)

Animation of the quantum dynamical propagations shown in Figure 3b

(AVI)

Animation of the quantum dynamical propagations shown in Figure 3c

(AVI)

Animation of the quantum dynamical propagations shown in Figure 3d (AVI)

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#### REFERENCES

- (1) Sagan, C. J. Theor. Biol. 1973, 39, 195.
- (2) Beckstead, A. A.; Zhang, Y.; de Vries, M. S.; Kohler, B. Phys. Chem. Chem. Phys. 2016, 18, 24228.

(3) Kang, H.; Lee, K. T.; Jung, B.; Ko, Y. J.; Kim, S. K. J. Am. Chem. Soc. 2002, 124, 12958.

(4) He, Y.; Wu, C.; Kong, W. J. Phys. Chem. A 2003, 107, 5145.

(5) Crespo-Hernández, Č. E.; Cohen, B.; Hare, P. M.; Kohler, B. Chem. Rev. 2004, 104, 1977.

(6) Ullrich, S.; Schultz, T.; Zgierski, M. Z.; Stolow, A. Phys. Chem. Chem. Phys. 2004, 6, 2796.

(7) Canuel, C.; Mons, M.; Piuzzi, F.; Tardivel, B.; Dimicoli, I.; Elhanine, M. J. Chem. Phys. 2005, 122, 074316.

(8) Middleton, C. T.; de La Harpe, K.; Su, C.; Law, Y. K.; Crespo-Hernández, C. E.; Kohler, B. Annu. Rev. Phys. Chem. 2009, 60, 217.

(9) Kotur, M.; Weinacht, T. C.; Zhou, C.; Matsika, S. IEEE J. Sel. Top. Quantum Electron. 2012, 18, 187.

(10) Tommasi, S.; Denissenko, M. F.; Pfeifer, G. P. Cancer Res. 1997, 57, 4727.

(11) Esposito, L.; Banyasz, A.; Douki, T.; Perron, M.; Markovitsi, D.; Improta, R. J. Am. Chem. Soc. **2014**, 136, 10838.

(12) Martínez-Fernández, L.; Pepino, A. J.; Segarra-Martí, J.; Jovaišaitė, J.; Vaya, I.; Nenov, A.; Markovitsi, D.; Gustavsson, T.; Banyasz, A.; Garavelli, M.; Improta, R. J. Am. Chem. Soc. **2017**, 139, 7780.

(13) Schreier, W. J.; Schrader, T. E.; Koller, F. O.; Gilch, P.; Crespo-Hernandez, C. E.; Swaminathan, V. N.; Carell, T.; Zinth, W.; Kohler, B. *Science* **2007**, *315*, 625.

(14) Kwok, W.-M.; Ma, C.; Phillips, D. L. J. Am. Chem. Soc. 2008, 130, 5131.

(15) Schreier, W. J.; Kubon, J.; Regner, N.; Haiser, K.; Schrader, T. E.; Zinth, W.; Clivio, P.; Gilch, P. J. Am. Chem. Soc. **2009**, 131, 5038.

(16) Ákos Bányász; Douki, T.; Improta, R.; Gustavsson, T.; Onidas, D. Varís I. Parron M. Markavitsi D. J. Am. Chem. Sac. 2012, 124

D.; Vayá, I.; Perron, M.; Markovitsi, D. J. Am. Chem. Soc. 2012, 134, 14834.

(17) Pilles, B. M.; Bucher, D. B.; Liu, L.; Clivio, P.; Gilch, P.; Zinth, W.; Schreier, W. J. J. Phys. Chem. Lett. **2014**, *5*, 1616.

(18) Liu, L.; Pilles, B. M.; Gontcharov, J.; Bucher, D. B.; Zinth, W. J. Phys. Chem. B 2016, 120, 292.

(19) Conti, I.; Martínez-Fernández, L.; Esposito, L.; Hofinger, S.; Nenov, A.; Garavelli, M.; Improta, R. *Chem. - Eur. J.* 2017, 23, 15177.
(20) Wurtmann, E. J.; Wolin, S. L. *Crit. Rev. Biochem. Mol. Biol.* 2009, 44, 34.

(21) Keefer, D.; Thallmair, S.; Matsika, S.; de Vivie-Riedle, R. J. Am. Chem. Soc. 2017, 139, 5061.

(22) Photoinduced Phenomena in Nucleic Acids I; Barbatti, M., Borin, A. C., Ullrich, S., Eds.; Springer International Publishing: Basel, Switzerland, 2015.

(23) Improta, R.; Santoro, F.; Blancafort, L. Chem. Rev. 2016, 116, 3540.

(24) Tinoco, I. J. Am. Chem. Soc. 1960, 82, 4785.

(25) Eisinger, J.; Shulman, R. G. Science 1968, 161, 1311.

(26) Crespo-Hernández, C. E.; Cohen, B.; Kohler, B. Nature 2005, 436, 1141.

(27) Buchvarov, I.; Wang, Q.; Raytchev, M.; Trifonov, A.; Fiebig, T. Proc. Natl. Acad. Sci. U. S. A. 2007, 104, 4794.

(28) Kadhane, U.; Holm, A. I. S.; Hoffmann, S. V.; Nielsen, S. B. *Phys. Rev. E* 2008, 77, 021901.

(29) Takaya, T.; Su, C.; de La Harpe, K.; Crespo-Hernandez, C. E.; Kohler, B. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 10285.

(30) Lange, A. W.; Herbert, J. M. J. Am. Chem. Soc. 2009, 131, 3913.
(31) Markovitsi, D.; Gustavsson, T.; Banyasz, A. Mutat. Res., Rev. Mutat. Res. 2010, 704, 21.

(32) Chen, J.; Zhang, Y.; Kohler, B. In *Photoinduced Phenomena in Nucleic Acids II*; Barbatti, M., Borin, A. C., Ullrich, S., Eds.; Springer International Publishing: Basel, Switzerland, 2014; p 39.

(33) Nogueira, J. J.; Plasser, F.; González, L. Chem. Sci. 2017, 8, 5682.

(34) Conti, I.; Altoè, P.; Stenta, M.; Garavelli, M.; Orlandi, G. *Phys. Chem. Chem. Phys.* **2010**, *12*, 5016.

(35) Warshel, A.; Levitt, M. J. Mol. Biol. 1976, 103, 227.

(36) Thallmair, S.; Zauleck, J. P. P.; de Vivie-Riedle, R. J. Chem. Theory Comput. 2015, 11, 1987.

(37) Roßbach, S.; Ochsenfeld, C. J. Chem. Theory Comput. 2017, 13, 1102.

(38) Matsika, S. J. Phys. Chem. A 2004, 108, 7584.

(39) Yoshikawa, A.; Matsika, S. Chem. Phys. 2008, 347, 393.

DOI: 10.1021/jacs.8b02962 J. Am. Chem. Soc. 2018, 140, 8714–8720

8719

(40) Stroud, J. *Make-NA*, v. 0.10; http://structure.usc.edu/make-na/ server.html (accessed Oct 23, 2017).

- (41) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. J. Chem. Phys. **1983**, 79, 926.
- (42) Pronk, S.; Páll, S.; Schulz, R.; Larsson, P.; Bjelkmar, P.; Apostolov, R.; Shirts, M. R.; Smith, J. C.; Kasson, P. M.; van der
- Spoel, D.; Hess, B.; Lindahl, E. Bioinformatics **2013**, *29*, 845.
- (43) Abraham, M. J.; Murtola, T.; Schulz, R.; Páll, S.; Smith, J. C.; Hess, B.; Lindahl, E. SoftwareX 2015, 1, 19.
- (44) Graf, J.; Nguyen, P. H.; Stock, G.; Schwalbe, H. J. Am. Chem. Soc. 2007, 129, 1179.

(45) Wickstrom, L.; Okur, A.; Simmerling, C. Biophys. J. 2009, 97, 853.

(46) Lindorff-Larsen, K.; Piana, S.; Palmo, K.; Maragakis, P.; Klepeis, J. L.; Dror, R. O.; Shaw, D. E. *Proteins: Struct., Funct., Genet.* **2010**, *78*, 1950.

(47) Nguyen, H.; Roe, D. R.; Simmerling, C. J. Chem. Theory Comput. 2013, 9, 2020.

(48) Swope, W. C.; Andersen, H. C.; Berens, P. H.; Wilson, K. R. J. Chem. Phys. **1982**, *76*, 637.

(49) Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; DiNola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684.

(50) Andersen, H. C. J. Comput. Phys. 1983, 52, 24.

(51) ChemShell, v. 3.6; a Computational Chemistry Shell; http:// www.chemshell.org, accessed July 2, 2017.

(52) Sherwood, P.; de Vries, A. H.; Guest, M. F.; Schreckenbach, G.; Catlow, C. R. A.; French, S. A.; Sokol, A. A.; Bromley, S. T.; Thiel, W.; Turner, A. J.; Billeter, S.; Terstegen, F.; Thiel, S.; Kendrick, J.; Rogers, S. C.; Casci, J.; Watson, M.; King, F.; Karlsen, E.; Sjøvoll, M.; Fahmi, A.; Schäfer, A.; Lennartz, C. J. Mol. Struct.: THEOCHEM **2003**, 632, 1.

(53) Metz, S.; Kästner, J.; Sokol, A. A.; Keal, T. W.; Sherwood, P. WIREs Comput. Mol. Sci. 2014, 4, 101.

(54) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. J. Chem. Phys. 2010, 132, 154104.

(55) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, revision D.01; Gaussian, Inc.: Wallingford, CT, 2009.

(56) Smith, W.; Forester, T. J. Mol. Graphics 1996, 14, 136.

(57) Bakowies, D.; Thiel, W. J. Phys. Chem. 1996, 100, 10580.

- (58) Eichler, U.; Kölmel, C. M.; Sauer, J. J. Comput. Chem. 1997, 18, 463.
- (59) Tal-Ezer, H.; Kosloff, R. J. Chem. Phys. 1984, 81, 3967.
- (60) Schaad, L. J.; Hu, J. J. Mol. Struct.: THEOCHEM 1989, 185, 203.
- (61) Kowalewski, M.; Mikosch, J.; Wester, R.; de Vivie-Riedle, R. J. Phys. Chem. A **2014**, 118, 4661.

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# 3

## On the Road to Artificial Photosynthesis



**Chapter 3 Title Graphic:** Photosystem I embedded in a metal-organic framework is envisaged to act as a biological light-harvesting component, driving chemical reactions in an artificial photosynthetic device.

Moving on from femtosecond dynamics to the spatial and temporal nanoscale, the three studies presented in this chapter deal with new ways for sustainable energy conversion, aimed in particular towards artificial photosynthesis. A photosynthetic device in its most general form requires a light-harvesting antenna, a photosensitizer, an electron donor and a fuel generator.<sup>[204]</sup> The light-harvesting antenna absorbs light and transfers it to the photosensitizer, where the energy is used to initiate a charge-separation. Ideally, the oxidizing potential of the generated hole could be used to drive reactions in chemical synthesis. In practice however, the hole is usually filled by either an oxygen-evolving catalyst or a sacrificial electron donor.<sup>[205]</sup> The released electron is eventually transferred to a catalytic site, where it is used to generate a fuel, usually hydrogen. While all components could also be created artificially,<sup>[206–208]</sup> there are growing efforts to employ natural light-harvesting systems that have been optimized by millions of years of evolution.<sup>[209–211]</sup> PS I offers a particularly attractive platform due to its robustness, high quantum efficiency, strong reduction potential and its inter-species variability.<sup>[209]</sup> In a device, PS I fulfills the double role of the light-harvesting system and the charge separation site (figure 3.1). Sunlight is absorbed by an arrangement of chlorophylls and carotenoids that make up the antenna complex. Through resonance energy transfer, the created exciton is moved to the reaction center where it triggers charge separation. The primary electron donor in PS I is generally assumed to be a special pair of chlorophylls, labeled P700 after its characteristic bleach signal around 700 nm in the optical difference spectrum of the charge-separated state.<sup>[212]</sup> From there, the electron is transferred from the lumenal to the stromal side of the photosystem via a series of chlorophylls, phylloquinones, and iron-sulfur clusters that make up the electron transfer chain (ETC) (figure 3.1, right). The ETC consists of two branches, A and B, which are both thought to be active in the transfer of electrons.<sup>[213–216]</sup> However, primary charge separation and electron transfer to the phylloquinone are slightly faster in branch A, whereas the final transfer from branch A to the first iron-sulfur cluster  $F_X$  is slower by an order of magnitude.<sup>[215,216]</sup> This discrepancy can only be a result of the different local environment surrounding the otherwise symmetric branches.<sup>[217]</sup> The final iron-sulfur cluster in the ETC, F<sub>B</sub>, can transfer the electron out of the photosystem to an external catalytic site where the hydrogen evolution takes place. The connection to the catalyst can be realized *via* molecular wires,<sup>[218]</sup> carbon nanostructures,<sup>[219]</sup> or direct coupling through self-association<sup>[220,221]</sup> The H<sub>2</sub> evolving catalyst itself can in principle take many different forms, with strategies ranging from the use of natural hydrogenase enzymes,<sup>[222–224]</sup> over precious metal nanoparticles<sup>[218,220,225]</sup> and functionalized nanostructures<sup>[226-229]</sup> to transition metal complexes using earth abundant metals.<sup>[230–238]</sup> The latter have the advantage of cost-effectiveness due to their use of readily available starting materials. Moreover, a wide variety of redox-active ligands allows operating metal-complex catalysts in diverse environments, both acidic and alkaline. However, reducing the overpotentials for H<sub>2</sub> evolution is still a key challenge in catalyst design that requires detailed knowledge of the respective catalytic mechanism. Finally, integrating all components for artificial photosynthesis in a single platform can be achieved via encapsulation in a glass,<sup>[221,239]</sup> polymer,<sup>[240]</sup> or an external



Figure 3.1: Schematic representation of artificial photosynthesis using PS I as a biological lightharvesting component. After light excites the antenna complex in PS I, the absorbed energy is transferred to the reaction center, where it initiates a charge separation. The positive hole is filled by a sacrificial electron donor, while the electron travels out of the photosystem via the A- or B-branch in the ETC (detailed view on the right) and drives catalytic hydrogen evolution. Cofactors in the ETC are labeled according to Jordan et al.<sup>[244]</sup>

microstructure,<sup>[241]</sup> such as a MOF.<sup>[242,243]</sup> Encapsulation both immobilizes the individual components and stabilizes the device against environmental damage. Certain microenvironments have even proven to enhance the function of the embedded photosystem.<sup>[240,241,243]</sup>

The bottom-up design and tuning of an artificial photosynthetic device requires understanding the complex interplay of energy, electron and proton transfer processes that govern its function. Computational modeling can complement experiments in this endeavor with microscopic insights. The three studies presented in this chapter will provide such insights to the key steps of H<sub>2</sub> evolution, light-harvesting and stabilization of the biological component. Section 3.1 investigates the mechanism of  $H_2$  evolution catalyzed by the [Co(Mabiq)] complex. Previous studies had indicated the existence of two intermediates in the reaction, which could not be further characterized experimentally. Therefore, the consecutive reduction and protonation steps are simulated in this work, along with absorption spectra to identify the elusive intermediates and arrive at a mechanistic scheme for the H<sub>2</sub> evolution. Subsequently, section 3.2 introduces a new computational model of PS I, including the dynamic and fully atomistic local environment of each chlorophyll as well as the strong static correlation that governs chlorophyll excitations. The dynamic perspective combined with state-of-the-art quantum chemistry provides new insights into the light-harvesting by wild-type PS I. Building on this, section 3.3 discusses the impact of encapsulating PS I in the MOF ZIF-8 in order to stabilize it against harmful external conditions. The encapsulation process is simulated via MD, allowing a detailed analysis of the structural changes in PS I as well as the electronic interactions at the PS I/ZIF-8 interface.

### 3.1 Hydrogen Evolution via CoMabiq

The [Co(Mabiq)] complex catalyzes  $H_2$  evolution in acidic conditions (pH=4.85) at a cathodic peak potential of -1.1 V vs. the ferrocene (0/1+) internal standard (V<sub>FC</sub>). Previous work<sup>[245]</sup> indicated addition of two electrons and at least one proton to the catalyst in an electrochemical-chemical-electrochemical (ECE) or electrochemical-chemical-electrochemical (ECE) or electrochemical-chemical-electrochemical (ECE) mechanism. The one-electron reduced complex, i.e., after the first electrochemical step of the reaction, had been characterized<sup>[245]</sup> as an open-shell singlet with strong ligand contributions, whereas the subsequent intermediates could not be isolated. However, the doubly protonated [Co(MabiqH<sub>2</sub>)] had been ruled out as an intermediate, being inconsistent with the established ECE pathway. Thus, the intermediates of the H<sub>2</sub> evolution catalyzed by the [Co(Mabiq)] complex were characterized through spectroelectrochemistry and theory in the article "H<sub>2</sub> Evolution from Electrocatalysts with Redox-Active Ligands: Mechanistic Insights from Theory and Experiment Vis-à-Vis Co-Mabiq", published 2021 in *Inorg. Chem.* An overview of the investigated two-electron reduced and protonated species with the nomenclature used in the article is available in figure 3.2. The most important results of the article are summarized below:

- Cyclic voltammetry (CV) of [Co<sup>II</sup>(Mabiq)]<sup>+</sup> shows electrocatalytic H<sub>2</sub> evolution below -0.84 V<sub>FC</sub> with two redox events at -1.1 V<sub>FC</sub> and -1.32 V<sub>FC</sub>. Bulk electrolysis at -0.84 V<sub>FC</sub> yields an intermediate species Co<sub>Mbq</sub>-H<sup>2</sup> with a characteristic absorption at 411 nm. CV of this species shows only one redox event at -1.32 V<sub>FC</sub>. Thus, there must be another intermediate responsible for the H<sub>2</sub> evolution at -1.1 V<sub>FC</sub>, which will be referred to as Co<sub>Mbq</sub>-H<sup>1</sup>. This intermediate is formed at lower potential but not stable over time, so that Co<sub>Mbq</sub>-H<sup>2</sup> is the dominant species after bulk electrolysis.
- The formation of the intermediates also depends on the strength of the employed acid. Presence of *p*-bromoanilinium (*p*BrA) leads to the predominant formation of  $\mathbf{Co}_{\mathbf{Mbq}}$ -H<sup>2</sup>, while the stronger *p*-cyanoanilinium (*p*CA) also generates  $\mathbf{Co}_{\mathbf{Mbq}}$ -H<sup>1</sup>. This suggests that the protonation site of  $\mathbf{Co}_{\mathbf{Mbq}}$ -H<sup>1</sup> is less basic than that of  $\mathbf{Co}_{\mathbf{Mbq}}$ -H<sup>2</sup> so that the two competing intermediates can be selectively formed by varying the acid strength. Using the even weaker acid *p*-anisidinium (*p*An) also leads to H<sub>2</sub> generation but CV experiments point to a different mechanism (EEC rather than ECE) that was not further explored in this work.
- As neither  $\mathbf{Co}_{\mathbf{Mbq}}$ -H<sup>2</sup>, nor  $\mathbf{Co}_{\mathbf{Mbq}}$ -H<sup>1</sup> could be crystallized or otherwise characterized experimentally, quantum chemical calculations were performed to characterize four candidates for the elusive intermediates. These were selected based on the spin density distribution of the one-electron reduced species  $[\mathbf{Co}^{II}(\mathbf{Mabiq})]^0$ , which indicated possible protonation sites at either of the two diketiminate sites of the ligand (denoted  $\mathbf{Co}_{\mathbf{Mbq}}$ -H<sup>DK1</sup> and  $\mathbf{Co}_{\mathbf{Mbq}}$ -H<sup>DK2</sup>), at the imine site ( $\mathbf{Co}_{\mathbf{Mbq}}$ -H<sup>Im</sup>) or at the metal center ( $\mathbf{Co}_{\mathbf{Mbq}}$ -H<sup>Co</sup>).



Figure 3.2: Overview of the differently protonated, two-electron reduced [Co(Mabiq)] species investigated here. The two experimentally suggested intermediates  $Co_{Mbq}$ -H<sup>1</sup> and  $Co_{Mbq}$ -H<sup>2</sup> were identified as  $Co_{Mbq}$ -H<sup>Im</sup> and  $Co_{Mbq}$ -H<sup>DK1</sup>, respectively, in this work. The top right shows the spin density of the one-electron reduced precursor [Co<sup>II</sup>(Mabiq)]<sup>0</sup>, with blue denoting excess  $\alpha$ -density and yellow excess  $\beta$ -density (Isovalue: 0.002). Electrons added upon reduction are highlighted in red to aid in understanding the reactivity. In reality, the unpaired electron density is rarely localized on a single site, as illustrated in figure C.4 in the appendix.

- Structure optimizations and thermodynamics calculations at the CAM-B3LYP level show that  $Co_{Mbq}$ -H<sup>Im</sup> is the most stable candidate after the protonation step, whereas  $Co_{Mbq}$ -H<sup>DK2</sup> is the most stable intermediate after the subsequent reduction step.
- The intermediates were further characterized by calculating absorption spectra for four possible candidates. Notably, TD-DFT using hybrid functionals did not allow for reliable band assignment due to the strong multireference character of the complexes. The DFT/MRCI method provided an attractive solution in this regard, offering the advantages of a multireference method at affordable computational cost.
- Out of the computed spectra, the one for  $\mathbf{Co_{Mbq}}$ - $\mathbf{H^{DK1}}$  provides the best match for the experimental spectrum after bulk electrolysis in the presence of *p*CA. The spectrum of  $\mathbf{Co_{Mbq}}$ - $\mathbf{H^{DK2}}$ , which was identified as the thermodynamically most stable product, also matches the experimental reference well but lacks some intensity in

the critical range around 411 nm. Thus the calculated spectra identified  $\mathbf{Co}_{\mathbf{Mbq}}$ - $\mathbf{H}^{\mathbf{DK1}}$  as the main intermediate  $\mathbf{Co}_{\mathbf{Mbq}}$ - $\mathbf{H}^2$  after bulk electrolysis but left open the possibility that both diketiminate species were formed.

- The calculated absorption spectrum of Co<sub>Mbq</sub>-H<sup>Im</sup> exhibited a broad band in the range between 500 to 600 nm, where a gradual decrease in absorbance could be observed experimentally in the presence of *p*CA but not in the weaker acid *p*BrA. This led to the conclusion that the second, elusive intermediate Co<sub>Mbq</sub>-H<sup>1</sup>, which was only generated in *p*CA, was the imine-protonated species Co<sub>Mbq</sub>-H<sup>Im</sup>. While the calculated energy barrier of 162 kJ mol<sup>-1</sup> was found to be too high for a direct conversion from Co<sub>Mbq</sub>-H<sup>Im</sup> to Co<sub>Mbq</sub>-H<sup>DK1</sup>, the possibility of a multi-step conversion process or gradual chemical degradation was left for future work to address in explaining the decreasing absorption signal.
- Based on the two thus identified intermediates  $\mathbf{Co}_{\mathbf{Mbq}}-\mathbf{H}^{\mathbf{DK1}}$  and  $\mathbf{Co}_{\mathbf{Mbq}}-\mathbf{H}^{\mathbf{Im}}$ , a mechanism for the hydrogen evolution reaction could be formulated by simulating the subsequent protonation and reduction steps at the CAM-B3LYP level. The resulting charge distributions allowed conclusions about possible reaction pathways and revealed that the main intermediate  $\mathbf{Co}_{\mathbf{Mbq}}-\mathbf{H}^{\mathbf{DK1}}$  favors a ligand-centered hydrogen evolution reaction, whereas the second intermediate  $\mathbf{Co}_{\mathbf{Mbq}}-\mathbf{H}^{\mathbf{Im}}$  likely induces metal-centered reduction and protonation steps, which occur at lower energy.
- Future ligand design could therefore focus on suppressing protonation at the diketiminate sites to enable a more energy-efficient hydrogen evolution *via* the imine site of the Mabiq ligand.

At the time of publication, DFT/MRCI had emerged as the most suitable method to calculate absorption spectra for [Co(Mabiq)], as TD-DFT at the hybrid density functional level suffered from the lack of multireference effects as well as self-interaction errors and wave function based methods were not computationally feasible for application in this work. However, only 50 electronic states could be calculated in this way. Even though the data in its entirety pointed to  $Co_{Mbq}$ -H<sup>Im</sup> as one of the intermediates, this technical limitation prevented an unambiguous assignment of its spectral signature.

Shortly after the investigation was concluded, a new generation of long-range corrected double-hybrid density functionals<sup>[148]</sup> became available in the *Orca 5.0* software package<sup>[246]</sup> allowing to recalculate the spectra of the one-electron reduced species presented in figure 8 of the article. These new spectra were calculated with *Orca 5.0.3*<sup>[246]</sup> at the SCS- $\omega$ PBEPP86/def2-TZVPD level of theory,<sup>[148,247,248]</sup> modeling solvation in acetonitrile with the conductor-like polarizable continuum model (C-PCM).<sup>[249]</sup> To accelerate the evaluation of Coulomb and exchange integrals, the RIJCOSX approximation<sup>[250,251]</sup> was used with the def2/J<sup>[252]</sup> and def2-TZVPD/C<sup>[253,254]</sup> auxiliary basis sets. The results are depicted in figure 3.3 and confirm the assignment of Co<sub>Mbq</sub>-H<sup>DK1</sup> and Co<sub>Mbq</sub>-H<sup>Im</sup> as the most likely intermediates in the H<sub>2</sub> evolution reaction.



Figure 3.3: Calculated absorption spectra for the four investigated species after the addition of two electrons and one proton to  $[Co^{II}(Mabiq)]^+$  in comparison to the experimental spectrum after 8 h of bulk electrolysis in the presence of 10 equiv of *p*CA. Line spectra were convoluted with Gaussians with fwhm = 0.1 eV.

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### H<sub>2</sub> Evolution from Electrocatalysts with Redox-Active Ligands: Mechanistic Insights from Theory and Experiment vis-à-vis Co-Mabig

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electron transfer steps en route to H<sub>2</sub> evolution still need to be established, and redox-active ligands could play an important role in this context. In this study, we explore the role of the redox-active Mabiq (Mabiq = 2-4:6-8-bis(3,3,4,4-tetramethlyldihydropyrrolo)-10-15-(2,2-biquinazolino)-[15]-1,3,5,8,10,14-hexaene1,3,7,9,11,14- $N_6$ ) ligand in the hydrogen evolution reaction (HER). Using spectro-electrochemical studies in conjunction with quantum chemical calculations, we identified two precatalytic intermediates formed upon the addition of two electrons and one proton to  $[Co^{II}(Mabiq)(THF)](PF_6)$  (Co<sub>Mbq</sub>). We further examined the acid



strength effect on the generation of the intermediates. The generation of the first intermediate, Co<sub>Mbq</sub>-H<sup>1</sup>, involves proton addition to the bridging imine-nitrogen atom of the ligand and requires strong proton activity. The second intermediate, Co<sub>Mbg</sub>-H<sup>2</sup>, acquires a proton at the diketiminate carbon for which a weaker proton activity is sufficient. We propose two decoupled H<sub>2</sub> evolution pathways based on these two intermediates, which operate at different overpotentials. Our results show how the various protonation sites of the redox-active Mabiq ligand affect the energies and activities of HER intermediates.

#### INTRODUCTION

As an appealing fuel for electrochemical devices and solar fuel systems, H<sub>2</sub> has sparked widespread efforts to develop effective molecular catalysts for its production-with an emphasis on earth-abundant transition metal complexes.<sup>1-4</sup> While proton reduction is seemingly simple, the design of complexes that can effectively manage the series of electron transfer (ET) and proton transfer (PT) events presents significant challenges. These steps can either occur sequentially or concertedly (proton coupled electron transfer, PCET), whereby the concerted pathway can circumvent high energy intermediates and coincides with diminished overpotentials.<sup>5-7</sup> In H<sub>2</sub> evolution catalyzed by transition metal complexes, both reduction and protonation can occur solely at the metal center, such that the metal hydricity must be tuned for both favorable hydride formation and release.<sup>8,9</sup> However, the use of ligands that can take part in the chemistry has garnered significant attention, since alternate pathways promoted by the coordination environment could result in enhanced activities.<sup>10,11</sup>

Ligands can participate in the H<sub>2</sub> evolution reaction (HER) in a number of ways, acting as proton or electron storage sites, or both.<sup>10-17</sup> The hydrogenases<sup>18</sup> have inspired the design of complexes with proton relay sites that can mediate proton movement between the acid and the second coordination sphere. For example, the pendant amine groups of the wellstudied Ni-diphosphine complexes facilitate rapid transfer of the ligand-bound proton to the Ni-H, thereby affecting rapid electrocatalytic rates.<sup>13,19</sup> Hangman porphyrins, containing the pendant carboxylic acid groups, also utilize this strategy-but these complexes further highlight the entanglement of redox noninnocent ligands in such processes.<sup>20,21</sup> As a consequence of accumulated electron density on the porphyrin, a ligandcentered pathway for H<sub>2</sub> evolution becomes available. Synergistic interactions between the metal and ligand offer various routes for the HER among complexes containing redox-active ligands. Cu-thiosemicarbazone complexes operate via metal-assisted ligand-centered pathways (Scheme 1a), in

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which reduction of the copper center is required for the addition of the second proton, yet both PT and  $H_2$  release occur at the ligand.<sup>22</sup> In contrast, Co-dithiolene complexes exemplify ligand-assisted metal-centered pathways (Scheme 1b): while a conventional metal hydride is generated, both reduced and protonated dithiolene intermediates are additionally produced during the catalytic cycle.<sup>12,14,23,24</sup> In Ni-thiosemicarbazones<sup>16,25,26</sup> as well as Rh-cyclopentadiene complexes,<sup>27,28</sup> M–H and L–H tautomerism underlies  $H_2$  production. Finally, several complexes with redox-active ligands evolve  $H_2$  via purely ligand-centered pathways (Scheme 1c).<sup>17,29</sup>

Adding to the complexity of the HER is that the intermediates and catalytic pathways can differ substantially among metal complexes based on the same or similar ligands. As noted above, thiosemicarbazone complexes operate via all of the aforementioned metal-assisted ligand-centered (Scheme 1a), ligand-assisted metal-centered (Scheme 1b), and ligand-centered (Scheme 1c) mechanisms, depending on the nature of the metal ion.<sup>22,25,29</sup> Ligand modifications, and/or the geometry of a complex, can likewise affect the catalytic pathways.<sup>12,14,30</sup> The mechanisms of many systems also can be switched by changes to the reaction conditions: changes in the acid strength affect the degree of ligand participation in the HER by metal hangman porphyrins, Rh-Cp, Fe-azadithiolate, and Co-polypyridyl complexes.<sup>20,21,27,28,31,32</sup>

There have been several excellent reviews that provide a more detailed overview on the topic of noninnocent ligands in  $H_2$  evolution catalysts,<sup>10,11,33</sup> and significant progress has been made in the effective use of redox active ligands and proton relay sites for catalysis. However, while it is clear that "there is more than one way to skin a cat" when it comes to the HER, less clear are the types of motifs that support the different pathways or an overarching strategy for promoting the different pathways. Each of the above-mentioned systems is unique and affected by different conditions.<sup>34,35</sup> Saveant<sup>36</sup> highlighted competing factors concerning the use of proton relays, and the factors that allow such functional groups to provide a "boosting effect" for catalysis. Redox-active ligands similarly offer a powerful synergistic tool. However, further studies are required before one can effectively control PT and ET steps in such systems and design optimized motifs.

We have been investigating the H<sub>2</sub> evolution activity of a cobalt-Mabiq complex,  $[Co^{II}(Mabiq)(THF)](PF_6)$  (Mabiq = 2–4:6–8-bis(3,3,4,4-tetramethyldihydropyrrolo)-10–15-(2,2-biquinazolino)-[15]-1,3,5,8,10,14-hexaene1,3,7,9,11,14-N<sub>6</sub>).<sup>35</sup> We will subsequently abbreviate the corresponding cationic

complex  $[Co^{II}(Mabiq)]^+$  as  $Co_{Mbq}$ . The redox activity of the macrocyclic ligand was previously established; both the diketiminate and bipyrimidine moieties<sup>37</sup> of the Mabiq can store electrons. Our prior studies showed that H<sub>2</sub> evolution by  $Co_{Mbq}$  is preceded by the formation of an intermediate, which is likely generated upon protonation of the reduced Mabiq ligand. These studies also suggested that there is a competing pathway in operation, which leads to catalyst deactivation. We hypothesized that the Mabiq ligand could be protonated at multiple sites and that the various protonated  $Co_{Mbq}$  species displayed differing H<sub>2</sub> evolution activities. Therefore, understanding the reactivity of the  $Co_{Mbq}$  complex and its pathways can provide further insight into ET and PT steps at redoxactive ligands.

In the present work, we employ spectro-electrochemical studies in conjunction with quantum chemical calculations, to identify the precatalytic intermediate and to gain greater insight into the requirements for  $H_2$  evolution by  $Co_{Mbq}$ . We show that  $Co_{Mbq}$  can generate more than one intermediate upon cathodic activation depending on the acidic media employed. The  $H_2$  evolution overpotential differs significantly between the two intermediates, underscoring the role of the ligand protonation sites on the  $Co_{Mbq}$   $H_2$  evolution mechanisms.

#### RESULTS

**Two Intermediates in the Precatalytic Step.** In our previous study,<sup>35</sup> we demonstrated that H<sub>2</sub> evolution by  $Co_{Mbq}$  in the presence of *para*-cyanaonilinium (*p*CA, *pK*<sub>a</sub> = 7, *p*H = 4.85 in acetonitrile (MeCN), see section pH-Dependent Potential Correction, Supporting Information) occurs at a cathodic peak potential ( $E_{p,c}$ ) of ca. –1.1 V vs Fc<sup>+/0</sup> ( $V_{Fc}$ ). This potential is 300 mV cathodically shifted vs the  $[Co^{II}(Mabiq)]^+/[Co^{II}(Mabiq^{\bullet})]^0$  couple in the absence of acid (see Figure 1 inset). In addition, a series of redox events were observed at  $E_{p,c}$ = –0.58 V<sub>Fc</sub> which correspond to the addition of two electrons and at least one proton, according to



**Figure 1.** Spectral evolution of 0.2 mM  $Co_{Mbq}$  in the presence of 2 mM *p*CA in 0.1 M LiBF<sub>4</sub>/MeCN in time during bulk electrolysis. Red trace, 0 h-prior to bulk electrolysis; orange trace, 2 h; yellow trace, 4 h; green trace, 6 h; blue trace, 8 h of bulk electrolysis. Inset graph: Cyclic voltammogram of 0.2 mM  $Co_{Mbq}$  plus 2 mM *p*CA in 0.1 M LiBF<sub>4</sub>/MeCN, conducted with a glassy carbon electrode in the RDE setup, at 100 mV/s, under an Ar atmosphere. The vertical dashed black line indicates the applied potential for bulk electrolysis.

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an electrochemical–chemical–electrochemical (ECE) mechanism (a subsequent protonation, with an electrochemical–chemical–chemical–electrochemical–chemical (ECEC) mechanism could not be excluded). No change in the absorption spectrum was observed upon the addition of *p*CA to a solution of the divalent  $Co_{Mbq}$  complex, further indicating that any modification to  $Co_{Mbq}$  occurs only after cathodic reduction.<sup>35</sup>

On the basis of our findings, we proposed a mechanism in which the reduction and protonation processes involved the Mabiq ligand (see Scheme 2). In the current study, we set out

Scheme 2. Proposed ECE pathway for formation of the precatalytic species. Possible protonation sites studied in this work are color-coded and assigned distinct labels. The candidate protonation sites were derived from the spin density of the  $[Co^{II}(Mabiq^{\bullet})]^{0}$  species, calculated with DFT



to characterize the intermediate through a series of spectroelectrochemical experiments. The distinctive spectroscopic features of the electron transfer series of Co-Mabiq compounds<sup>37,38</sup> are advantageous in this regard. The previously isolated  $[Co(MabiqH_2)]^{,38}$  which results from protonation of the two electron reduced  $[Co^{II}(Mabiq^{\bullet \bullet})]^{-}$ , is inconsistent with the ECE pathway, and was previously ruled out as an intermediate.<sup>35</sup> However, given the electronic structure of the one electron reduced  $[Co^{II}(Mabiq^{\bullet})]^{0}$  species, several protonation sites still could be envisioned (Scheme 2). Depending on the extent of metal ion involvement, the resultant protonated precatalytic species could contain either a  $Co^{I}$ ,  $Co^{II}$  or  $Co^{III}$  center.

To generate the precatalytic intermediate, we now carried out bulk electrolysis in an RDE setup, using 0.2 mM Co<sub>Mba</sub> in the presence of 2 mM pCA (Co/pCA = 1:10; 0.1 M LiBF<sub>4</sub>/ MeCN), at a potential of  $-0.84 V_{Fc}$  (see Figure 1, vertical line in inset graph). An 80% conversion of  $Co_{Mbq}$  (for details, see Experimental Section, eq 1) to a precatalytic species referred to as  $Co_{Mbq}$ -H<sup>2</sup> was achieved following 8 h of applied potential. The spectral evolution of the Co/pCA solution over this period shows a slight alteration in the band shape and position of the [Co<sup>II</sup>(Mabiq)]<sup>+</sup> transitions in the 500–700 nm region. Furthermore, a prominent new band, with  $\lambda_{max} = 411$  nm, appears after 4 h. The final spectrum of the Co/pCA solution after 8 h of bulk electrolysis does not resemble any of the previously synthesized [Co<sup>III</sup>(Mabiq)]<sup>2+</sup>, [Co<sup>II</sup>(Mabiq<sup>•</sup>)]<sup>0</sup>, [Co<sup>II</sup>(Mabiq••)]<sup>-</sup>, or [Co(MabiqH<sub>2</sub>)] compounds.<sup>37,38</sup> Notably, no new features are observed in the near IR region; transitions in this region are indicative of the one-electron

reduced Mabiq ligand. However, the sharp, intense transition at 411 nm in the final product spectrum suggests that the ligand has been modified. The final species generated at the end of the bulk electrolysis experiment features the distinctive 411 nm band and corresponds to one precatalytic species, for now denoted as  $Co_{Mbq}$ -H<sup>2</sup>. Comparison of the absorption spectrum at the end of bulk electrolysis with quantum chemical calculations indicate that this species is protonated at the diketiminate site  $CoMbq-H^{DK1}$ ; see section Calculated Absorption Spectra Identify the Intermediates. We note that comparison of the spectra after 6 and 8 h of bulk electrolysis shows a slight decrease of the absorbance around 411 nm that might stem from a decrease in a broader background feature. This could correspond to the generation of more than one intermediate in the bulk electrolysis experiment, which is consistent with the lack of an isosbestic point in the spectral evolution. The proportion of the two species seems to be time dependent.

The behavior of the bulk electrolysis product with respect to  $H_2$  evolution was subsequently examined by cyclic voltammetry (CV). The CV of  $Co_{Mbq}$ - $H^2$  shows several important differences from the CV of the initial  $Co_{Mbq}/pCA$  solution. A redox event at  $-0.63 V_{Fc}$  (blue trace Figure 2) is still present,



Figure 2. Cyclic voltammograms (including inset graph) of 0.2 mM  $Co_{Mbq}$  plus 2 mM *p*CA in 0.1 M LiBF<sub>4</sub>/MeCN; solid green trace, prior to bulk electrolysis; solid blue trace, after bulk electrolysis, conducted with a glassy carbon electrode in the RDE setup, at 100 mV/s, under an Ar atmosphere. The dashed black trace shows the CV of 2 mM *p*CA on the glassy carbon disk only.

albeit of lower current magnitude—roughly 1/5 compared to the CV prior to bulk electrolysis. Considering the incomplete conversion of  $Co_{Mbq}$  to  $Co_{Mbq}$ -H<sup>2</sup> during bulk electrolysis (roughly 80%), we assign the redox event in this region after bulk electrolysis to residual  $Co_{Mbq}$ . Any current observed below  $-0.84 V_{Fc}$  (just after the formation of the precatalytic species) stems from H<sub>2</sub> evolution by the electrochemically formed intermediates. Hence, a change in the CV in this lower potential region correlates with a change in the intermediate formed. Indeed, the CV after bulk electrolysis displays only a minor reduction feature at  $-0.98 V_{Fc}$  which we attribute to the same catalytic H<sub>2</sub> evolution event occurring at  $-1.1 V_{Fc}$  before bulk electrolysis, but with a significantly reduced contribution to the overall H<sub>2</sub> evolution pathway. The predominant current increase instead occurs at  $-1.32 V_{Fc}$ . This event was also observed in the CV of the initial  $Co_{Mbq}/pCA$  solution, as a shoulder to the primary catalytic process. Therefore,  $Co_{Mbq}$ - $H^2$ , the species characterized by the 411 nm absorption band, facilitates  $H_2$  evolution at  $-1.32 V_{Fc}$  and is generated on the time scale of the electrocatalytic CV experiments. Its formation accounts for the loss of activity that we previously observed in the OEMS studies when we examined  $H_2$  evolution after 8 h of applied potential at  $-1.1 V_{Fc}$ .<sup>35</sup> The fact that  $Co_{Mbq}$ - $H^2$  does not evolve  $H_2$  at  $-1.1 V_{Fc}$  again indicates that there is a second but elusive intermediate, which we refer to as  $Co_{Mbq}$ - $H^1$ . The theoretical investigations presented later in this article will show that this species is most likely protonated at the imine site CoMbq- $H^{Im}$ .

The combined data thus demonstrate that the initial proton coupled reduction processes at -0.63 V<sub>Fc</sub> give rise to two distinct intermediates and that two competing pathways for H<sub>2</sub> evolution are available to the complex (Scheme 3). One of

Scheme 3. Formation of the Two Precatalytic Species Based on Competing ECE Pathways



these intermediates  ${\bf Co_{Mbq}}{\text{-}}{\bf H}^1$ , represents the active species that evolves  $H_2$  at  $-1.1~V_{Fc}.$  The other intermediate,  ${\bf Co_{Mbq}}{\text{-}}{\bf H}^2$ , is not inactive, as we had initially presumed based on OEMS studies. Rather, as noted above,  ${\bf Co_{Mbq}}{\text{-}}{\bf H}^2$  requires a larger overpotential to affect  $H_2$  production.

The fact that catalysis is observed at  $-1.1 V_{Fc}$  in the beginning of the bulk electrolysis, yet  $\mathbf{Co}_{Mbq}$ - $\mathbf{H}^2$  is the dominant species present after 8 h of applied potential resulting in  $H_2$  evolution around  $-1.32 V_{Fc}$  implies that  $\mathbf{Co}_{Mbq}$ - $\mathbf{H}^1$  is formed from  $\mathbf{Co}_{Mbq}$  but is not stable over the time period of the bulk electrolysis.

**Generation of Intermediates Depends on Acid Strength.** We subsequently carried out electrochemical studies in the presence of a weaker acid, *para*-bromoanilinium (*p*BrA, *pK*<sub>a</sub> = 9.43, *p*H = 6.06 in MeCN; see section pHdependent potential correction, Supporting Information)<sup>39,40</sup> to examine whether the acid strength would affect the distribution of the two postulated intermediates. As previously noted, the acid strength can have a significant influence on the mechanism and led to the formation of varied intermediates in the HER pathway of other molecular catalysts.<sup>31,32,34</sup>

The CV of 0.2 mM  $Co_{Mbq}$  in the presence of 2 mM *p*BrA (Co/*p*BrA = 1:10; 0.1 M LiBF<sub>4</sub>/ MeCN) displays similar features to that of the Co/*p*CA solution: a series of precatalytic redox events are followed by catalytic H<sub>2</sub> evolution at more negative potentials (Figure 3b). [The precatalytic steps are anodically shifted as expected for a proton dependent process. Analysis of the current magnitudes before and after bulk electrolysis indicated conversion between  $Co_{Mbq}$ -H<sup>2</sup> and  $Co_{Mbq}$  may not be fully reversible. See the SI for further details of the analysis.] A small wave is still observed at -1.1 V<sub>Fc</sub> the predominant H<sub>2</sub> evolution potential for Co/*p*CA (green trace, Figure 3a). After the 8 h of applied potential at



**Figure 3.** Cyclic voltammograms of 0.2 mM Co<sub>Mbq</sub> plus 2 mM (a) pCA or (b) pBrA in 0.1 M LiBF<sub>4</sub>/MeCN; green trace, prior to bulk electrolysis; blue trace, after bulk electrolysis, conducted with a glassy carbon electrode in the RDE setup, at 100 mV/s, under an Ar atmosphere. The vertical dashed lines are positioned at -1.32 V<sub>Fc</sub> and -1.1 V<sub>Fc</sub> respectively. The arrows represent the applied potentials for bulk electrolysis experiments. The stars indicate cathodic peak potentials for the precatalytic step.

 $-0.95 V_{Fc}$ —the potential of the precatalytic process in the case of Co/pBrA—the shoulder at  $-1.1 V_{Fc}$  completely disappears (blue trace, Figure 3b). Interestingly,  $H_2$  evolution by the Co/ pBrA solution occurs at -1.32 V<sub>Fc</sub> (green trace, Figure 3b), which coincides with the potential for H<sub>2</sub> evolution by the  $Co_{Mbq}$ -H<sup>2</sup> intermediate identified in the Co/pCA experiments. The catalytic process at -1.32 V<sub>Fc</sub> is observable both before and after bulk electrolysis with the same current magnitude. Therefore,  $Co_{Mbq}$ -H<sup>2</sup> is generated in the presence of both *p*BrA and pCA. However, the formation of and  $H_2$  evolution from  $Co_{Mbq}$ -H<sup>2</sup> dominate using pBrA as a proton source. The formation of  $Co_{Mbq}$ -H<sup>1</sup> appears to be negligible with the weaker acid, suggesting that pBrA is not strong enough to protonate the site that leads to this species, such that no significant  $H_2$  evolution is observed at  $-1.1 V_{Fc}$ . The combined Co/pCA and Co/pBrA data further signify that two competing pathways for H<sub>2</sub> evolution are available, which are dependent on the acid strength. Nevertheless, after 8 h of applied potential, the more stable  $Co_{Mbq}$ -H<sup>2</sup> intermediate accumulates with both pCA and pBrA, and only the pathway for H<sub>2</sub> production at higher overpotentials is available.

The nature of the intermediates was further examined by absorption spectroscopic studies in conjunction with bulk electrolysis of a Co/pBrA solution carried out for 8 h of applied potential at -0.95 V<sub>Fc</sub>—just below the activation region for the weaker acid (vertical line, inset, Figure 4a). In Co/pBrA, Co<sub>Mbq</sub>-H<sup>2</sup> is unquestionably produced, as evidenced by the appearance of the distinctive absorbance at 411 nm (Figure 4). This species emerges earlier (solid blue line, Figure 4a) in comparison to its evolution with Co/pCA. The characteristic absorbance bands of Co<sub>Mbq</sub> between 500 and 600 nm are unaltered (solid blue line and dashed black line, Figure 4c), indicative of residual Co<sub>Mbq</sub> in the solution, which is consistent with the 60% conversion of Co<sub>Mbq</sub> to Co<sub>Mbq</sub>-H<sup>2</sup> after 8 h of applied potential in Co/pBrA (see Experimental Section, eq 1).



**Figure 4.** UV–vis absorption spectra of 0.2 mM  $Co_{Mbq}$  in the presence of 2 mM *p*BrA (Co/*p*BrA) or *p*CA (Co/*p*CA) in 0.1 M LiBF<sub>4</sub>/MeCN in time during bulk electrolysis at potentials of -0.95 V<sub>Fc</sub> or -0.84 V<sub>Fc</sub>, respectively. (a) 2 h, (b) 4 h, (c) 8 h of potential hold. Dashed black line, 0.2 mM  $Co_{Mbq}$ ; solid red trace, Co/*p*CA; solid blue trace, Co/*p*BrA.

The lower conversion of  $Co_{Mbq}$  to  $Co_{Mbq}\text{-}H^2$  in Co/pBrA compared to Co/pCA partly explains the differences in absorbance between 500 and 600 nm in the respective spectra, as well as the higher current observed in the activation region in the CV after bulk electrolysis. The final products generated after electrolysis with either acid have virtually the same absorption intensity at 411 nm. However, the additional absorbance bands in the pCA experiment, blue-shifted from the  $Co_{Mbq}$ -H<sup>2</sup> associated absorbance at 411 nm, can be correlated to the  $Co_{Mbq}$ -H<sup>1</sup> intermediate since  $Co_{Mba}$ -H<sup>1</sup> is dominant at the beginning of the bulk electrolysis with pCA based on the CV but not generated in any appreciable amount using pBrA. Thus, both the CV and spectroscopic data further evidence that two intermediates,  $\hat{Co}_{Mbq}$ -H<sup>1</sup> and  $Co_{Mbq}$ -H<sup>2</sup>, arise from protonation of two distinct Mabiq sites, with differing  $pK_a$ 's.

Acid Strength Influence on the Mechanism. Electrochemical studies in the presence of *para*-anisidinium (*p*An; *pK*<sub>a</sub> = 11.86, pH = 7.28 in MeCN)<sup>39,40</sup> were carried out to further assess the acid strength effect on the HER. Figure 5 compares the CVs of  $Co_{Mbq}$  in the absence of acid<sup>35</sup> with the CVs obtained upon the addition of the three different acids—*pCA*, *pBrA*, and *pAn*. The additional oxidation features above 0 V<sub>Fc</sub> originate from the acid source itself. In the presence of both *pCA* (orange trace, Figure 5a) and *pBrA* (orange trace, Figure



Figure 5. Cyclic voltammograms of 0.2 mM Co<sub>Mbq</sub> plus 2 mM (a) pCA, (b) pBrA, or (c) pAn in 0.1 M LiBF<sub>4</sub>/MeCN; blue trace, 0.2 mM Co<sub>Mbq</sub> in the absence of acid source; orange trace, in the presence of acid source; conducted with a glassy carbon electrode in the RDE setup, at 100 mV/s, under an Ar atmosphere. For the CV in the absence of acid, the redox couples of Co<sub>Mbq</sub> are assigned as follows:  $[Co^{III}(Mabiq)]^{2+}/[Co^{II}(Mabiq)]^+$ ,  $E_{p,c}$ = 0.08 V;  $[Co^{II}(Mabiq)]^+/[Co^{II}(Mabiq^*)]^0$ , -0.76 V;  $[Co^{II}(Mabiq^*)]^0/[Co^{II}(Mabiq^*)]^-$ , -1.56 V<sub>FC</sub>.

5b), the precatalytic event is anodically shifted compared to the  $[Co^{II}(Mabiq)]^+/[Co^{II}(Mabiq^{\bullet})]^0$  couple. In the presence of pAn, two one-electron redox events are again observed prior to H<sub>2</sub> evolution. However, the first reduction occurs at a potential that is identical to that of the [Co<sup>II</sup>(Mabiq)]<sup>+</sup>/  $[Co^{II}(Mabiq^{\bullet})]^0$  couple, while the following reductive event is 160 mV cathodically shifted. To verify the proton dependency of the processes, CVs were recorded at varied pAn concentration (Figure S1, Supporting Information). From the calculated theoretical potential shift based on the Nernst equation (eq S4, Supporting Information) and the experimentally observed [pAn]-dependent potential shifts, we confirm that only the second reduction feature at  $-0.95 V_{Fc}$ is proton-dependent. The redox events preceding H<sub>2</sub> evolution are therefore consistent with an EEC mechanism, rather than the ECE process observed for the two stronger acids. The proton activity of *p*An is not high enough to protonate the one electron reduced form of  $\hat{Co}_{Mbq'}$  and protonation only becomes feasible after the addition of the second electron. H<sub>2</sub> evolution also requires further reduction of the complex
and an even higher overpotential ( $E_{\rm cat} = -1.48 V_{\rm Fc}$ ). Since the present study was focused on resolving the ECE mechanism available to  ${\bf Co}_{\rm Mbq\prime}$  we did not characterize the Co/pAn intermediates further. Nevertheless, the studies with pAn clearly demonstrate the effect of acid strength on the Co-Mabiq catalyzed HER—the proton source affects the formation of precatalytic intermediates and can alter the order of PT and ET steps.

On the basis of the experimental results, we conclude that two intermediates are generated in the electrocatalytic  $H_2$ evolution pathway using acids with  $pK_a$ 's in the range of 7.0 to 9.43,  $Co_{Mbq}$ -H<sup>1</sup> and  $Co_{Mbq}$ -H<sup>2</sup> (Scheme 4). However, over

Scheme 4.  $Co_{Mbq}$  Mechanisms and Initially Formed Intermediates in Different Acidic Media



time, any  $\mathbf{Co}_{\mathbf{Mbq}}$ - $\mathbf{H}^1$  generated in the reaction with *p*CA also is depleted.  $\mathbf{Co}_{\mathbf{Mbq}}$ - $\mathbf{H}^2$  features a distinctive 411 nm absorption band and is associated with a higher overpotential for  $\mathbf{H}_2$ evolution. Attempts to crystallize or otherwise experimentally characterize this intermediate were unsuccessful. Consequently, we performed quantum chemical calculations to examine the relative energies and spectroscopic properties of possible protonation products and thereby identify  $\mathbf{Co}_{\mathbf{Mbq}}$ - $\mathbf{H}^1$ and  $\mathbf{Co}_{\mathbf{Mbq}}$ - $\mathbf{H}^2$ . The computational studies focused on both the protonated one- and two-electron reduced species.

Thermodynamics Calculations Specify Favorable Protonation Sites. We started our theoretical investigation with protonation of the [Co<sup>II</sup>(Mabiq<sup>•</sup>)]<sup>0</sup> complex, in accord with the established mechanism for the precatalytic event, where the first proton transfer coincides with the first electron transfer. On the basis of the electronic structure of  $[Co^{II}(Mabiq^{\bullet})]^{0,37}$  we identified four molecular sites where protonation is likely to occur (Figure 6)-one on the metal center and three on the ligand. We subsequently examined the reduced forms of these species, corresponding to the ECE mechanism determined from the experimental studies, and the products of the above-described bulk electrolysis studies. We denote each of the calculated candidate structures with a unique name (Figure 6) and assign a structure to the experimentally determined intermediates  $Co_{Mbq}$ -H<sup>1</sup> and  $Co_{Mbq}$ -H<sup>2</sup> at the end of the theoretical investigation.

We first optimized the structures of the four cations and the corresponding reduced intermediates, as well as that of *p*CA in its protonated (*p*CA) and deprotonated form (D-*p*CA) at the CAM-B3LYP level of theory (see Computational Details) and calculated the Gibbs free energies of protonation  $\Delta G_{\text{prot}}$  as the difference between reactant and product free energies *G*:

$$\Delta G_{\text{prot}} = (G_{\text{D-}p\text{CA}} + G_{\text{intermediate}}) - (G_{p\text{CA}} + G_{[\text{Co}^{II}(\text{Mabiq}^{\bullet})]^0})$$
(2)



Figure 6. Structures of investigated intermediates after the addition of one proton to the one-electron reduced  $[Co^{II}(Mabiq^{\bullet})]^0$ , referred to by the "+" superscript. Subsequent reduction of these intermediates will be referred to without the "+" superscript in the following sections.

Table 1. Calculated Gibbs Free Reaction Energies for the Protonation of  $[Co^{II}(Mabiq^{\bullet})]^{0}$  with pCA ( $\Delta G_{prot}$ ) to Form Four Different Cationic Species, and for the Subsequent Reduction of the Cations ( $\Delta G_{red}$ ) to Yield Neutral Intermediates

cation	$\Delta G_{\rm prot}  [{\rm kJ/mol}]$	intermediate	$\Delta G_{\rm red}  [{\rm kJ/mol}]$
$(Co_{Mbq}-H^{DK1})^+$	-14.7	Co <sub>Mbq</sub> -H <sup>DK1</sup>	-517.5
$(Co_{Mbq}-H^{DK2})^+$	-26.7	Co <sub>Mbq</sub> -H <sup>DK2</sup>	-527.1
$(Co_{Mbq}-H^{Co})^+$	-42.2	Co <sub>Mbq</sub> -H <sup>Co</sup>	-360.6
$(Co_{Mbq}-H^{Im})^+$	-108.9	$\mathrm{Co}_{\mathrm{Mbq}}\text{-}\mathrm{H}^{\mathrm{Im}}$	-299.1

Analogously, the Gibbs free energies of reduction  $\Delta G_{red}$  were calculated as the difference between the optimized cationic and neutral species (Table 1). The neutral diketiminate products  $\mathbf{Co}_{Mbq}$ - $\mathbf{H}^{DK1}$  and  $\mathbf{Co}_{Mbq}$ - $\mathbf{H}^{DK2}$  are significantly more stable (~200 kJ/mol) than the other two investigated species. Thus their formation is thermodynamically favored upon the addition of two electrons and one proton to  $\mathbf{Co}_{Mbq}$ . However, considering only the protonation step after the initial one-electron reduction of  $\mathbf{Co}_{Mbq}$  (i.e direct protonation of  $[\mathrm{Co}^{II}(\mathrm{Mabiq}^{\bullet})]^{0}$ ), we observe the opposite trend. Here, the imine site ( $\mathbf{Co}_{Mbq}$ - $\mathbf{H}^{Im}$ ) is favored for protonation, followed by the cobalt center ( $\mathbf{Co}_{Mbq}$ - $\mathbf{H}^{Co}$ ). The diketiminate-based products have extraordinarily high protonation energies. The reason for this is the strong structural distortion and the breaking of ligand aromaticity introduced by protonation at any of the diketiminate sites (Figure S2, Supporting Information).

The opposite trends for the thermodynamics of protonation and reduction allow us to draw conclusions about the coupling of the two steps in the reaction mechanism: If the proton addition is strongly coupled to the first electron added to  $Co_{Mbq}$ , forming  $[Co^{II}(Mabiq^{\bullet})]^0$ , the protonation step becomes a limiting factor, and the most stable cation  $(Co_{Mbq} \cdot H^{Im})^+$  may be formed as a side product. A strong acid would be beneficial for this reaction pathway as the one electron reduced form  $[Co^{II}(Mabiq^{\bullet})]^0$  can be readily stabilized by proton addition. On the other hand, if the

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proton addition is strongly coupled to the second electron in the ECE activation process, we expect formation of the most stable reduced intermediate, i.e., one (or both) of the diketiminate products. The CV data in Figure 3 show the apparent dissociation of EC and E mechanisms in the precatalytic process with the stronger acid, pCA, i.e., the two electron addition steps are well enough separated in potential to generate two distinct reduction peaks in the current profile of the CV. The separation of the ECE mechanism is not observed with the weaker acid, pBrA, however, leading only to one broad reduction event in the precatalytic step. The weak acid is not able to protonate the imine site and can therefore not stabilize the cation, which leads to direct formation of the most stable protonated and two electron reduced intermediate: one of the diketiminate products. Therefore, only one species,  $Co_{Mbq}$ -H<sup>2</sup>, is formed with the weaker acid pBrA, while the stronger acid pCA initially leads to  $Co_{Mbq}$ -H<sup>1</sup>, which disappears over time.

Calculated Absorption Spectra Identify the Intermediates. Excited states of Co-Mabiq complexes are an especially challenging problem for most computational methods. Time-dependent density functional theory (TD-DFT) is widely used to compute excited states of transition metal complexes<sup>41-45</sup> due to its comparably low cost and its ability to include electron correlation, depending on the chosen functional. We performed initial test calculations for the [Co<sup>II</sup>(Mabiq<sup>•</sup>)]<sup>0</sup> species using the CAM-B3LYP functional (Figure S3, Supporting Information) and found that reliable band assignment to the experimental spectra was not possible with TD-DFT, due to the strong multiconfigurational character of the open-shell singlet ground state. Therefore, we decided to use the DFT/MRCI method,<sup>46-51</sup> which combines a multireference configuration interaction (MRCI) ansatz with orbitals derived from a ground state DFT calculation, thereby ideally recovering both dynamic and static electron correlation at a feasible cost. DFT/MRCI has proven to produce highly accurate absorption spectra for molecules and complexes with either closed-shell or single-open-shell ground states.<sup>46</sup> On the downside, open-shell ground states with more than one unpaired electron, as is the case for most of the investigated Co-Mabiq complexes, are known to pose a particular challenge.

Using a large basis set with diffuse functions in the DFT part of the calculation helped to overcome some of the issues and made it possible to compute an absorption spectrum for [Co<sup>II</sup>(Mabiq<sup>•</sup>)]<sup>0</sup>, where the relevant experimental bands are unambiguously reproduced (Figure 7). All bands have strong metal contributions originating from the  $d_{xz}$ ,  $d_{yz}$ , and  $d_{z2}$ orbitals. Below 450 nm, doubly excited states start to dominate. The calculated absorption lines between 500 and 600 nm are red-shifted compared to the measurement, but the double-peak absorption is clearly visible. Both peaks correspond to  $d-\pi$  transitions from the  $d_{xz}$  and  $d_{yz}$  orbitals of the metal to the ligand. Though the oscillator strength of the band at 411 nm is quantitatively too small, we argue that the basic band structure is reproduced well enough to use this method for predicting which intermediates are formed in the experiments.

We therefore calculated DFT/MRCI absorption spectra for the four possible species after the addition of two electrons and one proton to  $[{\rm Co}^{II}({\rm Mabiq})]^+$  (Figure 8). Protonation at the cobalt center  $({\rm Co}_{Mbq}\text{-}{\rm H}^{Co})$  produces a strong and broad absorption band around 411 nm but also leads to absorption in



**Figure 7.** DFT/MRCI spectrum of  $[Co^{II}(Mabiq^{\bullet})]^0$  in comparison to the synthesized  $[Co^{II}(Mabiq^{\bullet})]^0$  absorption spectrum.<sup>37</sup> The line spectrum was convoluted with Gaussians with fwhm = 0.24 eV. The convoluted spectrum was normalized such that the highest absorption is one.

the red and NIR spectral region beyond 700 nm. As this is not observed experimentally (Figure 1), we conclude that the metal is not protonated at this stage of the reaction, in agreement with conclusions from the previous study.<sup>35</sup> Out of the four computed spectra, the one for  $Co_{Mbq}$ -H<sup>DK1</sup> agrees best with the experimental spectrum. It explains the rising absorption band at 411 nm, which is blue-shifted by ~30 nm in the calculations, as well as the shoulder at 340 nm and parts of the absorption after 600 nm. The other diketiminate product  $Co_{Mbq}$ -H<sup>DK2</sup> also shows an absorption line at 411 nm, but the oscillator strength is much lower than for  $Co_{Mbq}$ -H<sup>DK1</sup>. Since the rest of the spectral profile agrees well with the experimental spectrum, and  $Co_{Mbq}$ -H<sup>DK2</sup> is also the thermodynamically most stable product, closely followed by  $Co_{Mbq}$ -H<sup>DK1</sup>, we do not rule out the formation of both diketiminate products at this point. That said, our calculated absorption spectra indicate  $Co_{Mbq}$ -H<sup>DK1</sup> as the main product  $Co_{Mbq}$ -H<sup>2</sup> after bulk electrolysis.

For the spectrum of  $\mathbf{Co}_{Mbq}\text{-}\mathbf{H}^{Im}$  , the maximum number of 50 electronic states that could be calculated with the DFT/MRCI program prevented going below 504 nm. The corresponding cation spectrum (Figure S4, Supporting Information) shows no significant absorption at 411 nm, indicating that  $Co_{Mbq}\text{-}H^{Im}$ is not the final product after two-electron-one-proton addition to  $[Co^{II}(Mabiq)]^+$ . However, both the cation  $(Co_{Mbq}-H^{Im})^+$ and the reduced species  $\mathbf{Co}_{Mbq}\text{-}\mathbf{H}^{Im}$  exhibit broad absorption bands in the 500-600 nm region. Experimentally, absorption in this spectral range does not change during bulk electrolysis in the presence of pBrA, but it decreases over time in the presence of pCA. The spectral profile of the measured absorption bands fits that of the isolated Co<sub>Mbg</sub> complex, indicating that residues of the reactant are present in the final reaction mixture. However, this does not explain why the band decreases only with pCA. Since the CV results indicate the presence of another intermediate,  $Co_{Mbq}$ -H<sup>1</sup>, which evolves H<sub>2</sub> at -1.1 V and only forms in the presence of *p*CA, we attribute part of the absorbance between 500 and 600 nm in the presence of pCA to the imine-protonated species. Therefore, the  $Co_{Mbq}$ -H<sup>1</sup> species corresponds to the product arising from protonation of the imine group,  $Co_{Mbq}$ -H<sup>Im</sup>. According to our DFT calculations (Table 1), protonation at

According to our DFT calculations (Table 1), protonation at the imine site yields the thermodynamically most stable cation but the least stable reduced product. Therefore, we investigated a side reaction with *p*CA, where the cation  $(Co_{Mbq}-H^{Im})^+$  forms initially and then slowly transforms to the more stable  $Co_{Mbq}-H^{DK1}$  product upon reduction, decreasing



**Figure 8.** DFT/MRCI spectra obtained for the four investigated species after the addition of two electrons and one proton to  $[Co^{II}(Mabiq)]^+$  in comparison to the experimentally obtained spectrum after 8 h of bulk electrolysis in the presence of 10 equiv of *p*CA. The highest excited state for  $Co_{Mbq}$ -H<sup>Im</sup> that could be calculated with the DFT/MRCI method is located at 504 nm. Line spectra were convoluted with Gaussians with fwhm = 0.24 eV. Convoluted spectra were normalized such that the highest absorption is one, except for  $Co_{Mbq}$ -H<sup>Im</sup> which was normalized to 0.1 to reflect the low oscillator strength in that spectral region.

the absorbance around 500-600 nm over time. However, the calculated free energy activation barrier of 162 kJ/mol seems too high for this process to occur under experimental conditions. From this, we conclude that two decoupled reaction pathways are possible in the presence of *p*CA, one leading to the species protonated at the diketiminate site, the other one leading to the imine-protonated intermediate.

To test how well the two intermediates can explain the experimental absorption spectrum, we fitted a linear combination of the calculated spectra for  $Co_{Mbq}$ - $H^{DK1}$  and  $Co_{Mbq}$ - $H^{Im}$  to the experimental spectrum after bulk electrolysis with *p*CA (Figure 9). The majority of the experimental spectrum is



**Figure 9.** Fitted absorption spectrum composed of a linear combination of DFT/MRCI spectra of the diketiminate product  $Co_{Mbq}$ - $H^{DK1}$  and the imine product  $Co_{Mbq}$ - $H^{Im}$  in comparison to the experimentally obtained spectrum after 8 h of bulk electrolysis in the presence of 10 equiv of *p*CA. The fit was conducted in the range 320–700 nm.

explained by  $Co_{Mbq}$ - $H^{DK1}$ , underscoring that  $Co_{Mbq}$ - $H^{DK1}$  is an important intermediate in the reaction mechanism. As expected, the absorption beyond 500 nm can be partly attributed to the  $Co_{Mbq}$ - $H^{Im}$  species. As the rest of the 500–600 nm bands fit the measured spectrum of  $Co_{Mbq'}$  the relative contribution of  $Co_{Mbq}$ - $H^{Im}$  to the fit given in Figure 9 is an upper bound to the real share of  $Co_{Mbq}$ - $H^{Im}$  in the spectrum.

#### DISCUSSION

**Precatalytic Species.** The combined experimental and computational studies point to the formation of two intermediates in the precatalytic ECE processes,  $Co_{Mbq}$ -H<sup>DK1</sup> and  $Co_{Mbq}$ -H<sup>Im</sup>. The persistent precatalytic complex after 8 h of applied potential, using either *p*CA or *p*BrA, is  $Co_{Mbq}$ -H<sup>DK1</sup>. This compound acquires a proton at the diketiminate carbon and effectively describes a ligand-based hydride. In contrast, the formation of  $Co_{Mbq}$ -H<sup>Im</sup> involves the reduction of both the ligand and the metal center, such that this species is best described as  $[Co^{I}(MabiqH^{\bullet})]^{0}$ . The proton is added to the bridging imine-nitrogen atom of the Mabiq ligand. The generation of significant amounts of  $Co_{Mbq}$ -H<sup>Im</sup> requires a stronger acid, and this species is nevertheless depleted over time.

The reason for the loss of Co<sub>Mbq</sub>-H<sup>Im</sup> is not clear. However, three mechanisms could account for the loss of Co<sub>Mba</sub>-H<sup>Im</sup> (Scheme 5): (i) There may be an indirect conversion to  $Co_{Mbq}$ ·H<sup>DK1</sup> via the original  $Co_{Mbq}$  complex. A homolytic pathway of  $H_2$  evolution via the reaction of two  $Co_{Mbq}$ -H<sup>Im</sup> molecules to form the one-electron reduced  $[Co^{II}(Mabiq^{\bullet})]^0$ complex is unlikely, since no  $H_2$  evolution above the pCA background was observed at  $-0.8 \ V_{Fc}$  in our earlier study.<sup>35</sup> (ii) The chemical instability of the  $\mathbf{Co}_{Mbq}\text{-}\mathbf{H}^{Im}$  intermediate could result in a completely deactivated form of the catalyst. The ratio of catalytic currents at  $-1.1 V_{Fc}$  and  $-1.32 V_{Fc}$  in the CV prior to bulk electrolysis cannot be used to determine the  $Co_{Mbq}\text{-}H^{Im}/Co_{Mbq}\text{-}H^{DK1}$  ratio, as the turnover numbers for the two intermediates are unknown. It could be that only a minor portion of  $Co_{Mbq}$  is converted to  $Co_{Mbq}\text{-}H^{Im}\text{-}$  despite significant  $H_2$  evolution at -1.1  $V_{Fc}$ . Therefore, the degradation of  $Co_{Mbq}$ -H<sup>Im</sup> might not be observable in the absorption spectrum. Finally, (iii) one can envision a mechanism for interchange of the two intermediates-e.g., an equilibrium or comproportionation process-that allows for the accumulation of  $\dot{Co}_{Mbq}$ -H<sup>DK1</sup> over time in the presence of pCA with applied potential. The bridging imine groups of the Mabiq ligand correspond to the most favorable protonation sites in the one electron reduced Co-Mabiq complex, ( $Co_{Mbq}$ -



## Scheme 5. Possible Loss Channels of the $\mathrm{Co}_{\mathrm{Mbq}}\text{-}\mathrm{H}^{\mathrm{Im}}$ Intermediate^

<sup>*a*</sup>Indirect conversion to  $Co_{Mbq}H^{DK1}$  via pathway i would involve H<sub>2</sub> evolution at -0.8 V<sub>Fc</sub>, which is not observed experimentally. Chemical degradation via ii or direct conversion via pathway iii could be alternative options, though the latter is unlikely due to the high kinetic barrier.

Scheme 6. Possible HER Pathways Involving the  $Co_{Mbq}$ -H<sup>DK1</sup> (Top Pathway) and  $Co_{Mbq}$ -H<sup>Im</sup> (Bottom Pathway) Intermediates<sup>4</sup>



"The positions of the unpaired electron are based on DFT-derived spin densities (see Scheme 2 and Figure 10) and only show one of many possible resonance forms. Newly added electrons are highlighted in red in each reduction step.

 $H^{Im}$ )<sup>+</sup>. Among the protonated two-electron reduced forms we investigated,  $Co_{Mbq}$ - $H^{Im}$  was associated with the highest energy. Indeed, intramolecular PT has been established for the HER mechanism of the Cu-thiosemicarbazone complexes.<sup>22</sup> However, as noted above, the computational results indicate that the barrier for conversion between  $Co_{Mbq}$ - $H^{Im}$ and  $Co_{Mbq}$ - $H^{DK1}$  is too large. This calculation, however, only signifies that the direct conversion of both intermediates after two-electron–one-proton addition is unlikely. An interchange between the cationic species or from one cationic species to a fully activated form (i.e.,  $(Co_{Mbq}-H^{Im})^+$  to  $Co_{Mbq}-H^{DK1}$ ) might still be feasible. Our evidence currently supports formation of the two intermediates via two decoupled pathways, though the experimentally observed disappearance of  $Co_{Mbq}-H^{Im}$  over time is not understood yet from a mechanistic point of view.

**HER by Co<sub>Mbq</sub>.**  $H_2$  evolution by the modified cobalt complexes produced in the precatalytic processes clearly still requires further reduction and protonation of  $Co_{Mbq}$ - $H^{Im}$  or  $Co_{Mbq}$ - $H^{DK1}$ , and we therefore also considered the subsequent HER mechanisms (Scheme 6).

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Figure 10. Broken-symmetry DFT derived spin density plots for the intermediates generated in an (EC)EE mechanism from  $Co_{Mbq'}$  [ $Co^{II}(Mabiq)$ ]<sup>+</sup>.

Scheme 7. Proposed Pathways for  $H_2$  Evolution from  $Co_{Mbq}$ - $H^{DK1a}$ 



<sup>a</sup>The positions of the unpaired electron are based on DFT-derived spin densities (see Figure 10) and only show one of many possible resonance forms. Newly added electrons are highlighted in red in each reduction step.

The electronic structures of the two precatalytic complexes are highly distinctive. As noted,  $Co_{Mbq}$ -H<sup>Im</sup> is a low-valent Co(I) complex, whereas  $Co_{Mbq}$ -H<sup>DK1</sup> consists of a cobaltous ion coordinated to Mabiq-H. The differing oxidation states of the metal center will impact the ensuing ET and PT steps and further ligand participation in these processes. Although we have not established the order of these events, the electronic structures of the anionic species ( $Co_{Mbq}$ -H<sup>DK1</sup>) or ( $Co_{Mbq}$ -H<sup>Im</sup>), generated upon the addition of another electron to the two intermediates (Figure 10), are informative in considering possible HER pathways. According to the DFT derived Merz–Singh–Kollman (MK) charges (Table S2, Supporting Information), ( $Co_{Mbq}$ -H<sup>Im</sup>) contains a low-valent, almost

neutral Co atom coordinated to a ligand anion. In the unrestricted formalism, the spins on the ligand are paired, while the broken-symmetry DFT solution, which is about 29 kJ/mol more stable, predicts a ligand biradical. By design, the broken-symmetry DFT approach overly delocalizes spin densities to arrive at the most stable wave function.<sup>52</sup> The true spin situation of the ligand can thus be debated, but in light of the unfavorable charge distribution, we deem formation of this intermediate unlikely in the absence of a proton. On the other hand, direct protonation of  $Co_{Mbq}$ -H<sup>Im</sup> would lead to formation of a metal-hydride, the cationic  $(Co_{Mbq}-H_2^{Im,Co})^+$ . We have not seen any evidence for a metal hydride species after bulk electrolysis at  $-0.84 V_{Fc}$ . Thus, we

propose that the first step in the HER from  $\mathbf{Co}_{Mbq}$ -H<sup>Im</sup> instead involves a PCET process; metal-hydride formation coincides with electron addition to generate the neutral  $\mathbf{Co}_{Mbq}$ -H<sub>2</sub><sup>Im,Co</sup> (bottom pathway Figure 10). Once again, the brokensymmetry solution predicts biradical character for the ligand in  $\mathbf{Co}_{Mbq}$ -H<sub>2</sub><sup>Im,Co</sup>, while the unrestricted calculation yields a closed-shell ligand. The metal center is oxidized (MK charge 1.21), while the corresponding negative charge is spread across the Mabiq-ligand (sum of MK charge -1.04) and the Cobound hydride ion (MK charge -0.17). This species may be further protonated to release H<sub>2</sub> (Scheme 6, bottom path).

The reduction in the calculated ( $Co_{Mbq}$ - $H^{DK1}$ ) species again occurs at the ligand. In this case, prediction of a H<sub>2</sub> evolution mechanism is more complex. This species has high negative charge density at the bridging imine group, making this a likely protonation site, though a route involving protonation of the second diketiminate again offers a possibility. We speculate that H<sub>2</sub> evolution necessitates formation of the low-valent Co(I) species and subsequent metal protonation. However, even here a number of scenarios can be envisioned. For example, assuming involvement of a protonated imine-N, both direct protonation of a resultant metal-hydride (Scheme 7, pathway B, bottom) and a ligand-assisted pathway as established for Ni-thiosemicarbazone complexes (Scheme 7, pathway A, top),<sup>16,25</sup> can be envisioned.

Further studies are warranted to verify our proposed mechanisms. However, the suggested HER pathways already provide an explanation for the differing overpotentials for  $H_2$ evolution from  $Co_{Mbq}$ -H<sup>Im</sup> and  $Co_{Mbq}$ -H<sup>DK1</sup>. The former complex already contains a reduced Co(I) center—the protonated imine appears to enable reduction of the cobalt ion at lower overpotentials. The formation of a low-valent cobalt species would thus readily support a metal-hydride pathway. However, at least three electrons are accumulated on the ligand in the pathways involving  $Co_{Mbq}$ -H<sup>DK1</sup> before reduction of the metal center becomes favorable. Consequently, the redox-active ligand can also accumulate multiple protons. The higher overpotential for  $H_2$  from  $Co_{Mbq}$ -H<sup>DK1</sup> suggests that Mabiq acts as a hydride "sink," and access to an effective metal-centered HER pathway from this species requires additional electron transfer steps and thus also a higher energy input.

In our system, the formation of  $Co_{Mbq}$ -H<sup>Im</sup> and the HER at lower overpotential is promoted by stronger acids. The effect of acid strength was also investigated for H<sub>2</sub> evolution by the hangman porphyrins.<sup>20,21</sup> In this system, stronger acids also allowed for H<sub>2</sub> evolution from a metal-hydride intermediate, whereas using the weaker acids, the HER occurred via a ligandcentered pathway that also required additional electron and transfer steps. Therefore, our suggested pathways are consistent with the acid strength effects observed in other systems.

#### CONCLUSION

The Co-Mabiq complex is one of several compounds in which the redox-active ligand engages in the PT and ET steps associate with  $H_2$  evolution. However, a number of features are noteworthy and distinctive in the Mabiq system and provide general insight into the contribution of such ligands to the HER. In this regard, our studies also highlight how modern theoretical methods that can treat chemically relevant systems can greatly contribute to the understanding of experimental results. In particular, we point out the vital role of the computationally affordable DFT/MRCI method in bridging the gap between multireference quantum chemistry and experiments. The computational studies contribute to our understanding of the nature of proton and electron storage sites, and the degree of PCET affects the energy and activity of intermediates.

The energetically low-lying  $\pi^*$  orbitals of the extended Mabiq  $\pi$ -bonded framework can readily accept electrons. The one-electron reduction potential for  $\mathbf{Co}_{Mbq}$  in the absence of acid ( $E_{p,c} = -0.8 V_{Fc}$ ) is thus fairly high in comparison to the formal Co<sup>II/I</sup> couples of Co-porphyrin (-1.08  $V_{Fc}$ ),<sup>53</sup> diothiolene (-1.49 V vs SCE),<sup>12</sup> and many cobaloxime<sup>54</sup> catalysts. In accord with previous findings,<sup>55</sup> coupling of a proton to the reduction process shifts the potential to more positive values. In fact, the addition of the second electron to the protonated Co-Mabiq compound also becomes highly favorable, with <150 mV separation between the protoncoupled precatalytic one- and two-electron reductions, regardless of the acid. Therefore, proton and electron storage by Mabiq—and by redox-active ligands in general—clearly can be an advantage for accessing reduced forms. However, the hydride equivalent that is added to  $Co_{Mbq}$  in the precatalytic steps is not readily released at this stage. Nevertheless, the potentials for catalytic  $H_2$  evolution by  $Co_{Mbq}_{21,25}$  are also comparable to many redox-active ligand systems.

The Co-Mabiq complex offers a metal- and multiple ligandprotonation sites. Consequently, the studies with  $Co_{Mbq}$ uniquely demonstrate how various features of noninnocent ligands can influence catalysis. The formation of the two distinct precatalytic intermediates,  $Co_{Mbq}$ -H<sup>Im</sup> and  $Co_{Mbq}$ - $H^{DK1}$ , is dependent on the acid strength. The two species can both evolve H<sub>2</sub> but have dissimilar electronic structures and operate at different potentials. Co<sub>Mbq</sub>-H<sup>DK1</sup> represents a ligand hydride-further reduction of this species remains ligand centered, and H<sub>2</sub> evolution requires a higher overpotential. In contrast, metal-centered reduction is favored for  $(Co_{Mbq} - H^{Im})^+$ —the ensuing  $H_2$  evolution from  $Co_{Mbq} - H^{Im}$  involves metal protonation and occurs at lower energy. The implication is that pathways involving reduced metal centers, and thus metal-hydride species, may offer a more effective strategy for  $H_2$  evolution. In this regard, the protonated imine of  $\text{Co}_{\text{Mbq}}\text{-}$ H<sup>Im</sup> may further aid catalysis by serving as a proton relay site, whereas a similar role for the carbon bound hydrogen of  $Co_{Mbq}$ -H<sup>DK1</sup> is unlikely.

Catalyst design clearly plays a significant role in effecting the metal, ligand-based, and ligand/metal-assisted HER pathways. In our system, modifying the Mabiq ligand on the diketiminate unit may suppress the formation of  $Co_{Mbq}$ - $H^{DK1}$  and promote  $H_2$  evolution via  $Co_{Mbq}$ - $H^{Im}$ . Select metals coordinated to the outer bipyrimidine also could alter the electronic structure in favor of metal-centered pathways. Overall, there is still a way to go in optimizing the metal–ligand synergies for efficient  $H_2$  evolution. However, the mechanistic insights provided in this work shed further light on some of the competing factors to consider in the use of redox-active ligands for these processes and provide starting points for targeted ligand optimizations in future studies.

#### EXPERIMENTAL DETAILS

All chemicals were purchased from Sigma-Aldrich unless otherwise noted. Acetonitrile (MeCN) was dried by passage over activated alumina columns and stored over activated 3 Å molecular sieves. The water content in MeCN was determined to be below 1 ppm by Karl Fischer titration. As a supporting electrolyte salt, lithium tetrafluoroborate (LiBF<sub>4</sub>; BASF, Germany) was used in all cyclic voltammetry and bulk electrolysis experiments.  $[Co^{II}(Mabiq)(THF)](PF_6)^{38}$  and the selected proton sources *p*-cyanoanilinium, *p*-bromoanilinium, and *p*-anisidinium were synthesized according to the literature procedure.<sup>40,56</sup>

Bulk Electrolysis and Cyclic Voltammetry (CV). Bulk electrolysis and CV measurements were conducted in a four-neck jacketed cell that was previously employed by our group,<sup>35,57</sup> and the cell was assembled in the glovebox (Ar, MBraun, Germany, < 0.1 ppm of H<sub>2</sub>O and O<sub>2</sub>.) The PEEK shroud working electrode includes a glassy carbon disk with a 5.0 mm diameter, surrounded by a glassy carbon ring with a 6.5 mm internal diameter and 7.5 mm external diameter (Pine Research Instrumentation, Durham, NC). For both bulk electrolysis and the CV measurements, a potential was applied only to the glassy carbon disk working electrode. Prior to usage, the working electrode was polished with 1.0 and 0.05  $\mu m$  alumina suspensions (Buehler, Düsseldorf, Germany) and cleaned by sonication in ultrapure water. The electrode was subsequently dried for 12 h in an oven at 70 °C. A LiFePO<sub>4</sub> (BASF, Germany) electrode was employed as a counter electrode, which was separated from the working electrode part via a glass fitting. Li metal (Rockwood, USA) in 1 M LiPF<sub>6</sub> in EC/EMC 3:7, LP57 (BASF, Germany), was used as the reference electrode, separated via a Vycor 3535 frit (Advanced Glass & Ceramics, Holden, MA).

During the cell assembly, the working electrode rod was connected to the rotator, which was beneficial for the bulk electrolysis experiments. All measurements were recorded with an SP300 potentiostat (BioLogic, Grenoble, France). All potentials were recorded vs the Li<sup>+/0</sup> scale, and the potential scale conversion from Li<sup>+/0</sup> to Fc<sup>+/0</sup> was carried out experimentally by recording the Fc<sup>+/0</sup> redox couple in 0.1 M LiBF<sub>4</sub>/MeCN with a Li reference electrode. The CV and bulk electrolysis experiments were recorded at 0 and 800 rpm, respectively.

At the end of the bulk electrolysis experiments, the conversion of  $Co_{Mbq}$  in the presence of the acid source (*n*, mole of the complex) was calculated according to eq 1, based on the number of electrons transferred (*z*), Faraday constant (*F*), and charge (*Q*).

$$Q = zFn \tag{1}$$

Q is the integrated area on current vs the time graph of Co/pCA or Co/pBrA; z represents two electrons (based on the ECE mechanism of precatalytic step); F is the Faraday constant, 96485.33 C mol<sup>-1</sup>.

**UV–Vis Absorption Spectroscopy.** During the bulk electrolysis experiment, every 2 h, 100  $\mu$ L aliquots were removed from the bulk solution and diluted with 2.7 mL of acetonitrile in the spectrophotometer cuvettes. Due to the possible air sensitivity of the samples, airtight far-UV quartz cuvettes (Starna GmbH, Germany) were used. Prior to usage, the cuvettes were cleaned and dried overnight in an oven at 70 °C and subsequently transferred into the glovebox. After the sample preparation in the glovebox, UV–vis spectra of samples at varied time intervals were recorded using a Cary 60 UV–vis spectrophotometer (Agilent Technologies, USA) for regions up to 900 nm wavelength, and the near IR region between 900 and 1300 nm was recorded with a UV-3600 Plus spectrophotometer (Schimadzu, Japan).

**Computational Details.** Geometry optimizations and thermodynamic analyses were carried out with *Gaussian 16*,<sup>58</sup> using the rangeseparated CAM-B3LYP<sup>59</sup> density functional. The optimized structures were identified as energy minima by the absence of imaginary vibrational frequencies. The transition state between  $Co_{Mbq}$ -H<sup>Im</sup> and  $Co_{Mbq}$ -H<sup>DK1</sup> was verified by its single imaginary vibrational frequency and by computing the reaction path toward the reactant and product. In all geometry optimizations, the broken symmetry DFT ansatz was used after testing the starting wave function for internal instabilities (keyword *stable = opt*), though the calculation converged to the closed-shell solution for ( $Co_{Mbq}$ -H<sup>Co</sup>)<sup>+</sup>. The 6-31+G(d) basis set<sup>60-63</sup> was employed for all elements except cobalt. Here, the LANL2<sup>63</sup> pseudopotential replaced the inner core electrons [1s<sup>2</sup>2s<sup>2</sup>2p<sup>6</sup>], leaving the outer core and valence shells to be described with the corresponding double-ζ basis LANL2-DZ.<sup>63</sup> Implicit solvent effects were described by the polarizable continuum model (PCM) with standard parameters for acetonitrile.<sup>64</sup> Thermodynamic corrections to the electronic energies were computed in the harmonic approximation for a temperature of 298.15 K and a pressure of 1.0 atm.

TD-DFT absorption spectra were computed at the same level of theory as the geometry optimizations to assess the suitability of the method. However, due to the multiconfigurational nature of the complex, we eventually switched to the DFT/MRCI method<sup>46</sup> using the R2018 Hamiltonian.<sup>51</sup> Other common multiconfigurational methods, such as CASSCF or CASPT2, are computationally expensive, especially considering the extensive system of  $\pi$  electrons, and require careful selection of the active space. Multireference configuration interaction (MRCI) methods based on Hartree-Fock orbitals typically suffer from a lack of dynamical correlation and often require long expansions of high excitations.<sup>46</sup> DFT/MRCI is supposed to combine the best of both worlds-the description of dynamical correlation by DFT and the recovery of static correlation typical for multireference methods-all while keeping the computational effort at a feasible level. In contrast to CASSCF, there is no active space of carefully selected orbitals. Instead, a reference space of excited configurations is iteratively optimized, thereby removing any bias associated with manual orbital selection.

In preliminary test calculations for [Co<sup>II</sup>(Mabiq<sup>•</sup>)]<sup>0</sup>, a large and flexible basis set with diffuse functions emerged to be essential for a large enough configuration space to approximate the experimental spectrum. However, the size of the basis set is limited by technical constraints. To reconcile these conditions, we reduced the number of basis functions by replacing the methyl groups of the Mabiq ligand, which are unlikely to participate in any of the excitations we were interested in, with hydrogen atoms. The unrestricted DFT reference was calculated with *Orca* 4.2.1,<sup>65,66</sup> using the BHLYP<sup>67,68</sup> functional with the def2-TZVPD<sup>69,70</sup> all-electron basis set on the cobalt center and def2-SVPD<sup>69,70</sup> on all other atoms. The def2-TZVPD/C<sup>7</sup> and def2/JK<sup>72</sup> auxiliary basis sets were used within the resolution-of-theidentity formalism for coulomb and exchange integrals<sup>73</sup> (RI-JK) on all atoms. The only exception was  $Co_{Mbq}$ -H<sup>Im</sup>, where def2-SVP/C was the largest feasible basis set for the subsequent MRCI step. Symmetry was turned off, and a final SCF convergence threshold of  $10^{-7}$   $E_{\rm h}$ (keyword SCFCONV7) was used throughout with a 590-point Lebedev integration grid (keyword Grido). Solvation effects were taken into account by means of the C-PCM model<sup>74,75</sup> with default parameters for acetonitrile. The resulting unrestricted molecular orbitals were transformed to a set of quasi-restricted orbitals<sup>76</sup> and used as input to the DFT/MRCI program. The reference space was iteratively optimized, increasing the number of excited states in each iteration until either the technical limit of 50 excited states or an excited state energy of 300 nm was reached. In any case, one final iteration was performed to ensure that the leading configurations of all excited states were contained in the reference space. The obtained line spectra were convoluted with Gaussians (fwhm = 0.24 eV). Convoluted spectra depicted in this work were normalized such that the highest absorption is one.

Visualizations of molecular structures and spin densities were created with VMD 1.9.3.  $^{77}\,$ 

#### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.1c01157.

Details of pH-dependent potential correction; current response of the pre-catalytic step after the bulk electrolysis; CVs of  $Co_{Mbq}$  with varied *p*-anisidinium concentrations; visualization of structural distortions upon protonation of  $[Co(Mabiq^{\bullet})]$ ; TD-DFT absorption spectrum of  $[Co^{II}(Mabiq^{\bullet})]$ ; DFT/MRCI spectrum of  $(Co_{Mbq}$ -H<sup>Im</sup>)<sup>+</sup>; additional spin density plots; calculated energy levels of intermediates; electrostatic

potential and atomic charges for  $(Co_{Mbq}\text{-}H_2^{Im,Co})^{*}$  and  $Co_{Mbq}\text{-}H_2^{Im,Co}\text{;}$  and Cartesian coordinates of optimized geometries (PDF)

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<sup>II</sup>The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. G.C.T. and S.R. contributed equally.

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#### Notes

The authors declare no competing financial interest.

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#### ABBREVIATIONS

CV, cyclic voltammetry; DFT, density functional theory; ECE, electrochemical-chemical-electrochemical; ECEC, electrochemical-chemical-electrochemical-chemical; ET, electron transfer; MRCI, multireference configuration interaction; OEMS, online electrochemical mass spectrometry; PCET, proton coupled electron transfer; PT, proton transfer; RRDE, rotating ring disk electrode; TD-DFT, time-dependent density functional theory

#### REFERENCES

(1) McKone, J. R.; Lewis, N. S.; Gray, H. B. Will Solar-Driven Water-Splitting Devices See the Light of Day? *Chem. Mater.* **2014**, *26* (1), 407–414.

(2) Berardi, S.; Drouet, S.; Francas, L.; Gimbert-Surinach, C.; Guttentag, M.; Richmond, C.; Stoll, T.; Llobet, A. Molecular artificial photosynthesis. *Chem. Soc. Rev.* **2014**, 43 (22), 7501–7519.

(3) Brazzolotto, D.; Gennari, M.; Queyriaux, N.; Simmons, T. R.; Pecaut, J.; Demeshko, S.; Meyer, F.; Orio, M.; Artero, V.; Duboc, C. Nickel-centred proton reduction catalysis in a model of [NiFe] hydrogenase. *Nat. Chem.* **2016**, *8* (11), 1054–1060.

(4) McNamara, W. R.; Han, Z.; Alperin, P. J.; Brennessel, W. W.; Holland, P. L.; Eisenberg, R. A cobalt-dithiolene complex for the photocatalytic and electrocatalytic reduction of protons. *J. Am. Chem. Soc.* **2011**, *133* (39), 15368–15371.

(5) Hammes-Schiffer, S. Controlling Electrons and Protons through Theory: Molecular Electrocatalysts to Nanoparticles. *Acc. Chem. Res.* **2018**, *51* (9), 1975–1983.

(6) Huynh, M. H. V.; Meyer, T. J. Proton-Coupled Electron Transfer. Chem. Rev. 2007, 107 (11), 5004–5064.

(7) Warren, J. J.; Tronic, T. A.; Mayer, J. M. Thermochemistry of Proton-Coupled Electron Transfer Reagents and its Implications. *Chem. Rev.* 2010, 110 (12), 6961–7001.

(8) McKone, J. R.; Marinescu, S. C.; Brunschwig, B. S.; Winkler, J. R.; Gray, H. B. Earth-abundant hydrogen evolution electrocatalysts. *Chem. Sci.* **2014**, *5* (3), 865–878.

(9) Wiedner, E. S.; Chambers, M. B.; Pitman, C. L.; Bullock, R. M.; Miller, A. J.; Appel, A. M. Thermodynamic Hydricity of Transition Metal Hydrides. *Chem. Rev.* **2016**, *116* (15), 8655–8692.

(10) Das, A.; Hessin, C.; Ren, Y.; Desage-El Murr, M. Biological concepts for catalysis and reactivity: empowering bioinspiration. *Chem. Soc. Rev.* **2020**, 49 (23), 8840–8867.

(11) Luo, G.-G.; Zhang, H.-L.; Tao, Y.-W.; Wu, Q.-Y.; Tian, D.; Zhang, Q. Recent progress in ligand-centered homogeneous electrocatalysts for hydrogen evolution reaction. *Inorg. Chem. Front.* **2019**, *6* (2), 343–354.

(12) Solis, B. H.; Hammes-Schiffer, S. Computational study of anomalous reduction potentials for hydrogen evolution catalyzed by cobalt dithiolene complexes. *J. Am. Chem. Soc.* **2012**, *134* (37), 15253–15256.

(13) Fernandez, L. E.; Horvath, S.; Hammes-Schiffer, S. Theoretical Analysis of the Sequential Proton-Coupled Electron Transfer Mechanisms for H2 Oxidation and Production Pathways Catalyzed by Nickel Molecular Electrocatalysts. *J. Phys. Chem. C* **2012**, *116* (4), 3171–3180.

(14) Letko, C. S.; Panetier, J. A.; Head-Gordon, M.; Tilley, T. D. Mechanism of the electrocatalytic reduction of protons with diaryldithiolene cobalt complexes. *J. Am. Chem. Soc.* **2014**, *136* (26), 9364–9376.

(15) Rosenkoetter, K. E.; Wojnar, M. K.; Charette, B. J.; Ziller, J. W.; Heyduk, A. F. Hydrogen-Atom Noninnocence of a Tridentate [SNS] Pincer Ligand. *Inorg. Chem.* **2018**, *57* (16), 9728–9737.

(16) Straistari, T.; Fize, J.; Shova, S.; Réglier, M.; Artero, V.; Orio, M. A Thiosemicarbazone-Nickel(II) Complex as Efficient Electrocatalyst for Hydrogen Evolution. *ChemCatChem* **2017**, *9* (12), 2262–2268.

(17) Thompson, E. J.; Berben, L. A. Electrocatalytic Hydrogen Production by an Aluminum(III) Complex: Ligand-Based Proton and Electron Transfer. *Angew. Chem., Int. Ed.* **2015**, *54* (40), 11642– 11646.

(18) Lubitz, W.; Ogata, H.; Rudiger, O.; Reijerse, E. Hydrogenases. Chem. Rev. 2014, 114 (8), 4081-4148.

(19) DuBois, D. L. Development of molecular electrocatalysts for energy storage. *Inorg. Chem.* **2014**, *53* (8), 3935–3960.

https://doi.org/10.1021/acs.inorgchem.1c01157 Inorg. Chem. 2021, 60, 13888-13902 (21) Solis, B. H.; Maher, A. G.; Honda, T.; Powers, D. C.; Nocera, D. G.; Hammes-Schiffer, S. Theoretical Analysis of Cobalt Hangman Porphyrins: Ligand Dearomatization and Mechanistic Implications for Hydrogen Evolution. *ACS Catal.* **2014**, *4* (12), 4516–4526.

(22) Haddad, A. Z.; Cronin, S. P.; Mashuta, M. S.; Buchanan, R. M.; Grapperhaus, C. A. Metal-Assisted Ligand-Centered Electrocatalytic Hydrogen Evolution upon Reduction of a Bis(thiosemicarbazonato)-Cu(II) Complex. *Inorg. Chem.* **2017**, *56* (18), 11254–11265.

(23) Panetier, J. A.; Letko, C. S.; Tilley, T. D.; Head-Gordon, M. Computational Characterization of Redox Non-Innocence in Cobalt-Bis(Diaryldithiolene)-Catalyzed Proton Reduction. J. Chem. Theory Comput. 2016, 12 (1), 223–230.

(24) Zarkadoulas, A.; Field, M. J.; Papatriantafyllopoulou, C.; Fize, J.; Artero, V.; Mitsopoulou, C. A. Experimental and Theoretical Insight into Electrocatalytic Hydrogen Evolution with Nickel Bis(aryldithiolene) Complexes as Catalysts. *Inorg. Chem.* **2016**, 55 (2), 432–444.

(25) Jain, R.; Mamun, A. A.; Buchanan, R. M.; Kozlowski, P. M.; Grapperhaus, C. A. Ligand-Assisted Metal-Centered Electrocatalytic Hydrogen Evolution upon Reduction of a Bis(thiosemicarbazonato)-Ni(II) Complex. *Inorg. Chem.* **2018**, *57* (21), 13486–13493.

(26) Barrozo, A.; Orio, M. Unraveling the catalytic mechanisms of H2 production with thiosemicarbazone nickel complexes. *RSC Adv.* **2021**, *11* (9), 5232–5238.

(27) Johnson, S. I.; Gray, H. B.; Blakemore, J. D.; Goddard, W. A., 3rd Role of Ligand Protonation in Dihydrogen Evolution from a Pentamethylcyclopentadienyl Rhodium Catalyst. *Inorg. Chem.* **2017**, 56 (18), 11375–11386.

(28) Quintana, L. M.; Johnson, S. I.; Corona, S. L.; Villatoro, W.; Goddard, W. A., 3rd; Takase, M. K.; VanderVelde, D. G.; Winkler, J. R.; Gray, H. B.; Blakemore, J. D. Proton-hydride tautomerism in hydrogen evolution catalysis. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, *113* (23), 6409–6414.

(29) Haddad, A. Z.; Garabato, B. D.; Kozlowski, P. M.; Buchanan, R. M.; Grapperhaus, C. A. Beyond Metal-Hydrides: Non-Transition-Metal and Metal-Free Ligand-Centered Electrocatalytic Hydrogen Evolution and Hydrogen Oxidation. *J. Am. Chem. Soc.* **2016**, *138* (25), 7844–7847.

(30) Papanikolaou, M. G.; Elliott, A.; McAllister, J.; Gallos, J. K.; Keramidas, A. D.; Kabanos, T. A.; Sproules, S.; Miras, H. N. Electrocatalytic hydrogen production by dinuclear cobalt(II) compounds containing redox-active diamidate ligands: a combined experimental and theoretical study. *Dalton Trans.* **2020**, *49* (44), 15718–15730.

(31) Queyriaux, N.; Sun, D.; Fize, J.; Pécaut, J.; Field, M. J.; Chavarot-Kerlidou, M.; Artero, V. Electrocatalytic Hydrogen Evolution with a Cobalt Complex Bearing Pendant Proton Relays: Acid Strength and Applied Potential Govern Mechanism and Stability. J. Am. Chem. Soc. **2020**, 142 (1), 274–282.

(32) Aster, A.; Wang, S.; Mirmohades, M.; Esmieu, C.; Berggren, G.; Hammarstrom, L.; Lomoth, R. Metal vs. ligand protonation and the alleged proton-shuttling role of the azadithiolate ligand in catalytic H2 formation with FeFe hydrogenase model complexes. *Chem. Sci.* 2019, *10* (21), 5582–5588.

(33) Costentin, C.; Saveant, J. M.; Tard, C. Ligand "noninnocence" in coordination complexes vs. kinetic, mechanistic, and selectivity issues in electrochemical catalysis. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115* (37), 9104–9109.

(34) Maher, A. G.; Liu, M.; Nocera, D. G. Ligand Noninnocence in Nickel Porphyrins: Nickel Isobacteriochlorin Formation under Hydrogen Evolution Conditions. *Inorg. Chem.* **2019**, *58* (12), 7958–7968.

(35) Tok, G. C.; Freiberg, A. T. S.; Gasteiger, H. A.; Hess, C. R. Electrocatalytic H2 Evolution by the Co-Mabiq Complex Requires

Tempering of the Redox-Active Ligand. ChemCatChem 2019, 11 (16), 3973-3981.

(36) Saveant, J. M. Proton Relays in Molecular Catalysis of Electrochemical Reactions: Origin and Limitations of the Boosting Effect. *Angew. Chem., Int. Ed.* **2019**, 58 (7), 2125–2128.

(37) Puttock, E. V.; Banerjee, P.; Kaspar, M.; Drennen, L.; Yufit, D. S.; Bill, E.; Sproules, S.; Hess, C. R. A Series of [Co(Mabiq)Cl2-n] (n = 0, 1, 2) Compounds and Evidence for the Elusive Bimetallic Form. *Inorg. Chem.* **2015**, *54* (12), 5864–5873.

(38) Kaspar, M.; Altmann, P. J.; Pothig, A.; Sproules, S.; Hess, C. R. A macrocyclic 'Co(0)' complex: the relevance of ligand noninnocence to reactivity. *Chem. Commun.* **2017**, *53* (53), 7282–7285.

(39) Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. Extension of the Self-Consistent Spectrophotometric Basicity Scale in Acetonitrile to a Full Span of 28 pKa Units: Unification of Different Basicity Scales. J. Org. Chem. **2005**, 70 (3), 1019–1028.

(40) Appel, A. M.; Pool, D. H.; O'Hagan, M.; Shaw, W. J.; Yang, J. Y.; Rakowski DuBois, M.; DuBois, D. L.; Bullock, R. M. [Ni(PPh2NBn2)2(CH3CN)]2+ as an Electrocatalyst for H2 Production: Dependence on Acid Strength and Isomer Distribution. *ACS Catal.* **2011**, *1* (7), 777–785.

(41) Adamo, C.; Barone, V. Inexpensive and accurate predictions of optical excitations in transition-metal complexes: the TDDFT/PBE0 route. *Theor. Chem. Acc.* **2000**, *105* (2), *169*–172.

(42) Hay, P. J. Theoretical Studies of the Ground and Excited Electronic States in Cyclometalated Phenylpyridine Ir(III) Complexes Using Density Functional Theory. J. Phys. Chem. A 2002, 106 (8), 1634–1641.

(43) Petit, L.; Adamo, C.; Russo, N. Absorption Spectra of First-Row Transition Metal Complexes of Bacteriochlorins: A Theoretical Analysis. J. Phys. Chem. B 2005, 109 (24), 12214–12221.

(44) Andruniów, T.; Jaworska, M.; Lodowski, P.; Zgierski, M. Z.; Dreos, R.; Randaccio, L.; Kozlowski, P. M. Time-dependent density functional theory study of cobalt corrinoids: Electronically excited states of methylcobalamin. *J. Chem. Phys.* **2008**, *129* (8), 085101.

(45) Pastore, M.; Mosconi, E.; De Angelis, F.; Grätzel, M. A Computational Investigation of Organic Dyes for Dye-Sensitized Solar Cells: Benchmark, Strategies, and Open Issues. J. Phys. Chem. C 2010, 114 (15), 7205–7212.

(46) Marian, C. M.; Heil, A.; Kleinschmidt, M. The DFT/MRCI method. Wiley Interdiscip. Rev.: Comput. Mol. Sci. 2019, 9 (2), No. e1394.

(47) Grimme, S.; Waletzke, M. A combination of Kohn-Sham density functional theory and multi-reference configuration interaction methods. J. Chem. Phys. **1999**, 111 (13), 5645–5655.

(48) Kleinschmidt, M.; Marian, C. M.; Waletzke, M.; Grimme, S. Parallel multireference configuration interaction calculations on mini $\beta$ -carotenes and  $\beta$ -carotene. J. Chem. Phys. **2009**, 130 (4), 044708.

(49) Lyskov, I.; Kleinschmidt, M.; Marian, C. M. Redesign of the DFT/MRCI Hamiltonian. J. Chem. Phys. 2016, 144 (3), 034104.

(50) Heil, A.; Marian, C. M. DFT/MRCI Hamiltonian for odd and even numbers of electrons. J. Chem. Phys. 2017, 147 (19), 194104.

(51) Heil, A.; Kleinschmidt, M.; Marian, C. M. On the performance of DFT/MRCI Hamiltonians for electronic excitations in transition metal complexes: The role of the damping function. *J. Chem. Phys.* **2018**, *149* (16), 164106.

(52) Neese, F. Prediction of molecular properties and molecular spectroscopy with density functional theory: From fundamental theory to exchange-coupling. *Coord. Chem. Rev.* **2009**, 253 (5–6), 526–563.

(53) Lee, C. H.; Dogutan, D. K.; Nocera, D. G. Hydrogen generation by hangman metalloporphyrins. J. Am. Chem. Soc. 2011, 133 (23), 8775–8777.

(54) Hammes-Schiffer, S. Proton-Coupled Electron Transfer: Moving Together and Charging Forward. J. Am. Chem. Soc. 2015, 137 (28), 8860–8871. (55) Solis, B. H.; Hammes-Schiffer, S. Proton-coupled electron transfer in molecular electrocatalysis: theoretical methods and design principles. *Inorg. Chem.* **2014**, *53* (13), 6427–6443.

(56) Henry, R. M.; Shoemaker, R. K.; DuBois, D. L.; DuBois, M. R. Pendant Bases as Proton Relays in Iron Hydride and Dihydrogen Complexes. J. Am. Chem. Soc. **2006**, 128 (9), 3002–3010.

(57) Lu, Y.-C.; He, Q.; Gasteiger, H. A. Probing the Lithium-Sulfur Redox Reactions: A Rotating-Ring Disk Electrode Study. J. Phys. Chem. C 2014, 118 (11), 5733-5741.

(58) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian 16, rev. C.01; Gaussian Inc.: Wallingford, CT, 2016.

(59) Yanai, T.; Tew, D. P.; Handy, N. C. A new hybrid exchangecorrelation functional using the Coulomb-attenuating method (CAM-B3LYP). *Chem. Phys. Lett.* **2004**, 393 (1), 51–57.

(60) Hehre, W. J.; Ditchfield, R.; Pople, J. A. Self—Consistent Molecular Orbital Methods. XII. Further Extensions of Gaussian— Type Basis Sets for Use in Molecular Orbital Studies of Organic Molecules. J. Chem. Phys. **1972**, 56 (5), 2257–2261.

(61) Hariharan, P. C.; Pople, J. A. The influence of polarization functions on molecular orbital hydrogenation energies. *Theoret. Chim. Acta* **1973**, *28* (3), 213–222.

(62) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. V. R. Efficient diffuse function-augmented basis sets for anion calculations. III. The 3-21+G basis set for first-row elements, Li-F. *J. Comput. Chem.* **1983**, *4* (3), 294–301.

(63) Hay, P. J.; Wadt, W. R. Ab initio effective core potentials for molecular calculations. Potentials for K to Au including the outermost core orbitals. *J. Chem. Phys.* **1985**, *82* (1), 299–310.

(64) Tomasi, J.; Mennucci, B.; Cammi, R. Quantum Mechanical Continuum Solvation Models. *Chem. Rev.* 2005, 105 (8), 2999–3094.
(65) Neese, F. The ORCA program system. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* 2012, 2 (1), 73–78.

(66) Neese, F. Approximate second-order SCF convergence for spin unrestricted wavefunctions. *Chem. Phys. Lett.* **2000**, 325 (1), 93–98. (67) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, 37 (2), 785– 789.

(68) Becke, A. D. A new mixing of Hartree-Fock and local densityfunctional theories. J. Chem. Phys. **1993**, 98 (2), 1372–1377.

(69) Weigend, F.; Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **2005**, 7 (18), 3297–3305.

(70) Rappoport, D.; Furche, F. Property-optimized Gaussian basis sets for molecular response calculations. *J. Chem. Phys.* **2010**, *133* (13), 134105.

(71) Hellweg, A.; Rappoport, D. Development of new auxiliary basis functions of the Karlsruhe segmented contracted basis sets including diffuse basis functions (def2-SVPD, def2-TZVPPD, and def2-QVPPD) for RI-MP2 and RI-CC calculations. *Phys. Chem. Chem. Phys.* **2015**, *17* (2), 1010–1017.

(72) Weigend, F. Hartree-Fock exchange fitting basis sets for H to Rn †. J. Comput. Chem. 2008, 29 (2), 167–175.

(73) Weigend, F.; Kattannek, M.; Ahlrichs, R. Approximated electron repulsion integrals: Cholesky decomposition versus resolution of the identity methods. *J. Chem. Phys.* **2009**, *130* (16), 164106. (74) Kossmann, S.; Neese, F. Comparison of two efficient

(74) Kossmann, S.; Neese, F. Comparison of two encient approximate Hartee-Fock approaches. *Chem. Phys. Lett.* **2009**, 481 (4), 240–243.

(75) Barone, V.; Cossi, M. Quantum Calculation of Molecular Energies and Energy Gradients in Solution by a Conductor Solvent Model. *J. Phys. Chem. A* **1998**, *102* (11), 1995–2001.

(76) Neese, F. Importance of Direct Spin-Spin Coupling and Spin-Flip Excitations for the Zero-Field Splittings of Transition Metal Complexes: A Case Study. J. Am. Chem. Soc. **2006**, 128 (31), 10213– 10222.

(77) Humphrey, W.; Dalke, A.; Schulten, K. VMD: Visual molecular dynamics. J. Mol. Graphics 1996, 14 (1), 33–38.

## 3.2 The Light-Harvesting Network of Photosystem I

The [Co(Mabiq)] complex presented in the previous chapter is one candidate in a family of catalysts to drive  $H_2$  evolution reactions. In the transition to a sustainable energy supply, the required current is envisaged to be provided from renewable energy sources such as photovoltaics. Coupling the catalyst to a natural platform like PS I in a bio-nanohybrid system has the benefit of using the generated electrons directly without losses through intermediate storage.

Computational work can aid in the design of such devices by modeling the energy and electron flows inside the photosystem, which are notoriously difficult to access experimentally. In this context, the article "Thermal site energy fluctuations in photosystem I: new insights from MD/QM/MM calculations", published 2023 in *Chem. Sci.* provides a new model of cyanobacterial PS I in its natural environment. This system has repeatedly attracted the attention of computational research over the last few decades. However, none of the previous models<sup>[49,255–259]</sup> agreed on the excited state energies of the 96 chlorophylls in PS I (*site energies*), which are modulated by a heterogeneous local environment of protein residues, other cofactors and lipids. The current work aims to provide a new state of the art, which takes into account (i) the multireference nature of the chlorophyll excited states, (ii) the atomistic natural environment and (iii) the dynamics of the nanosystem.

The most important results of the article are summarized below:

- The presented model of cyanobacterial PS I is based on an experimental crystal structure (*T. elongatus*, PDB:  $1JB0^{[244]}$ ), which has been complemented by missing atoms and residues and trimerized by applying a  $C_3$  symmetry operation. The resulting trimeric protein complex is embedded in a lipid bilayer and solvated in 15 mM NaCl buffer to mimic realistic conditions.
- Two 15 ns MD simulations were carried out in an NPT ensemble, to sample structural fluctuations. The parameters for the protein, cofactors, lipids, and solvent were largely compiled from the literature and to a small extent generated for this work. Their mutual compatibility was carefully ensured by using only parameters derived according to the Amber parameterization protocol.
- Excited states for each of the 96 chlorophylls in a PS I monomer were calculated in a QM/MM ansatz at regular intervals of the MD trajectories, using the DFT/MRCI method in the QM region. Preceding benchmark calculations showed DFT/MRCI to be ideally suited, due to its ability to capture multireference effects, which are crucial even in the first few excited states of chlorophyll. The rest of the environment, containing the PS I trimer, lipid membrane, and water, was included as point charges which polarized the QM wave function. In this way, the site energies of the 90 antenna chlorophylls were calculated at 40 MD snapshots. For the 6 reaction center chlorophylls, the sampling was increased to 200 snapshots to reduce the statistical

uncertainty. Excitonic coupling between the pigments was evaluated in the dipole approximation, based on the transition dipole moments to the first excited state.

- The local environment of each chlorophyll shifts its excitation energy to the red or to the blue. Using the model introduced above, a series of energy sinks and barriers was identified in the antenna complex. The low energy chlorophylls in PS I, often referred to as red chlorophylls, are of special interest, as they are the dominant fluorescence emitters at low temperatures. Their role is not yet fully understood but they are generally thought to compete with energy transfer to the reaction center.<sup>[260]</sup> A definitive assignment of these red chlorophylls requires the simulation of excited state relaxation and fluorescence properties, which was outside the scope of this work. Nevertheless, a set of promising candidates was identified, based on excitation energies evaluated in the high-level QM/MM framework introduced above. This work and the associated data set therefore enable future studies on the subject of red chlorophylls.
- The site energy shifts were decomposed into an electrostatic and a structural component. While the structural part were explained by thermal noise, the electrostatic component clearly corresponds to the unique local environment of each chlorophyll. However, no general mapping from the electrostatic environment to the chlorophyll site energies could be determined.
- Comparing the two electron transfer branches A and B in the reaction center (cf. figure 3.1), the A branch exhibits slightly lower site energies. This asymmetry indicates that branch A may act as an energy sink, consistent with the experimental observation that branch A is the dominant electron transmitter.<sup>[215,216]</sup>
- As expected, the central pair of chlorophylls, labeled P700 and commonly referred to as the *special pair*, exhibits the strongest excitonic coupling, due to the close proximity of its pigments. However, its average excitation energy is in the center of the distribution across all chlorophylls, which maximizes the coupling efficiency with the entire antenna complex but seemingly contradicts the accumulation of energy at P700. Moreover, P700 is separated from the antenna complex by two high-energy chlorophylls. This calls into question common models of energy transfer in light-harvesting systems, which assume a downhill pathway from the antenna to the reaction center. The dynamical perspective in this work shows that such a persistent energy funnel may not be required, as energy transfer is mediated by thermal fluctuations, mainly in the site energies.
- While the excitonic couplings are stable with a standard deviation  $\sigma$  in the range of 0 to 5 meV, the site energies fluctuate much more strongly ( $\sigma = 30 \text{ to } 60 \text{ meV}$ ). This is enough to overcome transient energy barriers and transfer energy from the antenna complex to the reaction center. In this picture, the energy sinks in the antenna complex could even act as temporary energy storage, while the reaction center is in its oxidized state.



Figure 3.4: Excitonic spectrum of PS I compared to an experimentally determined spectrum at  $5 \text{ K.}^{[255]}$  Sticks denote the individual excitonic transitions, averaged over 40 (antenna) or 200 (reaction center) snapshots. Calculated energies have been red-shifted by 0.072 eV and convoluted with Gaussian functions with fwhm = 0.012 eV.

Based on the excitonic Hamiltonian, an absorption spectrum including the inter-chromophore dipole coupling can be simulated, complementing the site spectrum in fig. 4 of the article. To this end, the transition dipole moments of the individual chlorophylls  $\mu^{\text{site}}$  are transformed to the exciton basis *via* the eigenvector **c** of the excitonic Hamiltonian:

$$\mu^{\text{ex}} = \sum_{i} c_i \cdot \mu_i^{\text{site}}.$$
(3.1)

The resulting spectrum agrees well with the experimental reference, measured at  $5 \text{ K.}^{[255]}$  At this temperature, the ambient thermal energy is no longer sufficient to facilitate energy transfer from the red states, causing a visible side band in the red part of the spectrum. The same side band is observed in the simulation at 1.76 eV. It can be attributed to the triad of chlorophylls B31-B32-B33, which forms the lowest energy exciton. The additional broadening of the red band in the experimental spectrum might be due to coupling to CT states, which are not part of the simulation, or due to the presence of a conformational ensemble in multiple measured photosystems where the calculated spectrum only depicts the average band position. A full band assignment of the excitonic states is available in tab. S7 of the Supporting Information to the article (reprinted in table C.9 in appendix C.2).

While the QM/MM simulations in the article consider the trimeric protein complex in the form of point charges, the actual excited state calculations are carried out for the 96 chlorophylls in one PS I monomer. To simulate the excitonic interactions in the trimer, the site energies and transition dipole moments were replicated around the  $C_3$  axis and the



Figure 3.5: Excitonic network in the PS I trimer, averaged over 40 MD snapshots. Each data point represents the center of a chlorophyll molecule, colored by the lowest energy exciton it contributes to with a weight of more than 10%. Connecting lines illustrate the strength of the excitonic coupling with thicker lines denoting stronger coupling. For clarity, only couplings > 1 meV are visualized. The dashed green line denotes the PS I monomer corresponding to fig. 6 in the article. The data set of excitonic energies in the trimer is available in appendix C.3.

excitonic couplings were recalculated. The result is depicted in figure 3.5. Chlorophylls involved in the coupling are predominantly located in the peripheral subunit A (right quarter of the highlighted monomer in figure 3.5) and couple to the chlorophylls M1, B8, B9 and B11 of the adjacent monomer. Chlorophyll L1 is only weakly coupled (1 meV) to B37 and B38, despite its central position near the  $C_3$  axis on the stromal side (cf. figure 3.1) of the protein complex. In general, the inter-monomer coupling in the PS I trimer is weak, with the maximum interaction energy around 6 meV (A30  $\leftrightarrow$  M1).

The evolutionary advantages of the trimerization of cyanobacterial PS I are still subject of debate.<sup>[261]</sup> It is noteworthy that plant-based PS I occurs exclusively monomeric, while the oligomerization pattern in bacteria can vary between species and environments.<sup>[262]</sup> Low-light conditions favor the trimeric form, while monomeric PS I is the predominant form at medium light intensities<sup>[263]</sup> and high-light stress induces the formation of PS I dimers and tetramers.<sup>[264]</sup> Stabilization of the photosystem against loss of chromophores<sup>[263]</sup> and protection against reactive oxygen species<sup>[265]</sup> have been discussed as benefits of the trimeric form. Most importantly, trimerization allows for increased packing density in the membrane<sup>[262]</sup> and improves interactions with phycobilisomes,<sup>[261]</sup> which act as peripheral antennas, thus improving the light-harvesting at low-light conditions. The results in figure 3.5 suggest that energy transfer to the reaction center *via* inter-monomer coupling only plays a subordinate role.

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## 1 Introduction

In oxygenic photosynthesis, photoautotrophic organisms harvest solar energy to drive a light-induced cascade of electron and proton transfers.<sup>1</sup> Photosystem I (PSI) plays a crucial role in this process as it catalyzes the oxidation of plastocyanines to subsequently reduce ferredoxins. This energy conversion step occurs with a near-unity efficiency. An in-depth understanding of this remarkably high efficiency may guide future designs of artificial light harvesting (LH) systems.<sup>2-4</sup>

The cyanobacterial (*T. elongatus*) PSI is a trimeric transmembrane protein supercomplex.<sup>5-7</sup> Each monomer comprises twelve protein subunits, 96 chlorophylls, 22

# Thermal site energy fluctuations in photosystem I: new insights from MD/QM/MM calculations<sup>†</sup>

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Cyanobacterial photosystem I (PSI) is one of the most efficient photosynthetic machineries found in nature. Due to the large scale and complexity of the system, the energy transfer mechanism from the antenna complex to the reaction center is still not fully understood. A central element is the accurate evaluation of the individual chlorophyll excitation energies (site energies). Such an evaluation must include a detailed treatment of site specific environmental influences on structural and electrostatic properties, but also their evolution in the temporal domain, because of the dynamic nature of the energy transfer process. In this work, we calculate the site energies of all 96 chlorophylls in a membrane-embedded model of PSI. The employed hybrid QM/MM approach using the multireference DFT/MRCI method in the QM region allows to obtain accurate site energies under explicit consideration of the natural environment. We identify energy traps and barriers in the antenna complex and discuss their implications for energy transfer to the reaction center. Going beyond previous studies, our model also accounts for the molecular dynamics of the full trimeric PSI complex. Via statistical analysis we show that the thermal fluctuations of single chlorophylls prevent the formation of a single prominent energy funnel within the antenna complex. These findings are also supported by a dipole exciton model. We conclude that energy transfer pathways may form only transiently at physiological temperatures, as thermal fluctuations overcome energy barriers. The set of site energies provided in this work sets the stage for theoretical and experimental studies on the highly efficient energy transfer mechanisms in PSI.

> carotenoids, four lipids, three iron–sulfur clusters and two phylloquinones.<sup>6,7</sup> The chlorophyll *a* molecules are organized in an antenna complex of 90 pigments and a reaction center (RC) of six chlorophylls arranged in two pseudo-symmetrical branches, denoted A and B.<sup>6,7</sup> After the initial excitation of the PSI antenna complex, the generated Frenkel-exciton has an estimated lifetime of around 35 ps, followed by charge separation inside the RC.<sup>8-12</sup> At the very center of the RC lies the special pair P700, ultimately acting as the electron donor.<sup>13–15</sup>

> There are still many open questions regarding the funneling of energy from the antenna complex to the RC and the onset of charge separation therein.<sup>16</sup> The large amount of pigments and their strongly overlapping absorption bands obscure clear experimental access to the excited state processes inside PSI.<sup>8,17–21</sup> Here, theoretical insights can complement experiments in disentangling and explaining the measured optical responses to deduce mechanisms for the energy and charge transfer.<sup>18,19,22–27</sup>

> The popular funnel theory expects downhill energy transport from the antenna complex towards the RC.<sup>8,28,29</sup> However, experiments demonstrated reliable performance of PSI, even when excited in the red edge of the spectrum, which implicates an uphill energy transfer.<sup>8,23,30</sup> Concerning charge-separation, several theories agree on the special pair as the primary

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<sup>†</sup> Electronic supplementary information (ESI) available: Details on structure modelling; further details on the MD protocol and validation; chlorophyll absorption spectra with various QM methods; mean site energies and energy shifts of each chlorophyll, sorted according to Fig. 9; convergence of site energies with the number of snapshots; comparison of the present data set with literature data; excited states of selected chlorophyll dimers and the trimer B31– B32–B33; exciton energies. See DOI: https://doi.org/10.1039/d2sc06160k

electron donor in multiple LH complexes.<sup>8,19,31</sup> However, timeresolved experiments on PSI<sup>14,17</sup> as well as theoretical results for PSII<sup>32</sup> suggest the origin of the free charges in adjacent chlorophylls in one of the two branches, preferentially the A branch. The lack of agreement between theories, experiments and computational studies emphasizes the need for an accurate model of energy and charge transfer processes.

PSI also presents significant challenges to computational methods, especially regarding the chlorophylls governing the energy and charge transfer.<sup>4,18,33</sup> The protein environment in pigment–protein complexes such as PSI is specific for each chlorophyll, which leads to individual absorption spectra or site energies for each chromophore.<sup>32,34</sup> In accordance with the Gouterman-model,<sup>35</sup> these site energies correspond to the  $Q_y$  state as the lowest excited state of chlorophyll. The unordered nature of the PSI antenna complex compared to *e.g.* LH2 in purple bacteria,<sup>36</sup> creates additional challenges regarding the determination of the finely tuned site energies.

Given that theoretical models such as resonance energy transfers (RET) heavily depend on accurate excitation energies, the site energies lie at the core of every model for energy transfer.37-39 With previously accessible methods for the much smaller Fenna-Matthews-Olson (FMO) complex, an unambiguous assignment needs yet to be reached after more than three decades of computational and experimental studies.31,40 Similarly, there have been many attempts to obtain a set of conclusive site energies for PSI. Fitting procedures have resulted in accurate reproductions of optical spectra but did not reach a conclusive picture of energy transfer dynamics.41-43 Quantumchemically derived site energies for static structures obtained from crystallographic data44 or an optimization by density functional theory (DFT) methods<sup>22,45</sup> achieved predictions of the overall spectrum and an assignment of site energies. However, no study was able to prove or disprove the energy funnel theory. Subsequent works adding excitonic couplings to the site energy determination continued to refine some fundamentals of energy transfer, specifically the importance of long range electrostatics, the asymmetry in the charge transport and a lack of a continuous site energy gradient towards the RC.23,31 With increasing computational resources, site energies in other LH systems were determined computationally from samples of molecular dynamics simulations (MD).<sup>32,46-49</sup> Such an approach requires many single-point calculations for each chlorophyll, which often leads to compromises in the electronic structure theory to retain computational feasibility. Insights into the dynamic evolution of optical properties are therefore inherently limited by the typically employed lower-level quantum mechanical (QM) methods.32 Despite their importance in RET models as diagonal elements of the excitonic Hamiltonian, an accurate determination of the absolute site energies including their energy fluctuation dynamics remains elusive. Here, we aim to close this gap by presenting a new set of chlorophyll site energies in PSI, including (i) the molecular dynamics of the trimeric and membrane-embedded supercomplex, (ii) the electrostatic influence of the natural environment in a QM/MM approach and (iii) the multireference character inherent to chlorophyll excitations via the high-level DFT/MRCI method.

This work is structured as follows: first, we introduce the relevant computational protocols and justify our choice of method by comparison to other quantum chemical approaches and to experimental steady-state spectra. Next, we discuss the obtained site energies and exciton dipole couplings in the context of temporal averages with a focus on locating low-energy chlorophylls. While the functional role of these "red chlorophylls" remains to be elucidated in detail, they may act as kinetic traps for an exciton and impede the excitation energy transfer to the reaction center,<sup>10,21,50</sup> especially when adjacent to higher energy chlorophylls. Our findings are complemented by a dynamical perspective on site energy and exciton fluctuations, as well as electrostatic and structural influences, providing new insights on the energy funnel theory.

### 2 Methods

#### 2.1 Absorption of isolated chlorophyll

To assess the performance of different quantum chemical methods, we compared calculated absorption spectra to an experimental spectrum in diethyl ether.<sup>51,52</sup> For this purpose, the geometry of chlorophyll *a*, axially coordinated by two ether molecules was optimized at the r<sup>2</sup>SCAN-3c<sup>53</sup> level of theory with Orca 5.0.3<sup>54</sup> and verified as a minimum by the absence of imaginary vibrational frequencies. The r<sup>2</sup>SCAN-3c<sup>53</sup> composite method builds on the r<sup>2</sup>SCAN meta-GGA density functional and contains three empirical corrections, namely a custom triple- $\zeta$ basis set denoted def2-mTZVPP,53 a refitted D4 dispersion correction<sup>55</sup> and a geometric counter-poise correction<sup>56</sup> to account for London dispersion forces and the basis set superposition error. The method has proven to yield superior ground state geometries and energies for a large variety of organic molecules, on par with or even surpassing more expensive hybrid DFT approaches.53 Further solvation effects were accounted for by the conductor-like polarizable continuum model (C-PCM),  $^{\rm 57}$  using a relative permittivity of  $\varepsilon_{\rm r} = 4.27$   $^{\rm 58}$  and a refractive index of  $n_{\rm D}=$  1.3526  $^{58}$  for diethyl ether. Vertical excitation energies were calculated with the density functionals BHLYP, 59,60 M06-2X, 61 B3LYP, 59,60,62 CAM-B3LYP, 63 wB97X-D4 64 and SCS-wPBEPP86 65 using the Tamm-Dancoff approximation<sup>66</sup> (TDA) and the def2-TZVP<sup>67</sup> basis set. The RIJCOSX approximation68,69 was employed with the def2/J70 and def2-TZVP/C<sup>71</sup> auxiliary basis sets to speed up the calculations. At the lower level of theory, we also tested the Zerner's Intermediate Neglect of Differential Overlap with parameters for Spectroscopic properties (ZINDO/S) method,<sup>72</sup> which has been used frequently in previous studies73-77 on chlorophyll excitations. Here, the C-PCM was switched off, as the implementation of ZINDO/S we used is not parametrized for use with implicit solvation models. With each method, 20 roots were included in the calculation.

Additionally, we tested the DFT/MRCI method<sup>78,79</sup> in its parallel implementation.<sup>80</sup> The DFT reference was evaluated with the BHLYP<sup>59,60</sup> functional implemented in *Orca 4.2.1* <sup>81–83</sup> and the def2-SVP<sup>67</sup> basis set. To speed up the evaluation of Coulomb and exchange integrals, we employed the resolution of the identity (RI-JK) approximation<sup>84</sup> with the def2-SVP/C<sup>71</sup> and def2/JK<sup>85</sup>

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auxiliary basis sets. SCF convergence was set to  $10^{-7} E_{\rm h}$  (Orca keyword *SCFCONV7*) and a tighter-than-default integration grid was used (Orca keyword *GRID4*). The MRCI reference space was iteratively optimized, starting from a CISD expansion of four electrons in the four frontier orbitals, until it contained all leading configurations of the 10 roots included in the calculations. This starting guess corresponds to the most important transitions in the Gouterman picture.<sup>35</sup> The R2018 Hamiltonian<sup>86</sup> was employed with a selection threshold of 0.8  $E_{\rm h}$  and the tight parameter set to damp off-diagonal elements of the CI matrix, avoiding double counting of dynamical correlation.

#### 2.2 Structural model of PSI

As a starting point for our investigations of PSI, we used the asymmetric unit from the 2.5 Å crystal structure of cyanobacterial PSI7 in T. elongatus (PDB: 1JB0), consisting of one monomer of the trimeric protein supercomplex. Missing amino acids were added with the Modeller interface87 to UCSF Chimera<sup>88</sup> (cf. ESI Table S1<sup>†</sup>). Missing heavy atoms were added manually to the chlorophyll residues CLA A1402 and J1303, to βcarotene BCR A4009, and to the lipids LHG A5003 and B5004. Of the 96 Chla molecules in the asymmetric unit, 49 contain only partially resolved phytyl chains. As the phytyl chain's contributions to the absorption spectrum are negligible,<sup>89,90</sup> we kept the intact chains but replaced all damaged phytyl residues with methyl groups (cf. ESI Fig. S1<sup>†</sup>). While there are studies that point to the role of the phytyl chain in coordinating<sup>91</sup> or preventing coordination<sup>92</sup> to the central Mg<sup>2+</sup> ion, we argue that these structural effects are contained in the MD simulations. All crystal water was retained and hydrogens were added with pdb2gmx included in Gromacs 2020.1 93 or, for newly parametrized molecules, with reduce,94 distributed with AmberTools 20.

To mitigate steric clashes introduced by the addition of atoms, the total energy of the asymmetric unit was minimized with the steepest descent algorithm implemented in *Gromacs 2020.1* <sup>93</sup> until the residual force was smaller than 1000 kJ mol<sup>-1</sup> nm<sup>-1</sup>. For this, the prepared structure was placed in a cubic box with 17.664 nm edge length, solvated with TIP3P water molecules and charge neutralized by adding 15 Na<sup>+</sup> ions. The energy-minimized asymmetric unit was subsequently replicated three times to assemble the trimeric PSI supercomplex. In the process, crystal water L4042, located exactly on the  $C_3$  axis, was removed two out of three times.

Finally, a lipid bilayer consisting of 674 lumenal and 683 stromal molecules of 1-palmitoyl-2-oleoylphosphatidylcholine (POPC) was packed around the photosystem with *packmolmemgen*,<sup>95</sup> from *AmberTools 20*. The membrane-embedded protein was solvated with TIP3P water and the charge was neutralized, maintaining a physiological salt concentration of 0.15 mol L<sup>-1</sup> NaCl. The final structure contained 935 722 atoms and is illustrated in Fig. 1.

#### 2.3 Force field parameters

To ensure that the parameters for the protein and all cofactors were compatible to each other, we employed only parameters that were derived for use with the Amber family of force fields.



Fig. 1 Side and top view of the membrane-embedded PSI with final box dimensions after equilibration. The MD box is drawn in blue. Parts of the membrane and solvent layers were removed in the visualization for clarity.

The protein was described with the Amber14sb<sup>96,97</sup> force field. Parameters for the cofactors chlorophyll a and  $\beta$ -carotene were taken from related studies on PSII,98 which are in turn based on parameters by Ceccarelli et al.99 Iron-sulfur clusters and the coordinating CYS residues were described with parameters for oxidized, proximal Fe/S clusters derived by Smith et al.<sup>100</sup> The available CYS residue type in Amber14sb does not describe coordination to metal clusters. We therefore introduced a new residue type CYF for the iron-coordinating CYS residues by removing the S-bound hydrogen from the CYS entry in Amber14sb, substituting the  $C_{\beta}$  charge with the published one<sup>100</sup> (-0.01172) and patching the  $C_{\alpha}$  charge such that the overall charge of the  $[FeS]_4/CYF_4$  cluster was -2. The coordination bond between the sulfur and iron atoms was described by the published<sup>100</sup> bonded interaction parameters. The rest of the interactions between CYF and Fe<sub>4</sub>S<sub>4</sub> were purely non-bonded and the standard parameters for CYS as defined in Amber14sb were used for this purpose. The lipids 2,3 dipalmitoyl-D-glycero-1-phosphatidylglycerol (LHG) and 1,2-distearoylmonogalactosyl-diglyceride (LMG) were described with the LIPID17 force field.<sup>101-103</sup> As the head group for LMG was not contained in LIPID17, parameters were generated with antechamber<sup>104</sup> using the general Amber force field (GAFF).<sup>105</sup> RESP charges were derived from HF/6-31G\* calculations according to

the Amber protocol for lipids,<sup>101</sup> such that the total charge of the head group was zero. Parameters for phylloquinone were generated analogously.

#### 2.4 Molecular dynamics

Molecular dynamics (MD) simulations were performed with a single-precision version of *Gromacs 2020.1.*<sup>93</sup> The trimeric PSI complex was placed in a tetragonal simulation box with dimensions 26.0 nm  $\times$  26.0 nm  $\times$  14.5 nm. To minimize steric clashes introduced in the membrane packing process, the total energy was minimized with the steepest descent algorithm until the maximum force was below 1000 kJ mol<sup>-1</sup> nm<sup>-1</sup>. In all following steps, the leap-frog integrator was employed with a time step of 2 fs and bonds to hydrogens were constrained using the LINCS algorithm.<sup>106</sup> Short-range electrostatics were calculated using Verlet lists with a cutoff distance of 1.2 nm. Particle-mesh Ewald summation<sup>107</sup> was conducted for the longrange electrostatics using cubic interpolation and a Fourier grid spacing of 0.16 nm.

Equilibration was conducted in three phases. First, the system was heated from 10 K to 100 K over 50 ps in an NVT ensemble, controlled by the V-rescale thermostat108 with a time constant of 0.1 ps. The positions of the protein and all cofactors were restrained with a force of 1000 kJ mol<sup>-1</sup> nm<sup>-1</sup>. Two temperature coupling groups were employed, one for the membraneembedded protein and one for water and ions. The system was propagated for another 50 ps at a constant temperature of 100 K to further minimize clashes in the membrane and solvent. In the second equilibration step, the temperature was raised from 100 K to the production temperature of 300 K over 100 ps in the NPT ensemble, keeping the position restraints. The pressure was controlled by the Berendsen barostat with a semiisotropic reference pressure of 1 bar, a coupling constant of 5 ps and using an isothermal compressibility of  $4.5 \times 10^{-5}$  bar<sup>-1</sup>. After annealing, the system was propagated for 900 ps at the target temperature in the NPT ensemble. In the third step, the position restraints were lifted and the system was propagated for 15 ns in an NPT ensemble, controlled by the Nosé-Hoover thermostat109,110 and the Parrinello-Rahman barostat<sup>111,112</sup> with time constants of 0.5 ps and 5.0 ps, respectively. Proper equilibration was confirmed by the average temperature, pressure and density converging to their target values, as well as the total energy and box vectors remaining stable. The final box dimensions were 26.9 nm  $\times$  26.9 nm  $\times$ 12.6 nm (Fig. 1). From the last nanosecond of this converged NPT ensemble, five production simulations over 15 ns were started. Snapshots were extracted only from the last 10 ns of each production run. During the production trajectories, the RMSDs of the protein backbone as well as that of the cofactors chlorophyll, β-carotene and phylloquinone remained stable and between 1 Å to 2 Å, further indicating that the system was equilibrated. Similarly, the area-per-lipid of the membrane had converged at 0.64 nm<sup>2</sup>, in good agreement with literature values.<sup>113–115</sup>

#### 2.5 QM/MM protocol

Chlorophyll site energies were computed in a QM/MM scheme, where the two subsystems were coupled electrostatically.<sup>116,117</sup>

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Here, the environment of each chlorophyll is expressed as a distribution of classical point charges. By including the entire model of the photosystem in the point charge distribution, all short- and long-range electrostatic interactions between a chlorophyll and the rest of the photosystem are contained in the calculations. The vertical excitation energy E is given by

$$E = (E_{\rm ES}^{\rm QM} + E_{\rm ES}^{\rm coup}) - (E_{\rm GS}^{\rm QM} + E_{\rm GS}^{\rm coup}),\tag{1}$$

where  $E_{\rm ES}$  and  $E_{\rm GS}$  denote the energies of the excited state and ground state, respectively, and the superscript indicates either the energy of the QM subsystem (QM) or the coupling term induced by polarization of the QM wave function by the classical charge distribution (coup). In the case of DFT/MRCI, the coupling to the environmental point charges is included as a Coulomb term in the one-electron Hamiltonian of the DFT reference. As the energy of the MM subsystem is equal in the ground and excited state, no separate MM calculation is required.

Unless otherwise stated, the QM region contained the respective chlorophyll molecule without the phytyl chain, which was always capped at the first carbon by a hydrogen link atom.118-120 Omitting the phytyl chain from the QM region is commonplace in the literature, as its electronic contributions to the absorption are negligible.49,89,90,121-123 We have tested this truncation also for our particular QM/MM multireference workflow and found that it performs well (ESI Table S4<sup>†</sup>). The MM region consisted of the full MD simulation box, i.e. the trimeric PSI supercomplex embedded in the solvated lipid membrane. Overpolarization at the QM/MM boundary was avoided by shifting point charges away from the link atom and introducing artificial charges to preserve the dipole moment of the former bond.<sup>120</sup> Point charges were taken unmodified from the Amber-based classical force field (see above), where all charges were derived consistently via the established RESP protocol.124 The OM subsystem was centered in the simulation box to account for periodic boundary conditions.

#### 2.6 Calculation of site energies

Site energies for each of the 96 chlorophylls in one asymmetric unit were calculated with the DFT/MRCI method as described above, with five singlet roots included in the MRCI part. 20 evenly spaced snapshots were extracted from the last 10 ns of two production MD simulations, resulting in 40 samples with a temporal spacing of 0.5 ns. To separate structural from electrostatic effects, these calculations were performed with and without classical point charges, resulting in 7860 individual calculations. Additional sampling was performed for the RC chlorophylls due to their special significance. Here, a total of 200 snapshots were extracted from the last 10 ns of all five production MD simulations with a temporal spacing of 0.25 ns.

#### 2.7 Excitonic coupling

To get a first estimate of excitonic effects on the energy transfer, the coupling elements  $V_{ij}$  between pairs of chlorophylls *i* and *j* were evaluated in the point dipole approximation:

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$$V_{ij} = f \kappa \frac{\mu_i \mu_j}{r_{ij}^3} \tag{2}$$

here,  $\mu_i$  is the  $Q_v$  transition dipole moment of chlorophyll *i* in its respective environment and r<sub>ij</sub> denotes the center-of-mass distance between the coupled chlorophylls. Due to its simplicity, the dipole approximation is still widely used to quickly screen the magnitude of the coupling25,125-128 and has been shown to perform well in related photosystems when compared to more involved techniques.126,128 As the strength of the coupling depends on the magnitude of the calculated transition dipole moments, each  $\mu_i$  obtained from the DFT/ MRCI calculations was scaled by a factor of 0.79, such that the average  $\langle \mu \rangle$  over all snapshots and chlorophylls matched the measured transition dipole moment<sup>129</sup> of chlorophyll a in dielectric media (5.48 D). The orientation factor  $\kappa$  in eqn (2) is defined by the normalized transition dipole moment vectors  $\vec{\mu}_i$ and  $\vec{\mu}_i$  of the chlorophylls and the unit vector  $\vec{R}_{ii}$  connecting their centers of mass:

$$\kappa = (\vec{\mu}_i \cdot \vec{\mu}_j) - 3[(\vec{\mu}_i \cdot \vec{R}_{ij})(\vec{\mu}_j \cdot \vec{R}_{ij})].$$
(3)

To account for electrostatic screening effects by the environment, a screening factor f is introduced in eqn (2). Its value was fixed to 0.72 in this work, based on the findings by Renger *et al.*<sup>23</sup>

Using the site energies  $\varepsilon_i$  and couplings  $V_{ij}$ , an excitonic Hamiltonian *H* was constructed:

$$H = \begin{pmatrix} \varepsilon_1 & V_{1,2} & \dots & V_{1,96} \\ V_{2,1} & \varepsilon_2 & \dots & V_{2,96} \\ \vdots & \vdots & \ddots & \vdots \\ V_{96,1} & V_{96,2} & \dots & \varepsilon_{96} \end{pmatrix}.$$
 (4)

Diagonalization of *H* yields the excitonic energies as diagonal elements and the contribution coefficients  $c_i$  of each chlorophyll to a respective exciton as eigenvectors. The square of  $c_i$  gives the weight  $w_i$  of chlorophyll *i* in the exciton with  $\sum_i w_i = 1$ . This analysis was conducted for each MD snapshot as well as for the temporal mean of site energies and couplings.

## 3 Results and discussion

In the following, we will refer to the chlorophylls in PSI using the nomenclature introduced by Jordan *et al.*, where the pigments are numbered consecutively according to their associated protein subunit.<sup>7</sup> The chlorophylls in the electron transfer chain are additionally prefixed by 'eC'. For a translation between the naming schemes used in the crystal structure PDB, our MD simulations and the conventional nomenclature,<sup>7</sup> please refer to ESI Table S5.<sup>†</sup>

#### 3.1 Choice of method

When discussing the energy transfer in light-harvesting processes, the site energies vary in a small window of  $\pm 100$  meV.<sup>23,41-45</sup> If the error of the quantum chemical method is much larger than this in

the first place, it is hard to obtain a quantitative picture of the small energy fluctuations that govern the light-harvesting processes. The disagreement between existing sets of site energies in PSI (*cf.* ESI Fig. S11†) emphasizes the need for a method that can accurately reproduce not just energy differences but also the excitation energies themselves. At the same time, computational cost is a decisive factor in a problem of this scale.

To find a method that satisfies both criteria, we calculated the excitation energies of the first five roots for an optimized structure of chlorophyll *a* at different levels of theory, ranging from the semiempirical ZINDO/S method over TDA-DFT to multireference calculations with the DFT/MRCI method. For each method we evaluated how well the overall absorption spectrum of chlorophyll *a* is reproduced (Fig. 2 and ESI Fig. S7†) and especially how close the calculated energy of the  $Q_y$  state is to the experimentally<sup>51,52</sup> observed one (Table 1).

As a semiempirical method designed for biomolecules including porphyrin-based pigments, ZINDO/S is most affordable in terms of computational effort. However, any deviations from the fitting range of ZINDO/S reveal its shortcomings. The excitation energy of the  $Q_y$  band is underestimated by 0.25 eV, owing to the axial coordination with diethyl ether. Furthermore, the  $Q_x$  band, which in reality is closely mixed with the vibronic progression of  $Q_y$ ,<sup>123,130</sup> appears at an unreasonably high energy of 2.2 eV, separated by 0.6 eV from  $Q_y$  (Fig. 2). In ensemble simulations, ZINDO/S has been shown to overestimate the red tail of the spectrum, because of its parametrization only for equilibrium structures.<sup>46,131</sup> The hybrid density functionals vary strongly in their performance for different properties. While the



Fig. 2 Calculated absorption spectra for an optimized (r<sup>2</sup>SCAN-3c) structure of chlorophyll *a*, axially coordinated by two diethyl ether molecules, compared to an experimental spectrum in diethyl ether.<sup>51,52</sup> Stick spectra were convoluted by Gaussians ( $\sigma = 0.05$  eV). Excited states with an oscillator strength <0.1 are indicated by dotted lines. A comparison with all tested density functionals is available in Fig. S7 in the ESI.<sup>†</sup>

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Table 1 QM/MM excitation energies for the Qy (S<sub>1</sub>) state of chlorophyll *a*, axially coordinated by two diethyl ether molecules with different QM methods, compared to the experimental energy in diethyl ether.<sup>51,52</sup> Structure optimized at the r<sup>2</sup>SCAN-3c level

Method	E[eV]	f
ZINDO/S	1.622	0.3325
TDA-BHLYP	2.202	0.4953
TDA-B3LYP	2.148	0.4311
TDA-M062X	2.197	0.4388
TDA-CAM-B3LYP	2.158	0.4313
TDA-ωB97X-D4	2.140	0.3896
TDA-SCS-ωPBEPP86	1.811	0.3812
DFT/MRCI $(0.8 E_{\rm h})$	1.939	0.3473
DFT/MRCI $(1.0 E_{\rm h})$	1.903	0.3449
Exp. (diethyl ether)	1.876	—

 $Q_x - Q_y$  gap is best reproduced by CAM-B3LYP and M06-2X (ESI Fig. S7<sup>†</sup>), the error of the  $Q_{\nu}$  band energy is smallest with  $\omega$ B97X-D4 at the expense of a severely overestimated  $Q_x - Q_y$ gap. All of the tested hybrid density functionals blue-shift the entire absorption spectrum by  $\sim$ 0.3 eV. The blue shift is stronger for the B bands than for the Q bands, which can be explained by non-negligible contributions of doubly excited configurations to the higher excited states.122,132 These are partially accounted for by the perturbative doubles correction included in the recently introduced65 range-separated doublehybrid functional SCS-wPBEPP86, which is however much more expensive. At comparable cost, the DFT/MRCI method matches the experimental absorption spectrum almost exactly, in good accordance with another recent study on the spectral properties of photosynthetic pigments.<sup>133</sup> We only observe a minor systematic blue-shift of the entire spectrum by  $\sim$ 0.06 eV. Notably, we also do not observe a spurious doubly excited state between the Q- and B-bands, as predicted by earlier DFT/MRCI calculations,<sup>132</sup> which may be rooted in the use of the completely refitted R2018 Hamiltonian.86 These results indicate that the fundamental physics of chlorophyll excitations are correctly reproduced with the new DFT/MRCI Hamiltonian. In our tests, the calculation of 10 roots required only 21 h of wall time, running on 8 CPUs. We therefore regard the DFT/MRCI method, especially with the tight parameter set, as ideally suited to compute the spectroscopic properties of chlorophylls.

Although DFT/MRCI provides highly accurate energies for individual chlorophylls at an affordable cost, it would be too expensive for pairs of pigments. However, the antenna complex of PSI features many closely packed chlorophyll aggregates,<sup>7,41</sup> where excited state localization on one of the individual chromophores cannot be trivially assumed. We therefore tested our QM/MM partitioning scheme by computing the excitation energies for the five lowest roots of selected chlorophyll pairs from different spatial regions of PSI at the TD- $\omega$ B97X-D4/def2-TZVP level of theory. For each pair, the QM region contained both chlorophyll molecules. The natural transition orbitals of the dimer excited states (ESI Fig. S13†) confirm that the excitation is in most cases localized on one of the two pigments, supporting our QM/MM partitioning scheme and by extension affording us the high-level DFT/MRCI method.

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#### 3.2 Chlorophyll absorption in PSI

An important issue when analyzing dynamical site energy fluctuations by means of MD sampling is achieving convergence of the average energies. Fig. 3 illustrates the convergence of the arithmetic mean of the site energy for four representative chlorophyll residues with the number of considered snapshots. All other residues follow the same trend, with the average energies converged after  $\sim 20$  snapshots (ESI Fig. S10<sup> $\dagger$ </sup>). Thus, our sample size of 40 conformational snapshots per chlorophyll is clearly enough to obtain meaningful temporal averages. Given the importance of the six RC chlorophylls, we calculated their site energies in an additional 160 snapshots, thus increasing the data set to 200 samples. A one-way ANOVA analysis followed by Tukey's honest significant differencing (HSD) test (for details cf. ESI Section 5<sup>†</sup>) confirmed the statistical significance of the site energy differences discussed in this work.

The calculated absorption spectrum of all 96 chlorophylls in the PSI monomer (Fig. 4) is in excellent agreement with the experimental spectrum, measured previously by Di Donato *et al.*<sup>17</sup> The energy gap between the Q and B bands is reproduced correctly and only a minor red-shift of 0.07 eV needs to be applied to match the experimental  $Q_y$  band. This again corroborates the need for high-level quantum-chemical methods, ideally including multireference character, to model the chlorophyll absorption spectrum, as other methods exhibit much larger errors. The shoulder at 500 nm in the experimental absorption spectrum corresponds to the  $\beta$ -carotenes in PSI, which are not the subject of this study.

#### 3.3 Site energies and couplings

The excitation energy of each chlorophyll is tuned by the environment. These site energy shifts supposedly steer the energy transfer within the photosystem, culminating either in a redox event in the RC or in the trapping of excitation energy at lowenergy sites. The average site energy shift of each chlorophyll against the total mean is illustrated in Fig. 5. Including the coupling between the chlorophylls, the lowest energy excitons



**Fig. 3** Convergence of the average site energy for four representative chlorophyll residues with the number of snapshots. 40 snapshots from two trajectories cover a time scale of 20 ns.

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**Fig. 4** Calculated absorption spectrum of all Chla in PSI (solid green line) compared to an experimental absorption spectrum of trimeric PSI (dashed blue line) at 293 K.<sup>17</sup> The stick spectra signify the absorption lines of the four lowest excited states of each individual chlorophyll, colored by the energetic order of the excited state (S<sub>1</sub>: red, S<sub>2</sub>: yellow, S<sub>3</sub>: turquoise, S<sub>4</sub>: dark green). Each stick spectrum was convoluted with a Gaussian ( $\sigma = 0.025$  eV) and summed up to yield the broadened absorption. The intensity was scaled to match the experimental absorption of the  $Q_y$  state. A constant red-shift of 0.07 eV was applied to all calculated spectra.

are visualized in Fig. 6. In general, the mean site energies range between 1.85 eV and 1.93 eV, while the 100 largest mean couplings range between 4 meV and 43 meV. The strongest coupling is observed in P700.



**Fig. 6** Exciton energies in PSI, averaged over all sampled MD snapshots (40 for the antenna complex, 200 for the RC). Each dot signifies a chlorophyll and is colored by the lowest energy exciton domain that this chlorophyll belongs to ( $w_i > 0.1$ ). Connecting lines represent the coupling strength ( $V_{ij} > 1$  meV) with thicker lines denoting stronger coupling. The energy axis is centered around the mean of all exciton energies.

Many red chlorophylls, such as A10, A15, A20, A34, K1, B18 and PL1 appear in the peripheral regions of the antenna complex, far away from the RC. An often disputed red site in the periphery is the triad B31/B32/B33.<sup>20,134,135</sup> These three chlorophylls are special because their porphyrin planes are almost parallel and their  $Q_y$  transition dipole moments remain aligned with each other during the dynamics. Structural arguments<sup>7,41</sup> and fits of optical spectra<sup>42,43</sup> favor this triad as a red site. However, semiempirical methods,<sup>44</sup> early DFT calculations<sup>45</sup> and a study using the charge density coupling technique<sup>23</sup> yield



Fig. 5 Site energy shifts in PSI averaged over all sampled MD snapshots (40 for the antenna complex, 200 for the RC). Chlorophylls are colored according to their red- or blue-shift, relative to the mean site energy, obtained by averaging over all chlorophylls and snapshots (1.899 eV). View from the stromal side.

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contradictory site energies. We find that only the site energy of B32 (1.86 eV) is considerably red-shifted. However, this triad of chlorophylls is subject to strong excitonic coupling,<sup>41,45</sup> which causes an additional red-shift of the collective absorption band. The coupling matrix elements are 38 meV (B31/B32) and 33 meV (B32/B33) and thus the second largest in the entire PSI behind P700. Indeed, the time-averaged excitonic Hamiltonian yields the triad B31/B32/B33 as the lowest energy exciton domain with an excitation energy of 1.83 eV (Fig. 6). TD-DFT calculations of the entire triad, that also take short range exchange effects into account, confirm the red-shift (ESI Fig. S14<sup>†</sup>)). Considering these findings, our high-level computational results now corroborate the assignment of B31/B32/B33 as an energy sink. These results are also supported by fluorescence measurements.<sup>20,136</sup> While this correspondence is encouraging, we note that our results refer to the initial absorption process and do not include any excited state relaxation as needed to fully capture fluorescence experiments.

Another set of low energy chlorophylls where the middle pigment B5 exhibits the strongest red-shift, B4/B5/B24, stands out in Fig. 5. In the excitonic picture (Fig. 6), B25 is also coupled to this cluster of chlorophylls. Together, the four pigments give rise to two low-energy excitons, B4/B5 (1.86 eV) and B24/B25 (1.87 eV). The red-shifted pigment B1 is located in the same region but in the stromal layer of the antenna complex, while the dimers B4/B5 and B24/B25 are located in the lumenal layer.<sup>41</sup> While B24/B25 has been disputed before,<sup>44,45</sup> B4/B5 has not been identified as an energy sink in preceding studies, to our knowledge.<sup>23,41-45</sup>

The chlorophyll with the lowest average site energy (1.85 eV) is B22, in a distance of 1.9 nm from the RC chlorophyll eC-A3, which in turn exhibits one of the highest mean energies (1.92 eV) in the entire complex. Other notable red chlorophylls, both in the site energy and in the exciton picture, include the dimers A38/A39 and B7/A32. Both dimers are subject to excitonic coupling on the order of 17 meV (A38/A39) and 29 meV (B7/A32) and are situated in close vicinity to the end points eC-A3 and eC-B3 of the two electron transfer branches in the RC. The two branches themselves are similar in that the second chlorophylls, eC-B2 in branch A and eC-A2 in branch B, exhibit almost no red- or blue-shift, while the third chlorophylls eC-A3 and eC-B3 are shifted towards higher energies. This renders the asymmetry within P700 all the more interesting. Here, the mean site energy of eC-A1 in 200 snapshots is red-shifted against eC-B1 by about 10 meV, meaning that energy will preferentially gather on the A branch once it reaches the RC. Including the coupling between the chlorophylls, the pair eC-A1 and eC-B1 contributes to two excitons with energies 1.85 eV and 1.95 eV. Again, the contributions of the two branches are asymmetric in the sense that eC-A1 contributes 49% to the lower energy exciton, while eC-B1 contributes only 37% (ESI Table S7<sup>†</sup>). The asymmetry is even more apparent when the average energy shift of each chlorophyll against the mean energy of all chlorophylls is plotted as a function of distance from P700 (Fig. 7). While there is a statistically significant downhill pathway from eC-A3 to eC-B2 and eC-A1, the energy sink in branch B is the second chlorophyll eC-A2, rather than eC-B1. The probability to transfer energy into one of the branches increases the possible number of charge

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**Fig. 7** Total site energy shift of each chlorophyll against the distance of the magnesium atoms from the center of mass of P700. The zero line refers to the global mean of all chlorophylls (1.899 eV). The two electron transfer branches towards P700 are highlighted in green. The P700 chlorophylls are the left-most data points 'A1' and 'B1', where the prefix 'eC' has been omitted in the labels for clarity.

transfer events therein. Therefore, assuming that charge separation indeed starts not in the special pair but in one of the two branches,<sup>14,17,32</sup> our results correspond well with reports of branch A as slightly more active.<sup>14,137</sup> Nevertheless, both branches in PSI are known to participate in charge transport, though there is no final consensus on the branching ratio.<sup>13,14,138</sup>

Regarding the energy transfer to the RC, we observe that P700 is neither the only nor the lowest energy sink in PSI, nor is there a distinct energy transfer pathway from the antenna complex to the RC readily apparent from Fig. 5 and 7. Instead, the terminal chlorophylls eC-A3 and eC-B3 as well as the linkers A40 and B39 to the antenna complex constitute energy barriers to P700 in the temporal average. This leaves us with two possibilities for energy transfer between the antenna complex and P700. One pathway may lead via the RC, where excitonic coupling to P700 is strongest because of the spatial proximity (cf. Fig. 6). However, uphill energy transfer is required to reach the chlorophylls A40/eC-A3 and B39/eC-B3, connecting the RC (green lines) with the antenna complex (blue dots). Another possibility is direct energy transfer from the antenna complex to P700, bypassing these high-energy chlorophylls, albeit at lower efficiency because of the smaller excitonic coupling. An argument in favor of multiple energy transfer pathways is that P700 is excitonically coupled to the entire antenna complex, rather than just to the linker chlorophylls A40 and B39, as evident from the network of coupling matrix elements in Fig. 6. Indeed, early semiempirical rate-constant calculations139 suggest that the linker chlorophylls accelerate the energy transfer time to the RC but are not critical for the process. We will show in the next section how thermal fluctuations can open new pathways towards both branches of the RC, which would seem unfavorable in the temporal average.

#### 3.4 Thermal fluctuations

So far we have discussed the site energies and couplings in the context of temporal averages. However, when discussing energy transfer in biological systems as large and complicated as PSI, it

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is neither sufficient to study an average, nor a single structure, be it a crystal structure7,23,41-44 or an optimized geometry.22,45 Instead, the dynamics of the system are crucial to understand the impact of the site energy shifts in the light-harvesting process. Looking at the site and exciton energies in individual MD snapshots, we observe that chlorophylls can easily switch between higher and lower energies via thermal fluctuations. In Fig. 8, this is for example apparent for the P700 pigments, or for the chlorophyll clusters B7/A32 and B4/B5/B24/B25. In contrast, the exciton couplings are less sensitive to fluctuations, as the chlorophyll positions and orientations remain rather stable over time. The maximum standard deviation in the couplings occurs in P700 and is 5 meV. Any excitonic fluctuations are therefore mainly governed by the variance in the site energies, which will consequently be the focus of the following discussion.

The complete energy distribution for each chlorophyll at 300 K is shown in Fig. 9a, where the chlorophylls are sorted in ascending order by their mean energy (blue triangles). While higher- and lower-energy pigments can be clearly distinguished in the temporal averages, the energy distributions of all chlorophylls overlap strongly (green boxes). This allows some conclusions about the energy funnel mechanism in PSI. In equilibrium, the red chlorophylls may act as energy traps and thus compete with the RC. However, at physiological temperatures this effect is mostly compensated by thermal disorder such that energy transfer pathways can open and close dynamically. This suggests that there is not one fixed pathway from the antenna complex to the reaction core but rather that energy barriers which are initially present upon excitation can be overcome via thermal motion. This type of thermally mediated energy transfer has benefits for the light-harvesting process, as the entire antenna complex with its fluctuating red sites may serve as an energy reservoir, storing excess energy until it is needed in the RC.

Moreover, the average asymmetry between the P700 chlorophylls is 10 meV and thus well within the range of the thermal fluctuations on the order of  $\pm 100$  meV. This means that thermal fluctuations can open energy transfer pathways to the otherwise slightly unfavorable B-branch of the RC and thus explain the reported bidirectionality of charge transport.<sup>13,138</sup>

To further specify the time scale on which these changes happen, we computed the site energies of all chlorophylls in two consecutive MD snapshots, 10 ps apart (Fig. 8). Significant site energy fluctuations can occur on this time scale, which is well below the exciton lifetime of 35 ps between the initial excitation and a redox event in the RC.<sup>8,9</sup> We even observe that the energy barrier on eC-A3 is removed from one snapshot to the next. This again corroborates the idea of the energy funnel as a dynamic process rather than a static pathway.

#### 3.5 Electrostatics vs. conformation

The red- or blue-shift of the site energy  $E_{env}$  from the absorption maximum  $\langle E_{env} \rangle$  can be separated in two components  $\Delta E_{struct}$  and  $\Delta E_{elec}$ :

$$E_{\rm env} = \langle E_{\rm env} \rangle + \Delta E_{\rm struct} + \Delta E_{\rm elec}.$$
 (5)

The structural component  $\Delta E_{\text{struct}}$  (eqn (6)) contains most of the thermal disorder and accounts for steric restrictions imposed on the pigments by the environment. The electrostatic shift  $\Delta E_{\text{elec}}$  (eqn (7)) in turn contains only the electrostatic influence of the environment on the site energies. As the environment shifts the entire site energy distribution to the red by  $\langle E_{\text{env}} \rangle - \langle E_{\text{vac}} \rangle = 17$  meV, the respective absorption maxima in environment and *in vacuo* also enter in eqn (7).



Fig. 8 Site energy shifts against the global mean of all chlorophylls (1.899 eV) in three selected MD frames for the whole antenna complex (top) and the RC with the two connecting chlorophylls B39 and A40 (bottom). Strong fluctuations are visible, even on a time scale of 10 ps, supporting the idea of a dynamic energy funnel mechanism rather than a static pathway to the RC.

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**Fig. 9** (a) Site energy distribution for each chlorophyll residue, ordered by ascending arithmetic mean (blue triangles). Green boxes extend from the beginning of the second quartile to the end of the third quartile. Whiskers extend to the minimum and maximum values of the data or to 1.5 times the interquartile range in the case of outliers (gray diamonds). A more detailed graphic including all raw data points is provided in ESI Fig. S8.† (b) Electrostatic and structural components (*cf.* eqn (6) and (7) to the total site energy shift from the absorption maximum, *i.e.* from the arithmetic mean of all site energies. The total shift (black line) is the sum of both components. A list of the chlorophyll residue IDs with the standard naming convention<sup>7.41</sup> is available in ESI Table S5.†

$$\Delta E_{\rm struct} = E_{\rm vac} - \langle E_{\rm vac} \rangle \tag{6}$$

$$\Delta E_{\text{elec}} = (E_{\text{env}} - \langle E_{\text{env}} \rangle) - (E_{\text{vac}} - \langle E_{\text{vac}} \rangle)$$
(7)

Fig. 9b illustrates the average magnitude of both components for each chlorophyll. The red-, blue- and unshifted site energies, almost equally distributed in thirds, are the result of almost any combination of electrostatic and structural components. A red-shift is observed from either strongly dominating electrostatic, dominating structural or collaborative/samesigned contributions. The blue-shift is achieved mostly by collaborative effects or a dominating electrostatic shift. Neutral or unshifted site energies originate either from cancelation of the respective strong contributions or from small, negligible contributions. The strongest structural shift, complemented by a weak electrostatic shift is experienced by B22 (no. 0 in Fig. 9b), which is also the overall most red-shifted chlorophyll. The also strongly red-shifted chlorophyll B5 (no. 3 in Fig. 9b) shows the opposite trend. Here, the electrostatic influence of the environment dominates the total site energy shift and is counteracted by a weak structural shift. It is also apparent that the total shift (black line) is slightly asymmetric, favoring the low-energy components. This asymmetry in the red- and blue-shifts may become more relevant at low temperatures, where a distinct red absorption side band has been observed experimentally.8,41 Again, it is informative to look at the statistics of the samples, to assess the significance of both shift contributions.

Fig. 10 visualizes the distribution of both shifts for five exemplary chlorophylls, which cover the full range of calculated site energies. In all cases, the structural shift exhibits a much broader distribution than the electrostatic shift and the shifts of all chlorophylls overlap strongly. Tukey's HSD test (*cf.* ESI Section  $5^{+}$ ) reveals only 29 out of 4560 pairs of chlorophylls with

statistically significant differences in the structural shift. This leads us to conclude that steric hindrance by the environment, which could in principle favor certain high- or low-energy chlorophyll conformations, does not have a significant influence on the site energies. In contrast, the electrostatic impact of the protein environment is mostly responsible for the average site energy shifts discussed above, as its distribution is much narrower. Here, Tukey's HSD test reveals 1479 pairs of chlorophylls with statistically significant differences in  $\Delta E_{elec}$ .

Explaining the electrostatic shifts by changes in the environmental charge distribution is not a trivial undertaking. Previous studies have mapped the electrostatic potential (ESP) of the environment onto the porphyrin scaffold and discussed its impact on the difference ESP between ground and excited state.<sup>23,32</sup> While such an approach can be successful for individual pigments, a direct correlation between environmental electrostatics and site energy shifts for the entire antenna complex has yet to be discovered.

Here, we approach this challenge by investigating the axial coordination of the chlorophylls, which can reportedly tune the



Fig. 10 Distribution (kernel density estimate) of electrostatic and structural shifts in 40 sampled snapshots for selected chlorophylls.

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**Fig. 11** (Top) Mean (blue triangles) and median (black horizontal lines) site energy shifts for different axial coordinations. Green boxes extend from the beginning of the second quartile to the end of the third quartile. Whiskers extend to the minimum and maximum values of the data or to 1.5 times the interquartile range in the case of outliers (gray diamonds). Red horizontal lines indicate the bootstrapped 95% confidence interval of the median. (Bottom) Mean site energy shifts with standard deviation of the mean.

site energies,91,140,141 in a temporal picture. In our model, 28 chlorophylls are coordinated axially by HIS $_{\delta}$  residues which are protonated on the  $\delta$  position, 14 by HIS<sub> $\varepsilon$ </sub> residues protonated on the  $\varepsilon$  position and 39 by crystal water. The rest of the chlorophylls are coordinated by various different amino acids, where the sample size is not large enough to draw meaningful conclusions. Here, we define the coordinating residue as any residue within a distance of 4 Å of the central  $Mg^{2+}$  ion. Comparing the three classes of chlorophylls (Fig. 11), we find that  $HIS_{\varepsilon}$  coordinated chlorophylls exhibit on average 5 meV lower excitation energies than  $HIS_{\delta}$  coordinated chlorophylls and 5 meV higher site energies than H<sub>2</sub>O coordinated pigments. Note that this effect is not large and the energy distributions are again overlapping. Our findings are in good accordance with previous systematic studies of non-standard protonation patterns<sup>23</sup> and illustrate that seemingly minor changes in the local environment can already induce energy shifts. While axial ligation is often discussed as an important factor on chlorophyll absorption energies,142-145 there are certainly many more effects at play in PSI than just the coordination of the central ion. This is reflected in the example of chlorophyll PL1 (cf. Fig. 5, upper right part). Its  $Mg^{2+}$  ion is coordinated by the anionic phosphodiester group of one of the phospholipids and therefore experiences a particularly strong negative electric potential in the axial position. Nevertheless, its average site energy (1.88 eV) is only slightly red-shifted. Its surprisingly small electrostatic shift ( $\Delta E_{elec} = -12$  meV) indicates that collective electrostatic effects can compensate each other.

## 4 Conclusions

Although a long-standing subject of theoretical and experimental studies, the high efficiency of light-harvesting and charge separation in PSI is still not fully understood. In this study, we have presented a new set of quantum chemically derived chlorophyll site energies, under fully atomistic consideration of environmental effects and for the first time including molecular dynamics of the complete membrane-embedded and solvated system. Including the entire apparatus, containing the trimeric protein complex and the lipid membrane, in the simulations allows us to describe all chlorophylls in their particular natural environment. In a biological assembly, many of the antenna chlorophylls lie at protein–protein interfaces or at the outer perimeter, interacting with solvent molecules or the thylakoid membrane.<sup>146</sup> We therefore simulate all chlorophylls in physiological conditions without artifical restraints or the need for implicitly approximated environments.

The combination of the high-level DFT/MRCI method with a QM/MM approach allows an accurate reproduction of the chlorophyll absorption spectrum in PSI – a task where many other quantum chemical methods fail. Our results corroborate previously proposed red sites in the PSI antenna complex, and identify new sites of putative energy traps, which are promising targets for future experiments.<sup>21,50,147,148</sup> Moreover, we observe a fundamental asymmetry in the two branches of the RC. Whereas the first chlorophyll eC-A1 acts as the energy sink in branch A, this role is taken by the second chlorophyll eC-A2 in branch B. These findings can be relevant for locating the initial charge transfer event and thus identifying the primary electron donor in PSI as either P700 or an adjacent chlorophyll pair in the RC.<sup>14,17,32</sup>

The origin of the site energy shifts can be distinguished in a structural and an electrostatic component. The distribution of the structural component is broad, spanning ~100 meV and strongly overlapping in all chlorophylls. This indicates that the steric hindrance by the environment plays only a subordinate role in the observed site energy shifts. In contrast, the electrostatics clearly induce shifts of  $\pm 50$  meV in the individual site energies, though clear correlations between environmental charge distributions and site energies remain to be found. In this context, we expect breakthroughs by the application of machine learning techniques.

The set of site energies and exciton couplings derived here allows us to draw conclusions about the light-harvesting process in PSI. In particular, we find that the RC is on average separated from the antenna complex by an energy barrier in the linker chlorophylls eC-A3 and eC-B3. Such a barrier may be beneficial to prevent wasting of energy when the RC is in its oxidized state. The dynamical perspective in this work reveals strong fluctuations in the site energies which in turn govern the fluctuations in the excitonic energies. Thus, excitation energy transfer within PSI should be thought of as a highly flexible process where new pathways open and close transiently on a sub-10 ps time scale *via* thermal thermal fluctuations in the range of  $k_{\rm B}T$ .

This means that even low-energy excitations can eventually culminate in a redox event,<sup>19</sup> due to the efficient use of ambient heat,<sup>8,30</sup> possibly even by recycling of heat dissipated by other chromophores.<sup>149</sup> Combining these results, we propose that the antenna complex in PSI not only acts as an energy-transport system but can also store excess energy temporarily until it is needed in the RC, thereby increasing its overall efficiency. PSI has the potential to become an integral component in artificial light-harvesting devices, providing a sustainable alternative to inorganic components.<sup>150–152</sup> A detailed mechanistic understanding of governing energy transfer and conversion processes is crucial to harness its potential. We hope that the present work will contribute to this goal and guide future studies on the road to using PSI for green energy conversion.

## Data availability

Mean site energies and shifts are provided in the ESI.† Newly derived or modified force field parameters, an optimized structure of chlorophyll *a* in xyz format, an equilibrated structure of the full PSI in pdb format, raw data of spectra, site energies and exciton couplings as well as statistical analyses as csv tables are openly available at Zenodo (DOI: https://doi.org/ 10.5281/zenodo.6576313).

### Author contributions

Sebastian Reiter: conceptualization, data curation, formal analysis, investigation, methodology, software, validation, visualization, writing – original draft, writing – review & editing; Ferdinand L. Kiss: conceptualization, validation, writing – original draft, writing – review & editing; Jürgen Hauer: conceptualization, funding acquisition, supervision, writing – review & editing; Regina de Vivie-Riedle: conceptualization, funding acquisition, project administration, resources, supervision, writing – review & editing.

## Conflicts of interest

There are no conflicts to declare.

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### Notes and references

- 1 R. E. Blankenship, *Molecular Mechanisms of Photosynthesis*, Wiley, 3rd edn, 2021.
- 2 J. Kargul, J. D. Janna Olmos and T. Krupnik, *J. Plant Physiol.*, 2012, **169**, 1639–1653.
- 3 D. Ciornii, M. Riedel, K. R. Stieger, S. C. Feifel, M. Hejazi, H. Lokstein, A. Zouni and F. Lisdat, *J. Am. Chem. Soc.*, 2017, **139**, 16478–16481.
- 4 S. Osella, Nanomaterials, 2021, 11, 299.

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- 5 N. Krauß, W.-D. Schubert, O. Klukas, P. Fromme, H. T. Witt and W. Saenger, *Nat. Struct. Mol. Biol.*, 1996, 3, 965–973.
- 6 P. Fromme, P. Jordan and N. Krauß, *Biochim. Biophys. Acta, Bioenerg.*, 2001, **1507**, 5–31.
- 7 P. Jordan, P. Fromme, H. T. Witt, O. Klukas, W. Saenger and N. Krauß, *Nature*, 2001, **411**, 909–917.
- 8 L.-O. Pålsson, C. Flemming, B. Gobets, R. van Grondelle, J. P. Dekker and E. Schlodder, *Biophys. J.*, 1998, 74, 2611– 2622.
- 9 A. R. Holzwarth, G. Schatz, H. Brock and E. Bittersmann, *Biophys. J.*, 1993, **64**, 1813–1826.
- 10 B. Gobets and R. van Grondelle, *Biochim. Biophys. Acta, Bioenerg.*, 2001, **1507**, 80–99.
- 11 B. Gobets, I. H. M. van Stokkum, F. van Mourik, J. P. Dekker and R. van Grondelle, *Biophys. J.*, 2003, **85**, 3883–3898.
- 12 D. A. Cherepanov, N. G. Brady, I. V. Shelaev, J. Nguyen,
  F. E. Gostev, M. D. Mamedov, V. A. Nadtochenko and
  B. D. Bruce, *Biophys. J.*, 2020, **118**, 337–351.
- 13 S. Santabarbara, L. Galuppini and A. P. Casazza, *J. Integr. Plant Biol.*, 2010, **52**, 735–749.
- 14 M. G. Müller, C. Slavov, R. Luthra, K. E. Redding and A. R. Holzwarth, *Proc. Natl. Acad. Sci.*, 2010, **107**, 4123–4128.
- 15 H. Lokstein, G. Renger and J. P. Götze, *Molecules*, 2021, 26, 3378.
- 16 K. Brettel and W. Leibl, *Biochim. Biophys. Acta, Bioenerg.*, 2001, **1507**, 100–114.
- 17 M. Di Donato, A. D. Stahl, I. H. M. van Stokkum, R. van Grondelle and M.-L. Groot, *Biochemistry*, 2011, **50**, 480–490.
- 18 J. R. Reimers, M. Biczysko, D. Bruce, D. F. Coker, T. J. Frankcombe, H. Hashimoto, J. Hauer, R. Jankowiak, T. Kramer, J. Linnanto, F. Mamedov, F. Müh, M. Rätsep, T. Renger, S. Styring, J. Wan, Z. Wang, Z.-Y. Wang-Otomo, Y.-X. Weng, C. Yang, J.-P. Zhang, A. Freiberg and E. Krausz, *Biochim. Biophys. Acta, Bioenerg.*, 2016, 1857, 1627–1640.
- D. A. Cherepanov, I. V. Shelaev, F. E. Gostev, M. D. Mamedov, A. A. Petrova, A. V. Aybush, V. A. Shuvalov, A. Y. Semenov and V. A. Nadtochenko, *Biochim. Biophys. Acta, Bioenerg.*, 2017, **1858**, 895–905.
- 20 S. Hatazaki, D. K. Sharma, S. Hirata, K. Nose, T. Iyoda, A. Kölsch, H. Lokstein and M. Vacha, *J. Phys. Chem. Lett.*, 2018, 9, 6669–6675.
- 21 M. Russo, A. P. Casazza, G. Cerullo, S. Santabarbara and M. Maiuri, *J. Chem. Phys.*, 2022, **156**, 164202.
- 22 P. Canfield, M. G. Dahlbom, N. S. Hush and J. R. Reimers, *J. Chem. Phys.*, 2006, **124**, 024301.
- 23 J. Adolphs, F. Müh, M. E.-A. Madjet, M. S. am Busch and T. Renger, *J. Am. Chem. Soc.*, 2010, **132**, 3331–3343.
- 24 G. E. Milanovsky, V. V. Ptushenko, J. H. Golbeck, A. Y. Semenov and D. A. Cherepanov, *Biochim. Biophys. Acta, Bioenerg.*, 2014, 1837, 1472–1483.
- 25 C. Kreisbeck and A. Aspuru-Guzik, *Chem. Sci.*, 2016, 7, 4174–4183.
- 26 F. Häse, C. Kreisbeck and A. Aspuru-Guzik, *Chem. Sci.*, 2017, **8**, 8419–8426.
- 27 F. C. Ramos, M. Nottoli, L. Cupellini and B. Mennucci, *Chem. Sci.*, 2019, **10**, 9650–9662.

<sup>© 2023</sup> The Author(s). Published by the Royal Society of Chemistry

- 28 Y. Shibata, S. Nishi, K. Kawakami, J.-R. Shen and T. Renger, J. Am. Chem. Soc., 2013, 135, 6903–6914.
- 29 S. Baghbanzadeh and I. Kassal, Phys. Chem. Chem. Phys., 2016, 18, 7459-7467.
- 30 W. Giera, S. Szewczyk, M. D. McConnell, K. E. Redding, R. van Grondelle and K. Gibasiewicz, *Photosynth. Res.*, 2018, 137, 321–335.
- 31 J. Adolphs, F. Müh, M. E.-A. Madjet and T. Renger, *Photosynth. Res.*, 2007, **95**, 197.
- 32 A. Sirohiwal, F. Neese and D. A. Pantazis, *J. Chem. Theory Comput.*, 2021, **17**, 1858–1873.
- 33 E. Cignoni, V. Slama, L. Cupellini and B. Mennucci, *J. Chem. Phys.*, 2022, **156**, 120901.
- 34 T. Renger, V. May and O. Kühn, *Phys. Rep.*, 2001, **343**, 137–254.
- 35 M. Gouterman, J. Mol. Spectrosc., 1961, 6, 138-163.
- 36 R. J. Cogdell, N. W. Isaacs, A. A. Freer, T. D. Howard, A. T. Gardiner, S. M. Prince and M. Z. Papiz, *FEBS Lett.*, 2003, 555, 35–39.
- 37 S. Vassiliev and D. Bruce, Photosynth. Res., 2008, 97, 75-89.
- 38 M. Şener, J. Strümpfer, J. Hsin, D. Chandler, S. Scheuring, C. N. Hunter and K. Schulten, *ChemPhysChem*, 2011, 12, 518–531.
- 39 S. Vassiliev, A. Mahboob and D. Bruce, *Photosynth. Res.*, 2011, **110**, 25.
- 40 T. Reinot, A. Khmelnitskiy, A. Kell, M. Jassas and R. Jankowiak, *ACS Omega*, 2021, **6**, 5990–6008.
- 41 M. Byrdin, P. Jordan, N. Krauss, P. Fromme, D. Stehlik and E. Schlodder, *Biophys. J.*, 2002, **83**, 433–457.
- 42 B. Brüggemann, K. Sznee, V. Novoderezhkin, R. van Grondelle and V. May, J. Phys. Chem. B, 2004, 108, 13536– 13546.
- 43 S. Vaitekonis, G. Trinkunas and L. Valkunas, *Photosynth. Res.*, 2005, **86**, 185–201.
- 44 A. Damjanović, H. M. Vaswani, P. Fromme and G. R. Fleming, *J. Phys. Chem. B*, 2002, **106**, 10251–10262.
- 45 S. Yin, M. G. Dahlbom, P. J. Canfield, N. S. Hush, R. Kobayashi and J. R. Reimers, *J. Phys. Chem. B*, 2007, **111**, 9923–9930.
- 46 S. Maity, B. M. Bold, J. D. Prajapati, M. Sokolov, T. Kubař, M. Elstner and U. Kleinekathöfer, *J. Phys. Chem. Lett.*, 2020, **11**, 8660–8667.
- 47 S. Maity, V. Daskalakis, M. Elstner and U. Kleinekathöfer, *Phys. Chem. Chem. Phys.*, 2021, 23, 7407–7417.
- 48 A. Sirohiwal, F. Neese and D. A. Pantazis, J. Am. Chem. Soc., 2020, 142, 18174–18190.
- 49 A. Sirohiwal, F. Neese and D. A. Pantazis, *Chem. Sci.*, 2021, 12, 4463–4476.
- 50 M. Russo, A. P. Casazza, G. Cerullo, S. Santabarbara and M. Maiuri, *J. Phys. Chem. B*, 2021, **125**, 3566–3573.
- 51 H. Du, R.-C. A. Fuh, J. Li, L. A. Corkan and J. S. Lindsey, *Photochem. Photobiol.*, 1998, **68**, 141–142.
- 52 M. Taniguchi and J. S. Lindsey, *Photochem. Photobiol.*, 2021, **97**, 136–165.
- 53 S. Grimme, A. Hansen, S. Ehlert and J.-M. Mewes, *J. Chem. Phys.*, 2021, **154**, 064103.

- 54 F. Neese, Wiley Interdiscip. Rev.: Comput. Mol. Sci., 2022, e1606.
- 55 E. Caldeweyher, S. Ehlert, A. Hansen, H. Neugebauer, S. Spicher, C. Bannwarth and S. Grimme, *J. Chem. Phys.*, 2019, **150**, 154122.
- 56 H. Kruse and S. Grimme, J. Chem. Phys., 2012, 136, 154101.
- 57 M. Cossi, N. Rega, G. Scalmani and V. Barone, *J. Comput. Chem.*, 2003, 24, 669–681.
- 58 CRC Handbook of Chemistry and Physics: A Ready-Reference Book of Chemical and Physical Data, ed. W. M. Haynes, D. R. Lide and T. J. Bruno, CRC Press, 95th edn, 2014.
- 59 C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, 37, 785–789.
- 60 A. D. Becke, J. Chem. Phys., 1993, 98, 1372-1377.
- 61 Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215–241.
- 62 P. J. Stephens, F. J. Devlin, C. F. Chabalowski and M. J. Frisch, J. Phys. Chem., 1994, 98, 11623–11627.
- 63 T. Yanai, D. P. Tew and N. C. Handy, *Chem. Phys. Lett.*, 2004, **393**, 51–57.
- 64 A. Najibi and L. Goerigk, J. Comput. Chem., 2020, 41, 2562– 2572.
- 65 M. Casanova-Páez and L. Goerigk, J. Chem. Theory Comput., 2021, 17, 5165–5186.
- 66 S. Hirata and M. Head-Gordon, *Chem. Phys. Lett.*, 1999, **314**, 291–299.
- 67 F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, 7, 3297–3305.
- 68 F. Neese, F. Wennmohs, A. Hansen and U. Becker, *Chem. Phys.*, 2009, **356**, 98–109.
- 69 R. Izsák and F. Neese, J. Chem. Phys., 2011, 135, 144105.
- 70 F. Weigend, Phys. Chem. Chem. Phys., 2006, 8, 1057-1065.
- 71 A. Hellweg, C. Hättig, S. Höfener and W. Klopper, *Theor. Chem. Acc.*, 2007, **117**, 587–597.
- 72 J. Ridley and M. Zerner, *Theor. Chim. Acta*, 1973, **32**, 111–134.
- 73 C. Olbrich and U. Kleinekathöfer, J. Phys. Chem. B, 2010, 114, 12427–12437.
- 74 C. Olbrich, J. Strümpfer, K. Schulten and U. Kleinekathöfer, J. Phys. Chem. Lett., 2011, 2, 1771–1776.
- 75 C. Olbrich, T. L. C. Jansen, J. Liebers, M. Aghtar, J. Strümpfer, K. Schulten, J. Knoester and U. Kleinekathöfer, J. Phys. Chem. B, 2011, 115, 8609–8621.
- 76 J. Gao, W.-J. Shi, J. Ye, X. Wang, H. Hirao and Y. Zhao, J. Phys. Chem. B, 2013, 117, 3488–3495.
- 77 L. Zhang, D.-A. Silva, H. Zhang, A. Yue, Y. Yan and X. Huang, *Nat. Commun.*, 2014, 5, 4170.
- 78 S. Grimme and M. Waletzke, J. Chem. Phys., 1999, 111, 5645–5655.
- 79 C. M. Marian, A. Heil and M. Kleinschmidt, Wiley Interdiscip. Rev.: Comput. Mol. Sci., 2018, 9, e1394.
- 80 M. Kleinschmidt, C. M. Marian, M. Waletzke and S. Grimme, *J. Chem. Phys.*, 2009, **130**, 044708.
- 81 F. Neese, Wiley Interdiscip. Rev.: Comput. Mol. Sci., 2012, 2, 73–78.
- 82 F. Neese, Wiley Interdiscip. Rev.: Comput. Mol. Sci., 2018, 8, e1327.

<sup>© 2023</sup> The Author(s). Published by the Royal Society of Chemistry

- 83 F. Neese, F. Wennmohs, U. Becker and C. Riplinger, J. Chem. Phys., 2020, 152, 224108.
- 84 S. Kossmann and F. Neese, Chem. Phys. Lett., 2009, 481, 240–243.
- 85 F. Weigend, J. Comput. Chem., 2008, 29, 167-175.
- 86 A. Heil, M. Kleinschmidt and C. M. Marian, J. Chem. Phys., 2018, 149, 164106.
- 87 A. Sali and T. L. Blundell, J. Mol. Biol., 1993, 234, 779-815.
- 88 E. F. Pettersen, T. D. Goddard, C. C. Huang, G. S. Couch, D. M. Greenblatt, E. C. Meng and T. E. Ferrin, *J. Comput. Chem.*, 2004, 25, 1605–1612.
- 89 D. Sundholm, Chem. Phys. Lett., 1999, 302, 480-484.
- 90 D. Sundholm, Chem. Phys. Lett., 2000, 317, 545-552.
- 91 G. Mondragón-Solórzano and J. Barroso-Flores, Int. J. Quantum Chem., 2018, 118, e25663.
- 92 A. Agostini, D. M. Palm, F.-J. Schmitt, M. Albertini, M. D. Valentin, H. Paulsen and D. Carbonera, *Sci. Rep.*, 2017, 7, 7504.
- 93 M. J. Abraham, T. Murtola, R. Schulz, S. Páll, J. C. Smith, B. Hess and E. Lindahl, *SoftwareX*, 2015, 1–2, 19–25.
- 94 J. M. Word, S. C. Lovell, J. S. Richardson and D. C. Richardson, J. Mol. Biol., 1999, 285, 1735–1747.
- 95 S. Schott-Verdugo and H. Gohlke, *J. Chem. Inf. Model.*, 2019, 59, 2522–2528.
- 96 K. Lindorff-Larsen, S. Piana, K. Palmo, P. Maragakis, J. L. Klepeis, R. O. Dror and D. E. Shaw, *Proteins: Struct.*, *Funct., Bioinf.*, 2010, 78, 1950–1958.
- 97 J. A. Maier, C. Martinez, K. Kasavajhala, L. Wickstrom, K. E. Hauser and C. Simmerling, *J. Chem. Theory Comput.*, 2015, **11**, 3696–3713.
- 98 L. Zhang, D.-A. Silva, Y. Yan and X. Huang, J. Comput. Chem., 2012, 33, 1969–1980.
- 99 M. Ceccarelli, P. Procacci and M. Marchi, *J. Comput. Chem.*, 2003, **24**, 129–142.
- 100 D. M. A. Smith, Y. Xiong, T. P. Straatsma, K. M. Rosso and T. C. Squier, *J. Chem. Theory Comput.*, 2012, 8, 2103–2114.
- 101 A. g. A. Skjevik, B. D. Madej, R. C. Walker and K. Teigen, *J. Phys. Chem. B*, 2012, **116**, 11124–11136.
- 102 C. J. Dickson, B. D. Madej, A. g. A. Skjevik, R. M. Betz, K. Teigen, I. R. Gould and R. C. Walker, *J. Chem. Theory Comput.*, 2014, **10**, 865–879.
- 103 Z. Wu, Gromacs Port of the Amber LIPID17 Force Field, Version 0.21, Zenodo, 2019, DOI: 10.5281/ ZENODO.3560998.
- 104 J. Wang, W. Wang, P. A. Kollman and D. A. Case, *J. Mol. Graphics Modell.*, 2006, **25**, 247–260.
- 105 J. Wang, R. M. Wolf, J. W. Caldwell, P. A. Kollman and D. A. Case, *J. Comput. Chem.*, 2004, 25, 1157–1174.
- 106 B. Hess, H. Bekker, H. J. C. Berendsen and J. G. E. M. Fraaije, J. Comput. Chem., 1997, 18, 1463–1472.
- 107 T. Darden, D. York and L. Pedersen, J. Chem. Phys., 1993, 98. 10089.
- 108 G. Bussi, D. Donadio and M. Parrinello, J. Chem. Phys., 2007, **126**, 014101.
- 109 S. Nosé, Mol. Phys., 1984, 52, 255-268.
- 110 W. G. Hoover, Phys. Rev. A, 1985, 31, 1695-1697.

- 111 M. Parrinello and A. Rahman, J. Appl. Phys., 1981, 52, 7182– 7190.
- 112 S. Nosé and M. L. Klein, Mol. Phys., 1983, 50, 1055-1076.
- 113 A. Leftin, T. R. Molugu, C. Job, K. Beyer and M. F. Brown, *Biophys. J.*, 2014, **107**, 2274–2286.
- 114 A. g. A. Skjevik, B. D. Madej, C. J. Dickson, K. Teigen, R. C. Walker and I. R. Gould, *Chem. Commun.*, 2015, 51, 4402–4405.
- 115 G. Shahane, W. Ding, M. Palaiokostas and M. Orsi, *J. Mol. Model.*, 2019, **25**, 76.
- 116 A. Warshel and M. Levitt, J. Mol. Biol., 1976, 103, 227-249.
- 117 D. Bakowies and W. Thiel, *J. Phys. Chem.*, 1996, **100**, 10580–10594.
- 118 U. C. Singh and P. A. Kollman, J. Comput. Chem., 1986, 7, 718–730.
- 119 U. Eichler, C. M. Kölmel and J. Sauer, *J. Comput. Chem.*, 1997, **18**, 463–477.
- 120 P. Sherwood, A. H. de Vries, M. F. Guest, G. Schreckenbach, C. R. A. Catlow, S. A. French, A. A. Sokol, S. T. Bromley, W. Thiel, A. J. Turner, S. Billeter, F. Terstegen, S. Thiel, J. Kendrick, S. C. Rogers, J. Casci, M. Watson, F. King, E. Karlsen, M. Sjø voll, A. Fahmi, A. Schäfer and C. Lennartz, *J. Mol. Struct.: THEOCHEM*, 2003, **632**, 1–28.
- 121 A. Anda, T. Hansen and L. De Vico, *J. Chem. Theory Comput.*, 2016, **12**, 1305–1313.
- 122 A. Anda, T. Hansen and L. De Vico, *J. Phys. Chem. A*, 2019, **123**, 5283–5292.
- 123 S. Reiter, L. Bäuml, J. Hauer and R. de Vivie-Riedle, *Phys. Chem. Chem. Phys.*, 2022, **24**, 27212–27223.
- 124 C. I. Bayly, P. Cieplak, W. Cornell and P. A. Kollman, *J. Phys. Chem.*, 1993, **97**, 10269–10280.
- 125 B. P. Fingerhut and S. Mukamel, J. Phys. Chem. Lett., 2012, 3, 1798–1805.
- 126 P. López-Tarifa, N. Liguori, N. van den Heuvel, R. Croce and L. Visscher, *Phys. Chem. Chem. Phys.*, 2017, **19**, 18311– 18320.
- 127 A. Kimura and S. Itoh, *J. Phys. Chem. B*, 2018, **122**, 11852–11859.
- 128 A. Kimura, H. Kitoh-Nishioka, T. Aota, T. Hamaguchi, K. Yonekura, K. Kawakami, K. Shinzawa-Itoh, N. Inoue-Kashino, K. Ifuku, E. Yamashita, Y. Kashino and S. Itoh, *J. Phys. Chem. B*, 2022, **126**, 4009–4021.
- 129 R. S. Knox and B. Q. Spring, *Photochem. Photobiol.*, 2003, 77, 497–501.
- 130 J. R. Reimers, Z.-L. Cai, R. Kobayashi, M. Rätsep, A. Freiberg and E. Krausz, *Sci. Rep.*, 2013, **3**, 1–8.
- 131 N. H. List, C. Curutchet, S. Knecht, B. Mennucci and J. Kongsted, J. Chem. Theory Comput., 2013, 9, 4928–4938.
- 132 A. B. J. Parusel and S. Grimme, *J. Phys. Chem. B*, 2000, **104**, 5395–5398.
- 133 J. P. Götze, F. Anders, S. Petry, J. F. Witte and H. Lokstein, *Chem. Phys.*, 2022, **559**, 111517.
- 134 K. J. Riley, T. o. Reinot, R. Jankowiak, P. Fromme and V. Zazubovich, *J. Phys. Chem. B*, 2007, **111**, 286–292.
- 135 A. Khmelnitskiy, H. Toporik, Y. Mazor and R. Jankowiak, *J. Phys. Chem. B*, 2020, **124**, 8504–8515.

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- 136 H. Toporik, A. Khmelnitskiy, Z. Dobson, R. Riddle, D. Williams, S. Lin, R. Jankowiak and Y. Mazor, *Nat. Commun.*, 2020, **11**, 5279.
- 137 N. Dashdorj, W. Xu, R. O. Cohen, J. H. Golbeck and S. Savikhin, *Biophys. J.*, 2005, **88**, 1238–1249.
- 138 S. Santabarbara, P. Heathcote and M. C. W. Evans, *Biochim. Biophys. Acta, Bioenerg.*, 2005, **1708**, 283–310.
- 139 M. Yang, A. Damjanović, H. M. Vaswani and G. R. Fleming, *Biophys. J.*, 2003, **85**, 140–158.
- 140 J. Heimdal, K. P. Jensen, A. Devarajan and U. Ryde, *J. Biol. Inorg Chem.*, 2007, **12**, 49–61.
- 141 D. Rutkowska-Zbik and T. Korona, *J. Chem. Theory Comput.*, 2012, **8**, 2972–2982.
- 142 T. S. Balaban, P. Fromme, A. R. Holzwarth, N. Krauß and V. I. Prokhorenko, *Biochim. Biophys. Acta, Bioenerg.*, 2002, 1556, 197–207.
- 143 T. S. Balaban, P. Braun, C. Hättig, A. Hellweg, J. Kern, W. Saenger and A. Zouni, *Biochim. Biophys. Acta, Bioenerg.*, 2009, 1787, 1254–1265.

- 144 B. F. Milne, Y. Toker, A. Rubio and S. B. n. Nielsen, *Angew. Chem.*, 2015, **127**, 2198–2201.
- 145 M. Fortino, E. Collini, J. Bloino and A. Pedone, J. Chem. Phys., 2021, 154, 094110.
- 146 F. J. Van Eerden, M. N. Melo, P. W. J. M. Frederix and S. J. Marrink, *Biophys. J.*, 2017, **113**, 2669–2681.
- 147 A. Kell, X. Feng, C. Lin, Y. Yang, J. Li, M. Reus, A. R. Holzwarth and R. Jankowiak, *J. Phys. Chem. B*, 2014, 118, 6086–6091.
- 148 Y. Lee, M. Gorka, J. H. Golbeck and J. M. Anna, *J. Am. Chem. Soc.*, 2018, **140**, 11631–11638.
- 149 M. Zubik, R. Luchowski, D. Kluczyk, W. Grudzinski, M. Maksim, A. Nosalewicz and W. I. Gruszecki, *J. Phys. Chem. Lett.*, 2020, 3242–3248.
- 150 K. R. Stieger, S. C. Feifel, H. Lokstein and F. Lisdat, *Phys. Chem. Chem. Phys.*, 2014, **16**, 15667–15674.
- 151 S. C. Feifel, H. Lokstein, M. Hejazi, A. Zouni and F. Lisdat, *Langmuir*, 2015, **31**, 10590–10598.
- 152 S. C. Feifel, K. R. Stieger, H. Lokstein, H. Lux and F. Lisdat, *J. Mater. Chem. A*, 2015, **3**, 12188–12196.

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## 3.3 Stabilizing Photosystem I in a MOF

A major challenge in using biological systems for catalysis or energy conversion is ensuring their stability in harsh environments, for example in organic solvents or at non-neutral pH. One possibility in this context is encapsulation of the biological component in a MOF, which has been successfully demonstrated by embedding PS I in ZIF-8.<sup>[242]</sup> While the photosystem retained its function in that study, a reversible change in fluorescence was observed during the encapsulation-release cycle (figure 3.6). Encapsulation gives rise to a prominent emission at 680 nm which is indicative of isolated chlorophyll and disappears as soon as PS I is released from the MOF. Where spectroscopic techniques are hindered by the complexity of the system and especially the strong scattering of the MOF, computational models allow microscopic insights into the molecular interactions underlying this modified fluorescence.

This is where the article "Molecular Interactions of Photosystem I and ZIF-8 in Bio-Nanohybrid Materials" comes into play, where the structural and electronic effects of embedding PS I in the MOF ZIF-8 are investigated. The most important results of the article are summarized below:

- A bio-nanohybrid between PS I and ZIF-8 was synthesized and analyzed *via* absorption spectroscopy. Comparing the spectra of encapsulated and free PS I in buffer solution indicated that the photosystem remains intact in the presence of the MOF. The interactions at the PS I/ZIF-8 interface were subsequently investigated in detail computationally.
- To this end, the atomistic model of PS I introduced in the previous chapter was extended to include the MOF, using the force field *nb-ZIF-FF* to describe ZIF-8.



Figure 3.6: Change in fluorescence upon encapsulating PS I in ZIF-8 and again after dissolving the MOF in acidic conditions. Data extracted from fig. 6a of ref. 242.

In contrast to other MOF specific force fields, nb-ZIF-FF employs a non-bonded potential for the interaction between the building blocks  $Zn^{2+}$  and 2-methylimidazolate (2-MIm<sup>-</sup>) and thus allows the simulation of bond-breaking and -formation.

- With this model, the initial stage of the ZIF-8 crystallization process around PS I as well as the fully-formed PS I@ZIF-8 crystal was investigated by MD simulations. It was found that neither the protein structure nor the chlorophyll network are impacted by the encapsulation, thus ruling out large-scale structural modifications as the source for the observed change in fluorescence.
- Instead, the anionic MOF building blocks 2-MIm<sup>-</sup> frequently coordinate to the Mg<sup>2+</sup> ions of chlorophylls on the outside of the photosystem. High-level quantum chemical calculations at the DFT/MRCI and SCS-ωPBEPP86 levels showed strong CT contributions to the first excited state of these coordinated chlorophylls, transferring electron density from the 2-MIm<sup>-</sup> anion to the chlorophyll. By sampling the excited states of these chlorophylls in different MD snapshots at the DFT/MRCI level, the CT was confirmed as a frequent event inside the MOF.
- The CT contributions significantly alter the excited state energies and transition dipole moments of the affected chlorophylls, effectively preventing their excitonic coupling with other pigments in the light-harvesting network. This could explain the elusive fluorescence signal observed experimentally, as the excitonic network features nearly uncoupled chlorophylls upon encapsulation by the MOF.
- However, the primary function of the photosystem remains unaffected, as the reaction center is shielded from interactions with the MOF and the vast majority of the light-harvesting network stays intact. Encapsulation of PS I by ZIF-8 therefore offers an attractive route towards artificial photosynthetic devices that can operate in a variety of otherwise adverse environmental conditions.

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# Molecular interactions of photosystem I and ZIF-8 in bio-nanohybrid materials<sup>†</sup>

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Bio-nanohybrid devices featuring natural photocatalysts bound to a nanostructure hold great promise in the search for sustainable energy conversion. One of the major challenges of integrating biological systems is protecting them against harsh environmental conditions while retaining, or ideally enhancing their photophysical properties. In this mainly computational work we investigate an assembly of cyanobacterial photosystem I (PS I) embedded in a metal–organic framework (MOF), namely the zeolitic imidazolate framework ZIF-8. This complex has been reported experimentally [Bennett *et al., Nanoscale Adv.,* 2019, **1**, 94] but so far the molecular interactions between PS I and the MOF remained elusive. We show *via* absorption spectroscopy that PS I remains intact throughout the encapsulation-release cycle. Molecular dynamics (MD) simulations further confirm that the encapsulation has no noticeable structural impact on the photosystem. However, the MOF building blocks frequently coordinate to the Mg<sup>2+</sup> ions of chlorophylls in the periphery of the antenna complex. High-level quantum mechanical calculations reveal charge-transfer interactions, which affect the excitonic network and thereby may reversibly change the fluorescence properties of PS I. Nevertheless, our results highlight the stability of PS I in the MOF, as the reaction center remains unimpeded by the heterogeneous environment, paving the way for applications in the foreseeable future.

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## 1. Introduction

Harnessing solar energy for catalytic applications is a key aspect in the much-needed transformation to clean energy. Multiple avenues are being explored to create new materials and devices with increased durability and efficiency. These include functionalized photoelectrodes,<sup>1,2</sup> carbon-based nanomaterials,<sup>3</sup> or metal–organic frameworks (MOFs).<sup>4–6</sup> However, the multitude of free parameters in the design of novel photocatalysts poses a significant challenge.<sup>7</sup> A promising alternative to developing

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 † Electronic supplementary information (ESI) available: Details on porting the force field; further structural analyis of PS I@ZIF-8; detailed results of excited state calculations and excitons. See DOI: https://doi.org/10.1039/d4cp03021d
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catalytic materials from scratch may be the incorporation of natural light-harvesting systems into bio-nanohybrid devices.8-17 In such applications, the natural photosystems I and II (PS I and PS II) are prime candidates as catalytic units. Of the two, cyanobacterial PS I is especially attractive due to the strong reductive potential ( $E_{\rm m}$  = -1.3 V vs. SHE) of its electron donor.<sup>18</sup> Additionally, the spectral and redox properties of PS I are very diverse across different species,19,20 allowing fine-grained adaptations by selecting a different species as donor.<sup>18</sup> The cyanobacterial PS I (T. elongatus), which is the focus of this work, occurs naturally as a trimeric membrane protein complex.21 Each monomeric subunit is composed of 11 protein chains and a plethora of cofactors, namely 11 carotenoids, 3 structurally relevant lipid molecules, 2 phylloquinones, 3 iron-sulfur clusters and 96 chlorophylls. The latter can be categorized into an antenna complex of 90 chlorophylls and a reaction center of 6 chlorophylls. In the light-harvesting process, the antenna complex captures light and conducts the energy towards the reaction center via resonance energy transfer. The chlorophylls in the antenna complex are loosely arranged in two layers on the lumenal and stromal side of the membrane, and positioned around the perimeter of the protein complex.<sup>21</sup> The function of bio-nanohybrids incorporating PS I has been successfully demonstrated in combination with plasmonic nanoparticles,<sup>22-24</sup> carbon nanotubes,<sup>8,9</sup> and semiconductor surfaces.<sup>10,13,14,17,25</sup>

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However, any real-world applications of such bio-nanohybrids face the challenge of stabilizing the photosystem against harmful environments.<sup>26</sup> Another challenge to overcome is the weak absorption of PS I monolayers,<sup>25</sup> which decreases device efficiencies. Here, the encapsulation in a MOF offers the prospect of both, providing a stable microenvironment<sup>27,28</sup> and enabling the controlled assembly of multilayered nanostructures.

The integration of PS I in a MOF has been demonstrated experimentally in a recent study,<sup>29</sup> where the zeolitic imidazolate framework (ZIF-8) was chosen as the encapsulating agent. ZIF-8 is a MOF composed of divalent zinc cations and 2-methylimidazolate (MIm<sup>-</sup>) and offers a series of attractive physicochemical properties for applications in photocatalytic bio-nanohybrids. In particular, ZIF-8 can be synthesized under mild aqueous conditions and remains stable across a wide range of solvents and temperatures.<sup>29</sup> At the same time, it is optically transparent in the visible part of the spectrum, allowing its integration in light-harvesting devices.<sup>29</sup> Pump-probe experiments showed that PS I retains its function both upon encapsulation in ZIF-8 and after digestion of the MOF in acidic conditions.<sup>29</sup> However, the fluorescence signal of the encapsulated PS I exhibited an additional intense peak at 676 nm, apart from the characteristic broad excitonic band between 660 nm to 800 nm.<sup>29</sup> This new signal is attributed to the emission of excitonically uncoupled chlorophyll a and would normally be indicative of a denatured PS I releasing its chlorophylls into the solution. However, after digestion of the MOF, the authors observed the fluorescence returning back to the original, excitonic signal.<sup>29</sup> This allows the hypothesis that molecular interactions at the PS I/ZIF-8 interface can reversibly alter the emission properties of the photosystem, while preserving its principal structure and function.

As the mechanism of this process remains elusive to experimental techniques, theoretical investigations can provide new insights into the molecular interactions at an atomistic level. In particular, molecular dynamics (MD) simulations are a valuable tool in the study of photosynthetic processes.30 We recently presented a new computational model of PS I,<sup>31</sup> which accounts for the molecular dynamics of the chromophores in their natural environment, as well as the extensive multireference nature of chlorophyll excitations.<sup>32</sup> This enabled the calculation of the excitonic energies at an unprecedented high level of theory. In this work, we build on our previous results to investigate the interactions of PS I with ZIF-8, both in the beginning of the ZIF-8 selfassembly around PS I and after formation of the ZIF-8 crystal. We discuss the structural impact of the encapsulation via MD simulations and the coordination of ZIF-8 building blocks to the chlorophyll network. High-level quantum-mechanical calculations give insights into the electronic structure at the PS I/ZIF-8 interface and reveal possibly undesirable electron transfer from the MOF into the photosystem. Our results provide a potential explanation for the previously observed spectral anomalies upon encapsulation<sup>29</sup> and give general theoretical insights on potential pitfalls in the future design of bio-nanohybrid devices.

## 2. Methods

#### 2.1. Preparation and purification of PS I

The PSI purification and monomerization protocol was adapted from Baker et al.<sup>33</sup> and Dobson et al.<sup>34</sup> Cells from the model cyanobacterium Synechocystis sp. PCC6803 (wild type) were grown in BG11 liquid medium, supplemented with 15 mM glucose under continuous white light (50  $\mu$ mol photons m<sup>-2</sup> s<sup>-1</sup>) at 30 °C. Cells in the log phase were harvested by centrifugation at 5000g for 10 min at room temperature. The cell pellets were stored at -80 °C for further use. Frozen cell pellets were thawed and resuspended in STN1 buffer (30 mM Tricine-NaOH pH 8, 15 mM NaCl, 0.4 M sucrose) and glass beads (212 µm to 300 µm, 425 µm to 600 µm, Sigma®) were added. Cells were broken using a Tissue Lyser II bead mill (Qiagen®) for 5 cycles, each cycle consisting of 3 min at 30 Hz, followed by 5 min cooling on ice. The lysate was cleared of cell debris and glass beads by centrifuging at 5000g for 5 min at 4  $^{\circ}$ C. Thylakoid membranes were pelleted by ultracentrifugation using Beckman SW40i at 40 000 rpm for 1 h at 4 °C. The membranes were then resuspended and incubated in STN2 buffer (30 mM Tricine-NaOH pH 8, 150 mM NaCl, 0.4 M sucrose) on ice for 30 min. The ultracentrifugation was repeated to pellet thylakoid membranes again. The membranes were resuspended in resuspension buffer (30 mM Tricine-NaOH pH 8, 15 mM NaCl) and n-dodecyl  $\beta$ -maltoside (DDM, ANAGRADE<sup>®</sup>) was added to achieve a mass ratio of 15:1 DDM-to-chlorophyll. The samples were gently mixed by pipetting and incubated on ice for 30 min. Insoluble materials were removed by ultracentrifugation at 40 000 rpm for 1 h at 4 °C, and the supernatant was collected and applied to an ion-exchange column (Toyopearl DEAE-650M, 5 mL, TOSOH BIOSCIENCE<sup>®</sup>) on Äkta. Proteins were eluted with a linear NaCl gradient from 15 m to 350 m in a buffer of 30 mM Tricine-NaOH (pH 8) and 0.2% DDM. The dark green fractions were collected and loaded on 10% to 30% sucrose gradient, followed by centrifugation at 36 000 rpm for 16 h at 4 °C using a Beckman SW40i rotor. The lower green bands, corresponding to the PS I trimer, were collected and 8% PEG3350 was added to precipitate the protein. Precipitated protein was resuspended in resuspension buffer for further use.

For monomerization, the PS I trimer was diluted to 1 mg mL<sup>-1</sup> chlorophyll concentration and 0.375% detergent octylthioglucoside (OTG) was added. The mixed samples were incubated at 55 °C for 5 min and cooled down on ice for 2 min. This cycle was repeated 18 times. The treated sample was loaded on 10% to 30% glucose gradient, followed by centrifugation at 36 000 rpm for 16 h at 4 °C, and the upper green bands, corresponding to the PS I monomer, were collected and precipitated by 12% PEG3350. Proteins were then resuspended in resuspension buffer for further use.

MOF-encapsulated PS I complexes were formed in one cycle by precipitating the ZIF-8 matrix from PS I-containing solution, in line with earlier published procedures.<sup>29</sup> The resulting dispersions were decanted without centrifugation and the powders were washed with water, before redispersion in aqueous phosphate buffer.

#### 2.2. Optical spectroscopy

The UV/Vis spectra were measured on a Cary 60 UV/Vis spectrometer from Agilent Technologies. All spectra were measured at room temperature in the respective solvent. Measurements were taken in the range 200–800 nm. The utilized cuvette was made out of SUPRASIL<sup>®</sup> quartz glass with a layer thickness of 10 mm.

The diffuse-reflectance UV/Vis spectra were measured on a UV-3600 Plus with integrating sphere unit of the company Shimadzu. The reflection of the sample was measured in the range 200–800 nm. For the recording of the UV/Vis spectra, the samples were put between two quartz microscope slides. As a reference barium sulphate was used.

#### 2.3. Computational model of PS I

The molecular model and force-field parameters for PS I were adapted from a previous publication and only a brief overview is given here. For details, please refer to the original publication.<sup>31,35</sup>

The structural model<sup>35</sup> is based on the crystal structure of cyanobacterial PSI<sup>21</sup> in *T. elongatus* (PDB: 1JB0). In contrast to our previous study, a PS I monomer was used to reduce computational cost. The protein was described with Amber14sb<sup>36,37</sup> and all other parameters were carefully selected to be compatible with the Amber protocol, which has been shown to yield reasonable structures for photosynthetic complexes.<sup>38,39</sup> In this context, parameters for chlorophyll a and  $\beta$ -carotene were taken from the literature.40,41 Iron-sulfur clusters and the coordinating cysteine (CYS) residues were described with parameters for oxidized, proximal Fe/S clusters.42 The lipids 2,3 dipalmitoyl-D-glycero-1phosphatidylglycerol (LHG) and 1,2-distearoyl-monogalactosyldiglyceride (LMG), which occur naturally as cofactors within PS I, were described with the LIPID17 force field.  $^{\rm 43-45}$  Parameters for the head group of LMG were generated with antechamber<sup>46</sup> using the GAFF force field<sup>47</sup> and RESP charges derived according to the standard Amber protocol for lipids.43

For the MD simulations of pure PS I in water, the model was placed in a triclinic box with dimensions  $25 \times 25 \times 20$  nm and solvated by 394 405 water molecules. Charge neutralization was achieved by adding 15 Na<sup>+</sup> ions. The final system contained 1 232 600 atoms.

#### 2.4. Molecular models of ZIF-8 and PS I@ZIF-8

ZIF-8 was modeled with the non-bonded force-field nb-ZIF-FF,<sup>48</sup> which we adapted for use with Gromacs. In contrast to many other MOF force-fields, nb-ZIF-FF models the interactions between the ionic MOF building blocks by a purely non-bonded potential, allowing the breaking and formation of bonds over the course of an MD simulation. To retain information about the coordination symmetry, each Zn<sup>2+</sup> ion and each coordinating N atom is surrounded by a set of charged dummy atoms.<sup>48–50</sup> In the original formulation,<sup>48</sup> a Morse potential was used to model the interaction between the building blocks. However, as Gromacs does not natively support Morse potentials, a custom Lennard-Jones potential was fitted to the

original potential and used instead in this work (see ESI<sup>†</sup> for details).

Two MD simulations including ZIF-8 were conducted in the present work: First, the self-assembly of the MOF around PS I was investigated up until the amorphous stage. Here, the PS I monomer was placed in a triclinic box with an edge length of  $23 \times 23 \times 18$  nm and solvated with water. Subsequently, 4272 Zn<sup>2+</sup> ions and 8544 MIm<sup>-</sup> ions were randomly placed in the box by replacing water molecules. The number of molecules was chosen to model the experimentally used MIm<sup>-</sup> concentration of 1.49 mol L<sup>-1</sup>. Differing from the experimental conditions, a stoichiometric amount of Zn<sup>2+</sup> was used in the calculations to achieve charge neutralization. The remaining negative charge, due to anionic residues in the PS I backbone, was neutralized by adding 15 Na<sup>+</sup> ions. The final system contained 890 474 atoms.

As the actual crystallization process of ZIF-8 takes place on a timescale of several minutes and is out of reach even for metadynamics simulations,48 a second MD was performed with PS I embedded in a fully-formed ZIF-8 crystal. Here, a unit cell was constructed based on the experimentally determined crystal structure<sup>51</sup> (CCDB: 864310). Water and hydrogen atoms were removed and dummy atoms required by the force-field<sup>48</sup> were added by superimposing models of Zn<sup>2+</sup> and MIm<sup>-</sup> onto the crystal structure. Next, missing hydrogen atoms were added to the building blocks with the Gromacs function pdb2gmx. Redundant building blocks were removed in order to apply periodic boundary conditions. The resulting unit cell was replicated 12 times in x- and y-directions and 9 times in z-direction. Subsequently, monomeric PS I was embedded in the crystal center by deleting any ZIF-8 atoms in a distance of 5 Å around PS I. The composite was solvated with water and placed in a triclinic box with dimensions  $23 \times 23 \times 18$  nm. The charge imbalance caused by the creation of the crystal cavity was neutralized by randomly replacing solvent molecules outside the ZIF-8 crystal with 128 free Zn<sup>2+</sup> ions. The remaining negative charge from PS I was neutralized by adding 15 Na<sup>+</sup> ions. The final system contained 1014077 atoms.

#### 2.5. Classical molecular dynamics

Molecular dynamics simulations were performed with *Gromacs.*<sup>52</sup> A double-precision installation of *Gromacs 2022.2* was used for the simulation of encapsulated PS I, while the simulations of amorphous ZIF-8 and PS I in water were performed with a single-precision version of *Gromacs 2023.2* with GPU support.

Multiple MD simulations were conducted, which differ in the details but adhere to the same general protocol. The total energy of the system was minimized with the steepest descent algorithm until the maximum force fell below 1000 kJ nm<sup>-1</sup>.

In all following simulations, the leap-frog integrator was used with a time step of 2 fs and bonds to hydrogen atoms were constrained with the LINCS algorithm.<sup>53</sup> Short-range electrostatics were evaluated with Verlet lists<sup>54</sup> using a cutoff distance of 1.2 nm. The smooth Particle-mesh Ewald (SPME) scheme<sup>55,56</sup> was used to calculate long-range electrostatics, using fourthorder interpolation and a Fouier grid spacing of 0.16 nm.

The system was equilibrated in three phases: first, to relax the system further, it was annealed from 10 K to 100 K over 50 ps in an NVT ensemble, before propagating for another 50 ps at a constant temperature of 100 K. Temperature control was achieved with the V-rescale thermostat,57 using a time constant  $\tau_{\rm T}$  of 0.1 ps. In the second step, the ensemble was switched to NPT, controlled by the V-rescale thermostat<sup>57</sup> ( $\tau_{\rm T}$  = 0.1 ps) and the Berendsen barostat<sup>58</sup> ( $\tau_p$  = 2.5 ps). Here, the system was heated from 100 K to the target temperature of 300 K within 100 ps and propagated at 300 K for another 900 ps at constant temperature and pressure. The pressure was equilibrated to an isotropic reference pressure of 1 bar. An isothermal compressibility of 4.5  $\times$  10<sup>-5</sup> bar<sup>-1</sup> was used for simulations in water. In the final equilibration step, the system was propagated for 10 ns in an NPT ensemble at 300 K and 1 bar, controlled by the Nosé-Hoover thermostat<sup>59,60</sup> ( $\tau_{\rm T}$  = 2.5 ps) and the Parrinello-Rahman barostat<sup>61,62</sup> ( $\tau_p = 10.0$  ps).

Production simulations for PS I in water and PS I@ZIF-8 were carried out for 100 ns and 30 ns, respectively, in the fully equilibrated ensemble. The 100 ns production simulation of the ZIF-8 self-assembly around PS I was carried out already after the second equilibration step, to be able to follow the aggregation of the ZIF-8 nanoparticles. The MD trajectories were analyzed with the python library *MDAnalysis 2.7.0.*<sup>63,64</sup> Molecular visualizations were created with *VMD 1.9.3.*<sup>65</sup>

#### 2.6. Quantum chemical calculations

Geometry optimizations in the ground state were performed with *Orca 5.0.3* using the r<sup>2</sup>SCAN-3c composite method, which has been shown to provide reasonable structures for a wide variety of organic molecules at much lower cost than hybrid density functionals.<sup>66</sup> Optimized structures were verified as minima by the absence of imaginary vibrational frequencies. Excited state geometry optimizations were performed at the TD-CAM-B3LYP level<sup>67</sup> with the def2-TZVP basis set.<sup>68</sup> The RIJCOSX approximation<sup>69–71</sup> was used to speed up the calculations, in conjunction with the def2/J Coulomb fitting basis.<sup>72</sup> The rangeseparated hybrid functional CAM-B3LYP was chosen to deal with possible charge-transfer interactions. It has proven to provide qualitatively correct spectra and structures for chlorophylls,<sup>73–75</sup> even though recent benchmarks indicate that final excitation energies should be evaluated at higher levels of theory.<sup>76,77</sup>

Therefore, excited states were calculated in the Tamm– Dancoff approximation<sup>78</sup> using the range-separated doublehybrid functional SCS- $\omega$ PBEPP86<sup>79</sup> in combination with the def2-TZVP basis. Again, the RIJCOSX approximation<sup>69–71</sup> was used with the def2/J<sup>72</sup> and def2-TZVP/C<sup>80</sup> auxiliary basis sets. Eight roots were calculated. The excited state wavefunctions were analyzed with the *TheoDORE 2.4.0* program package<sup>81–83</sup> to identify charge-transfer (CT) states.

The TD-DFT results were compared against DFT/MRCI calculations,<sup>84–86</sup> which include multireference effects. Here, the DFT reference was calculated with *Orca 5.0.3* using the BHLYP<sup>87,88</sup> functional and the def2-SVP<sup>68</sup> basis set. Coulomb and exchange integral evaluation was accelerated with the RI-JK approximation<sup>69</sup> using the def2/J<sup>72</sup> and def2-SVP/C<sup>80</sup> bases. SCF

convergence was tightened to  $10^{-7}E_{\rm h}$  (Orca keyword SCFCONV7). Corresponding to the Gouterman model,<sup>89</sup> a CISD expansion of four electrons in the four frontier orbitals was used as an initial guess for the MRCI reference space. This reference space was iteratively optimized until it contained all leading configurations of the first 8 roots, using the R2018 Hamiltonian<sup>90</sup> with a selection threshold of  $0.8E_{\rm h}$  and the tight parameter set.

QM/MM excited state calculations using the DFT/MRCI method in the QM region were performed for eight Chl a chromophores in the PS I@ZIF-8 composite, which were mostly affected by the coordination with MIm<sup>-</sup>. DFT/MRCI has been used before in the context of QM/MM calculations and has repeatedly performed well in reproducing experimental reference energies.<sup>31,91-93</sup> For every chlorophyll molecule, 20 evenly spaced snapshots were sampled from the crystal MD simulation. The QM region contained the chlorophyll and any MIm<sup>-</sup> units within 4 Å of the central Mg2+ ion. The phytyl chain was capped at the first carbon by a hydrogen link atom.<sup>94,95</sup> Electrostatic embedding was used to describe the polarization of the QM wave function by the MM environment. Point charges were taken directly from the force field, including the dummy charges on the ZIF-8 building blocks. To prevent excessive polarization, point charges were shifted away from the link atom, and artificial charges were introduced along the bond axis to maintain the dipole moment.95 In each QM/MM calculation, the QM subsystem was centered in the box by applying periodic boundary conditions.

#### 2.7. Statistical analysis

The sampled data points were divided into three groups, based on the number of  $MIm^-$  ions within a 4 Å sphere around the chlorophyll's  $Mg^{2+}$  ion in the respective MD snapshot. A oneway ANOVA analysis<sup>96</sup> was conducted on the CT numbers and vertical excitation energies into S<sub>1</sub>, followed by Tukey's HSD test<sup>97</sup> to evaluate the statistical significance of the differences between the three groups. Reaction center chlorophylls were excluded from the analysis as they remained unaffected by the ZIF-8 encapsulation.

## 3. Results and discussion

Embedding an intricate biomolecular system like PS I in a MOF can affect its properties in two ways. First, the encapsulation process may alter the structure of the photosystem, either unfolding the protein itself or releasing previously bound chlorophyll molecules into the reaction mixture. Second, electronic interactions between the charged MOF building blocks and the PS I chromophores may alter the spectral properties of the latter. Both types of effects, structural and electronic, will be discussed in detail in the following.

#### 3.1. Absorption spectroscopy on PS I in diverse environments

In order to provide benchmarks and guidelines for our calculations, we measure optical spectra under experimental conditions covering the diverse range of PS I local environments. In particular, we rely on UV/Vis absorption and diffuse reflectance
spectroscopies to monitor the integrity of the PS I during the stages of MOF encapsulation.

In the top panel of Fig. 1 we show the UV-Vis absorption spectra of PS I in buffer solution and in the presence of the MOF matrix building block MImH (1.5 mM, pH 9). The direct comparison with the spectra of an aqueous phosphate buffer solution of PS I reveals that the presence of MImH has no significant effect on the optical properties of the photosynthetic complex. This suggests that electronic interactions between the MOF linker and PS I are negligible in solution.

While simply the presence of the MOF linker MImH clearly has negligible impact on the optical properties of PS I, interaction between the linker and PS I appears more substantial after formation of the MOF framework, as witnessed by the UV/ Vis absorption spectra in the bottom panel of Fig. 1. While the overall chlorophyll a-like spectral shape of PS I is similar before and after encapsulation, we observe peak broadening and slight shifts in the transition energies in both Q- and B-band regions. These effects are often observed on embedding chromophores in a more strongly interacting and heterogeneous environment, in agreement the expected behavior on changing the local PS I environment from aqueous buffer to the much more highly structured MOF framework.

Importantly, after digestion of the MOF by acidification of the dispersion, PS I is released back into solution. The corresponding spectrum, shown as a red line in the bottom panel of Fig. 1, shows complete recovery of the initial in-solution PS I



**Fig. 1** Top panel: absorption spectra of PS I in phosphate–(gray, 0.05 M, pH 7.4) and acetate buffer (blue, 0.5 M, pH 5.3). PS I absorption spectrum in phosphate buffer in the presence of 2-methylimidazole (1.5 mM MImH, pH 9) acting as a building block of the ZIF-8 framework shown in red. Bottom panel: comparison of PS I absorption spectra in phosphate buffer (gray), after MOF encapsulation (blue), and after release by digestion of the MOF (red). The scattering spectrum of a pure ZIF-8 MOF suspension shown as dashed gray line.

absorption spectrum, which provides strong evidence that the complex remains structurally intact and presumably functional throughout the entire encapsulation-release cycle. Thus, our experimental results corroborate previous accounts<sup>29</sup> and provide a starting point for theoretical investigations.

#### 3.2. Structural integrity of PS I in ZIF-8

The structural integrity of PS I was investigated via MD calculations both during the crystallization process of ZIF-8 around PS I and after the crystal had fully formed. As the crystalliation of ZIF-8 takes place on a timescale of several minutes,<sup>29,48</sup> only the early stages of the self-assembly process, up until an amorphous phase, are accessible with MD simulations.48 Therefore, we simulated the first 100 ns of self-assembly around PS I, starting from a homogeneous, stoichiometric mixture of Zn<sup>2+</sup> and MIm<sup>-</sup> ions, solvated in water. Early on, already after 1 ns, clusters of the MOF building blocks start to form and also attach to PS I. As time progresses, the clusters grow and form an amorphous mass, which is loosely bound to PS I (Fig. 2). Visual analysis of the MD trajectories (Fig. S9, ESI<sup>+</sup>) confirms that both Zn<sup>2+</sup> and MIm<sup>-</sup> permeate up to 1 nm into the protein matrix, especially in the peripheral antennas. However, these interactions induce no apparent changes in the secondary or tertiary structure of PS I. Most importantly, all 96 chlorophylls remain bound to the photosystem and are not being released into the solvent.

The visual impression from Fig. 2 can be quantified by calculating the RMSD of relevant PS I components with respect to an experimental crystal structure<sup>21</sup> over the course of the self-assembly process (Fig. 3a). The time-dependent, massweighted RMSD is generally defined as

$$\mathbf{RMSD}(t) = \sqrt{\frac{1}{N} \sum_{i=1}^{N} m_i |\mathbf{x}_i(t) - \mathbf{x}_i^{\text{ref}}|^2},$$
 (1)

where  $\mathbf{x}_i(t)$  and  $\mathbf{x}_i^{\text{ref}}$  are the Cartesian molecular coordinates at the current time step and at the reference structure, respectively, and the index *i* runs over the number of atoms *N*. Only non-hydrogen atoms were considered in the analysis. Translational and rotational degrees of freedom were removed in each time step by aligning<sup>98</sup> the protein  $C_{\alpha}$  backbone with the reference structure. Any structural changes induced by the encapsulation should increase the RMSD. However, the RMSD of the protein backbone as well as that of the cofactors, 96 chlorophyll *a* molecules, 22 carotenoids and 2 phylloquinones, remains stable over the entire 100 ns of the trajectory.

As a measure of the protein stability, the radius of gyration  $R_g$  was calculated.  $R_g$  measures the compactness of the protein and gives a quantitative estimate on whether the protein unfolds over time. It is calculated in each time step *t* as the mass-weighted mean distance from the center of mass  $\mathbf{x}_{COM}$ :

$$R_{g}(t) = \sqrt{\frac{1}{M} \sum_{i=1}^{N} m_{i} |\mathbf{x}_{i}(t) - \mathbf{x}_{COM}(t)|^{2}}, \quad \text{with } M = \sum_{i=1}^{N} m_{i}.$$
(2)

During the self-assembly process of ZIF-8 around PS I, the

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**Fig. 2** Visualization of the structural integrity of PS I in the early stages of the ZIF-8 self-assembly process. (a) Protein and chlorophyll network in 50 equidistant snapshots over 100 ns, colored by the time-averaged RMSD of each residue with respect to the first frame of the trajectory after alignment of the protein backbone. Higher RMSD indicates more mobile residues. (b) Selected snapshots of the MD trajectory, showing the clustering of the ZIF-8 building blocks. Water molecules are omitted for clarity. View from the stromal side, left panel in (a) rotated by 90° around *x*.

radius of gyration of the protein (Fig. 3c) remains stable at a mean value of 43.68(5) Å. In comparison, the  $R_{\rm g}$  of PS I in water is marginally lower with a mean value of 43.28(7) Å. The small discrepancy is explained by different orientations of the N-terminal loops of the protein subunits K and F in the two simulations (Fig. S8, ESI†), which is most likely a result of different initial conditions. Both the RMSD and the radius of gyration therefore indicate that PS I remains structurally intact during the early self-assembly process of the MOF.

Nevertheless, the amorphous phase may interact differently with PS I than a crystal. Therefore, a second MD simulation was performed with PS I encapsulated in a fully formed ZIF-8 crystal (Fig. 4). Due to the molecular setup, where the crystal cavity was perfectly shaped to accommodate the photosystem, PS I is tightly bound and its rotational and translational degrees of freedom are heavily restricted by the ZIF-8 crystal. Apart from the cavity, the periodicity of the crystal is perfectly preserved during the MD, as evident from the Zn<sup>2+</sup>-Zn<sup>2+</sup> radial distribution function (Fig. S4, ESI<sup>†</sup>). In a real crystal, the packing at the ZIF-8/PS I interface is possibly not as tight and may contain more imperfections. While this would increase the flexibility of the photosystem, it is unlikely to change the fundamental interactions at the interface. As for the amorphous phase, the encapsulation in the crystal induces no structural change observable in the RMSD or in the protein radius of gyration (Fig. 3b and c). Thus, the photosystem is structurally stable both during and after encapsulation in ZIF-8. Although this is an encouraging result in the context of bio-nanohybrid applications, it does not explain the observed spectroscopic changes upon encapsulation.<sup>29</sup>

Therefore, we now focus more closely on the interactions between the ZIF-8 building blocks and the chlorophylls at the ZIF-8/PS I boundary. In particular, the anionic MIm<sup>-</sup> building blocks are able to coordinate axially to the chlorophyll's Mg<sup>2+</sup> ions if the chlorophylls are exposed to the outside of the photosystem. To quantify the extent of such coordination, we analyzed the coordination of each of the 96 chlorophylls in PS I over the time of the crystal MD trajectory (Fig. S6, ESI<sup>†</sup>). Most chlorophylls do not interact with the ZIF-8 crystal, because they are deeply embedded in the protein framework. Few chlorophylls show weak interactions, where atoms belonging to MImdiffuse in and out of the pre-defined coordination sphere with radius 4.0 Å around the  $\mathrm{Mg}^{2\mathrm{+}}$  ion. In total, there are 32 chlorophylls which experience at least one coordination event over the course of the 30 ns MD trajectory in the ZIF-8 crystal. The eight most affected chlorophylls, coordinated for at least 40% of the total simulation time, are all located on the outskirts of the photosystem and thus not well-shielded by the protein against the environment (Fig. S12, ESI<sup>†</sup>). Looking at the early stages of the self-assembly, even more chlorophylls interact with MIm<sup>-</sup>, due to the higher mobility of the ZIF-8 building

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**Fig. 3** RMSD of key PS I components (a) in the early stage of cystallization and (b) in the fully formed ZIF-8 crystal.  $C_{\alpha}$ : protein backbone, CLA: chlorophyll *a*, BCR:  $\beta$ -carotine, PQN: phylloquinone. (c) Protein radius of gyration during and after crystallization. The RMSD in the reference trajectory of PS I in water is depicted in Fig. S5 in the ESI.†

blocks when they are not bound in a crystal. Here, 40 chlorophylls experience at least one coordination event over 100 ns, with 19 of them remaining coordinated for at least 40% of the trajectory (Fig. S6, ESI†). As the MD trajectory only samples a fraction of the phase space, it is conceivable that in reality, all chlorophylls located on the outer border of PS I experience significant coordination at one time or another in the selfassembly process. Such coordination can alter the spectroscopic properties of the photosystem *via* electronic interactions between ZIF-8 and the chlorophylls. These interactions at the PS I/ZIF-8 interface will therefore be investigated more closely in the following.

#### 3.3. Electronic interactions at the PS I/ZIF-8 interface

Quantum chemical calculations were performed to investigate the electronic effects of coordination by MIm<sup>-</sup> on the chlorophylls at the PS I/ZIF-8 interface. In a first step, the structure of an isolated chlorophyll was optimized at the r<sup>2</sup>SCAN-3c level of theory.<sup>66</sup> Additionally, the structure of a chlorophyll axially



**Fig. 4** PS I embedded in the ZIF-8 crystal and solvated by water. Chlorophylls are highlighted in red. Top view from the stromal side, box dimensions after equilibration.

coordinated by MIm<sup>-</sup> was optimized at the same level. Excited states were calculated using both the range separated doublehybrid functional SCS- $\omega$ PBEPP86<sup>79</sup> and the DFT/MRCI method.<sup>86</sup> Both methods have shown to yield excellent absorption properties for chlorophylls, which exhibit non-negligible multireference character, even in low-energy excited states.<sup>31,32,74</sup> SCS- $\omega$ PBEPP86 performs especially well for charge transfer excitations<sup>99</sup> and was thus used to double-check the DFT/MRCI results. For simplicity, the rest of the environment was not considered at this stage; its effect will be discussed later.

At the DFT/MRCI level, the first excited state of the Chl  $a \cdots MIm^-$  aggregate has non-negligible CT character at the Franck–Condon point, transferring electron density from the anionic ligand to the chlorophyll (Fig. 5a). At the SCS- $\omega$ PBEPP86 level, this CT is slightly higher in energy and predicted to be the third excited state. In both theoretical frameworks, the main character of the first excited state remains unchanged with respect to the isolated chlorophyll



Fig. 5 Difference density (DFT/MRCI) for Chl.  $a \cdots MIm^-$  at (a) the Franck–Condon point and (b) at the S<sub>1</sub> minimum. Electron density is transferred from blue to yellow regions (isovalue 0.002), indicating a CT from MIm<sup>-</sup> to the chlorophyll. (c) The transition dipole moment (DFT/MRCI) for uncoordinated Chl. *a* (black), is similar to that of Chl.  $a \cdots MIm^-$  at the Franck–Condon point (orange) but rotates out of the molecular plane upon relaxation to the S<sub>1</sub> minimum (short orange arrow, scaled up by factor 15 for visualization).

and the transition dipole moment stays oriented along the molecular *y*-axis. However, upon excited state relaxation, modeled by optimizing the geometry of the first excited state, the CT character begins to dominate and the transition dipole moment reorients until it is orthogonal to the chlorophyll's molecular plane (Fig. 5b and c). Additionally, the new S<sub>1</sub> at the excited state minimum is significantly lower in energy and almost dark, with a vertical emission energy of 0.65 eV and an oscillator strength of  $7 \times 10^{-5}$ . It is noteworthy that the CT occurs only if the ligand is in its fully deprotonated, anionic form. In a buffer solution, as used in the spectroscopy experiments in Fig. 1, 2-methylimidazole exists as a mixture of MImH and MImH<sub>2</sub><sup>+</sup>, which do not induce a CT (Tables S10–S14, ESI†), even though they also tend to coordinate (Fig. S7, ESI†).

Starting from the initial CT, two pathways are conceivable: either the chlorophyll relaxes back to the original ground state, regenerating a neutral chlorophyll with an anionic MImligand, or the CT creates a chlorophyll anion. The latter case would require the two molecular units to separate for the CT state to become the new ground state. This is unlikely, given the tight encapsulation by the crystal. Nevertheless, we investigated the spectral impact of chlorophyll anion formation by calculating excited states at the optimized geometry of a Chl  $a^-$  anion with the same protocol as before. The first excited state of Chl  $a^{-}$  is a weakly absorbing state with an oscillator strength of 0.0735 (SCS-ωPBEPP86). Its vertical excitation energy is 1.26 eV, significantly lower than that of a neutral Chl a (1.87 eV). This means that if an anion is formed, it will not be excitonically coupled with adjacent neutral chlorophylls due to the large energy gap. Instead, a chlorophyll anion should give rise to an additional fluorescence band in the NIR spectral range. In practice, the fluorescence signal of PS I@ZIF-8 only shows the characteristic sharp  $Q_y$  peak of isolated chlorophylls at 661 nm.<sup>29</sup> However, the measurement of NIR signals in the presence of ZIF-8 is challenging, due to the strong scattering by the nanoparticles. We therefore can not rule out formation of chlorophyll anions, although it appears unlikely.

To investigate the frequency of the discussed CT events, we performed a series of QM/MM excited state calculations at the DFT/MRCI level on the eight most-coordinated chlorophylls in the PS I@ZIF-8 crystal and on the reaction center chlorophylls labeled eC-A1 and eC-B1. Geometries were sampled from 20 evenly spaced MD snapshots. Out of 200 calculations, 195 terminated normally and were used for further analysis. The vertical excitation energies into the first excited state are summarized in Fig. 6, where each data point represents the respective chlorophyll in one snapshot. Additionally, the CT character of each state was quantified *via* analysis of the transition density.<sup>81–83</sup> The amount of CT is quantified by the CT number, which ranges between 0 (no CT) and 1 (single electron transfer).

It is immediately apparent from Fig. 6 that the reaction center chlorophylls remain unaffected by encapsulation in ZIF-8, corroborating that PS I retains its function in the bionanohybrid.<sup>29</sup> In contrast, the chlorophylls interacting directly with the MOF exhibit very different photophysics. The sampled data contains 104 coordination events, corresponding to 67% of the total number of data points outside the reaction center. Out of these, there are 11 cases, where two MIm<sup>-</sup> ions are closer than 4 Å to the chlorophyll's  $Mg^{2+}$  ion, which will be referred to as double coordination in the following. 92 of the 104 coordination events lead to a CT number >0.5. A one-way ANOVA analysis was carried out to compare the effects of MImcoordination on the CT numbers and vertical excitation energies into S<sub>1</sub> between the uncoordinated, singly coordinated and doubly coordinated chlorophylls. There is a significant effect of the coordination on the CT number for the three groups of samples [F(2192) = 568.617, p < 0.001]. Post-hoc analysis using Tukey's HSD test reveals that coordination significantly (p <0.001) raises the mean CT number of the singly and doubly coordinated samples by 0.800 and 0.893 with respect to the uncoordinated samples, whose CT number is 0 by definition. However, the difference between single and double coordination is not significant. Moreover, coordination by MIm<sup>-</sup> has a significant effect on the vertical excitation energies into S<sub>1</sub> [F(2192) = 71.962, p < 0.001]. Single coordination lowers the mean energy for excitation into S<sub>1</sub> by 0.46 eV, double coordination by 0.70 eV. Both energy differences are statistically significant (p < 0.001). We note that the interplay between force field and QM method can affect these results, as both

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**Fig. 6** Distribution of vertical excitation energies (DFT/MRCI) into the S<sub>1</sub> state of selected, frequently MIm<sup>-</sup>-coordinated chlorophylls in PS I. Data points are colored by the amount of CT character of the excitation. The shape of the data points signifies the number of coordinating MIm<sup>-</sup> ions within 4 Å of the respective Mg<sup>2+</sup> ion. The horizontal gray line illustrates the experimental excitation energy into  $Q_v$  in Chl *a*.

structures and point charges are taken directly from the classical MD simulations.<sup>100</sup> The strength of the non-bonded interactions between MIm<sup>-</sup> and the Mg<sup>2+</sup> ions is of particular importance in this regard, as it controls the distance between the two molecules. The average N–Mg distance in the snapshots sampled in Fig. 6 is 4.21 Å, slightly longer than in the optimized geometry of the Chl  $a \cdots$ MIm<sup>-</sup> aggregate (3.75 Å). Based on this, the QM/MM sampling likely rather underestimates the amount of CT events. We therefore conclude that coordination by MIm<sup>-</sup> significantly decreases the vertical excitation energy into S<sub>1</sub> and induces a CT towards the chlorophyll.

#### 3.4. Effects on the light-harvesting network

The results presented so far allow to draw conclusions about possible deactivation pathways following photo-excitation of the chlorophylls in PS I@ZIF-8. After population of the  $Q_v$  state of one of the chlorophylls, the exciton can delocalize via Coulomb interactions with another chlorophyll, lowering the energy of the collective excited state. Without the MOF, this delocalized exciton would eventually fluoresce back to the ground state, resulting in the characteristic exciton emission band in PS I. In the presence of MIm<sup>-</sup> however, a CT state localized on one of the chlorophylls is energetically below the excitonic state. The large energy difference to the S1 state of uncoordinated chlorophylls as well as the vanishing and reoriented transition dipole moment of this CT state effectively decouples the affected chlorophyll from the rest of the excitonic network. To assess the impact of these changes in the lightharvesting antenna, we simulated the exciton distribution once

including all chlorophylls and once without the eight most frequently coordinated chlorophylls (Fig. S12, ESI<sup>†</sup>).

Compared to the unperturbed light-harvesting system in PS I,<sup>31</sup> the energy distribution changes only minutely, as the coordinated chlorophylls are only weakly coupled to begin with. No changes are observed in the reaction center and in the red chlorophylls,<sup>31</sup> corroborating that the primary function of PS I remains unimpaired. However, a small part of previously delocalized excitons now localize more strongly on single pigments. For example, one exciton that was formerly delocalized across 11 pigments with a larger contribution by chlorophyll A8 (46%) is now localized by 88% on A8. Given that excitons generally quench fluorescence and chlorophyll on its own is a strong fluorophor, this MOF-induced excited state localization could contribute to the strong emission peak observed<sup>29</sup> in the PS I@MOF bio-nanohybrid.

## 4. Conclusions

In this work, we have investigated the structural and electronic impact of encapsulating cyanobacterial PS I in the MOF ZIF-8. Such encapsulation is desirable in the context of bionanohybrid applications, where the near-unity efficiency of PS I can be harnessed to catalyze chemical reactions<sup>10,13,14,17,25</sup> while the MOF protects the photosystem from harsh environments.

MD simulations show how PS I remains structurally intact upon encapsulation in ZIF-8, in both the early and late stages of the crystallization process. Neither does the protein unfold, nor is there any significant structural change in the chlorophyll network. Any observed spectral anomalies<sup>29</sup> must therefore stem from electronic interactions at the PS I/ZIF-8 interface. In this context, analysis of the MD trajectories reveals how the ZIF-8 building blocks coordinate to the Mg<sup>2+</sup> ion of peripheral chlorophylls in PS I. Such coordination enables CT excitations at the boundary, where the MOF can effectively photoreduce some of the chlorophylls. High-level QM calculations show that such photoinitiated CT lowers the energy of the first excited state, reorients the transition dipole moment and reduces its magnitude. QM/MM sampling along the MD trajectory show that these perturbations occur frequently at the PS I/ZIF-8 interface. As such, they decrease the excitonic coupling between the chlorophylls in PS I, which normally quenches the fluorescence signal. The resulting uncoupled chlorophylls provide a possible explanation for the reversible strong fluorescence signal in the spectrum of PS I@ZIF-8, compared to pure PS I.<sup>29</sup> Nonetheless, the reaction center and thus the primary function of the photosystem remains unaffected by the encapsulation in the MOF, encouraging future breakthroughs on this road to artificial photosynthesis.

#### Author contributions

Sebastian Reiter: conceptualization, methodology, software, validation, formal analysis, investigation, data curation, visualization, writing – original draft, writing – review & editing; Igor

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Gordiy: methodology, software, validation, formal analysis, investigation, visualization, writing – review & editing; Kathrin L. Kollmannsberger: investigation, formal analysis, writing – review & editing; Feng Liu: investigation, writing – original draft, writing – review & editing; Erling Thyrhaug: investigation, formal analysis, visualization, writing – original draft, writing – review & editing; Dario Leister: resources, supervision, funding aquisition, writing – review & editing; Julien Warnan: resources, supervision, funding aquisition, writing – review & editing; Jürgen Hauer: conceptualization, resources, supervision, funding aquisition, writing – review & editing; Regina de Vivie-Riedle: conceptualization, resources, supervision, funding aquisition, writing – review & editing, project administration.

# Data availability

The data supporting this article have been included as part of the ESI.† Parameter files for the Gromacs port of nb-ZIF-FF can be found at https://doi.org/10.5281/zenodo.12546403. Structure files and raw data used in this article are available at https://doi.org/10.5281/zenodo.13120983.

# Conflicts of interest

There are no conflicts to declare.

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# Notes and references

- 1 J. R. Swierk and T. E. Mallouk, *Chem. Soc. Rev.*, 2013, 42, 2357–2387.
- 2 J. Wang, G. Ni, W. Liao, K. Liu, J. Chen, F. Liu, Z. Zhang, M. Jia, J. Li, J. Fu, E. Pensa, L. Jiang, Z. Bian, E. Cortés and M. Liu, *Angew. Chem., Int. Ed.*, 2023, **62**, e202217026.
- 3 S. Singla, S. Sharma, S. Basu, N. P. Shetti and T. M. Aminabhavi, *Int. J. Hydrogen Energy*, 2021, 46, 33696–33717.
- 4 K. Sun, Y. Qian and H.-L. Jiang, Angew. Chem., Int. Ed., 2023, 62, e202217565.
- 5 P. M. Stanley, J. Haimerl, N. B. Shustova, R. A. Fischer and J. Warnan, *Nat. Chem.*, 2022, **14**, 1342–1356.
- 6 P. M. Stanley, V. Ramm, R. A. Fischer and J. Warnan, *Nat. Synth.*, 2024, **3**, 307–318.
- 7 K. Takanabe, ACS Catal., 2017, 7, 8006-8022.
- 8 S. M. Kaniber, F. C. Simmel, A. W. Holleitner and I. Carmeli, *Nanotechnology*, 2009, **20**, 345701.
- 9 S. M. Kaniber, M. Brandstetter, F. C. Simmel, I. Carmeli and A. W. Holleitner, *J. Am. Chem. Soc.*, 2010, 132, 2872–2873.

- 10 G. LeBlanc, G. Chen, E. A. Gizzie, G. K. Jennings and D. E. Cliffel, *Adv. Mater.*, 2012, 24, 5959–5962.
- 11 A. K. Manocchi, D. R. Baker, S. S. Pendley, K. Nguyen, M. M. Hurley, B. D. Bruce, J. J. Sumner and C. A. Lundgren, *Langmuir*, 2013, **29**, 2412–2419.
- T. Kothe, S. Pöller, F. Zhao, P. Fortgang, M. Rögner, W. Schuhmann and N. Plumeré, *Chem. – Eur. J.*, 2014, 20, 11029–11034.
- 13 S. C. Feifel, H. Lokstein, M. Hejazi, A. Zouni and F. Lisdat, *Langmuir*, 2015, **31**, 10590–10598.
- 14 S. C. Feifel, K. R. Stieger, H. Lokstein, H. Lux and F. Lisdat, J. Mater. Chem. A, 2015, 3, 12188–12196.
- 15 F. Zhao, A. Ruff, M. Rögner, W. Schuhmann and F. Conzuelo, J. Am. Chem. Soc., 2019, 141, 5102–5106.
- 16 A. H. Teodor and B. D. Bruce, *Trends Biotechnol.*, 2020, **38**, 1329–1342.
- 17 M. Izzo, M. Jacquet, T. Fujiwara, E. Harputlu, R. A. Mazur, P. Wróbel, T. Góral, C. G. Unlu, K. Ocakoglu, S. Miyagishima and J. Kargul, *Int. J. Mol. Sci.*, 2021, 22, 8396.
- 18 K. Nguyen and B. D. Bruce, Biochim. Biophys. Acta, Bioenerg., 2014, 1837, 1553–1566.
- 19 M. Schenderlein, M. Cetin, J. Barber, A. Telfer and E. Schlodder, *Biochim. Biophys. Acta, Bioenerg.*, 2008, 1777, 1400–1408.
- 20 A. Nakamura, T. Suzawa, Y. Kato and T. Watanabe, *Plant Cell Physiol.*, 2011, **52**, 815–823.
- 21 P. Jordan, P. Fromme, H. T. Witt, O. Klukas, W. Saenger and N. Krauß, *Nature*, 2001, **411**, 909–917.
- 22 I. Carmeli, I. Lieberman, L. Kraversky, Z. Fan, A. O. Govorov, G. Markovich and S. Richter, *Nano Lett.*, 2010, **10**, 2069–2074.
- 23 R. Pamu, V. P. Sandireddy, R. Kalyanaraman, B. Khomami and D. Mukherjee, *J. Phys. Chem. Lett.*, 2018, **9**, 970–977.
- 24 M. Szalkowski, D. Kowalska, J. D. J. Olmos, J. Kargul and S. Mackowski, *Int. J. Mol. Sci.*, 2022, 23, 2976.
- 25 P. I. Gordiichuk, G.-J. A. H. Wetzelaer, D. Rimmerman,
  A. Gruszka, J. W. de Vries, M. Saller, D. A. Gautier,
  S. Catarci, D. Pesce, S. Richter, P. W. M. Blom and
  A. Herrmann, *Adv. Mater.*, 2014, 26, 4863–4869.
- 26 K. D. Wolfe, D. Dervishogullari, J. M. Passantino, C. D. Stachurski, G. K. Jennings and D. E. Cliffel, *Curr. Opin. Electrochem.*, 2020, **19**, 27–34.
- 27 F. C. Herbert, S. S. Abeyrathna, N. S. Abeyrathna, Y. H. Wijesundara, O. R. Brohlin, F. Carraro, H. Amenitsch, P. Falcaro, M. A. Luzuriaga, A. Durand-Silva, S. D. Diwakara, R. A. Smaldone, G. Meloni and J. J. Gassensmith, *Nat. Commun.*, 2021, **12**, 2202.
- 28 W. Liang, P. Wied, F. Carraro, C. J. Sumby, B. Nidetzky, C.-K. Tsung, P. Falcaro and C. J. Doonan, *Chem. Rev.*, 2021, 121, 1077–1129.
- 29 T. H. Bennett, M. D. Vaughn, S. Ali Davari, K. Park, D. Mukherjee and B. Khomami, *Nanoscale Adv.*, 2019, 1, 94–104.
- 30 N. Liguori, R. Croce, S. J. Marrink and S. Thallmair, *Photosynth. Res.*, 2020, **144**, 273–295.

This journal is © the Owner Societies 2024

Phys. Chem. Chem. Phys., 2024, 26, 23228-23239 | 23237

- 31 S. Reiter, F. L. Kiss, J. Hauer and R. de Vivie-Riedle, *Chem. Sci.*, 2023, **14**, 3117–3131.
- 32 S. Reiter, L. Bäuml, J. Hauer and R. de Vivie-Riedle, *Phys. Chem. Chem. Phys.*, 2022, 24, 27212–27223.
- 33 D. R. Baker, A. K. Manocchi, M. L. Lamicq, M. Li, K. Nguyen, J. J. Sumner, B. D. Bruce and C. A. Lundgren, *J. Phys. Chem. B*, 2014, **118**, 2703–2711.
- 34 Z. Dobson, S. Ahad, J. Vanlandingham, H. Toporik, N. Vaughn, M. Vaughn, D. Williams, M. Reppert, P. Fromme and Y. Mazor, *eLife*, 2021, 10, e67518.
- 35 S. Reiter, F. L. Kiss, J. Hauer and R. de Vivie-Riedle, Thermal site energy fluctuations in photosystem I, 2023, Dataset (v1.1.0), *Zenodo*, https://doi.org/10.5281/zenodo.7610935.
- 36 K. Lindorff-Larsen, S. Piana, K. Palmo, P. Maragakis, J. L. Klepeis, R. O. Dror and D. E. Shaw, *Proteins: Struct.*, *Funct.*, *Bioinf.*, 2010, 78, 1950–1958.
- 37 J. A. Maier, C. Martinez, K. Kasavajhala, L. Wickstrom, K. E. Hauser and C. Simmerling, *J. Chem. Theory Comput.*, 2015, **11**, 3696–3713.
- 38 G. E. Milanovsky, V. V. Ptushenko, J. H. Golbeck, A. Y. Semenov and D. A. Cherepanov, *Biochim. Biophys. Acta, Bioenerg.*, 2014, **1837**, 1472–1483.
- 39 A. Sirohiwal, F. Neese and D. A. Pantazis, J. Am. Chem. Soc., 2020, 142, 18174–18190.
- 40 L. Zhang, D.-A. Silva, Y. Yan and X. Huang, J. Comput. Chem., 2012, 33, 1969–1980.
- 41 M. Ceccarelli, P. Procacci and M. Marchi, *J. Comput. Chem.*, 2003, 24, 129–142.
- 42 D. M. A. Smith, Y. Xiong, T. P. Straatsma, K. M. Rosso and T. C. Squier, J. Chem. Theory Comput., 2012, 8, 2103–2114.
- 43 A. g A. Skjevik, B. D. Madej, R. C. Walker and K. Teigen, J. Phys. Chem. B, 2012, 116, 11124–11136.
- 44 C. J. Dickson, B. D. Madej, A. G. A. Skjevik, R. M. Betz, K. Teigen, I. R. Gould and R. C. Walker, *J. Chem. Theory Comput.*, 2014, **10**, 865–879.
- 45 Z. Wu and P. Biggin, Gromacs Port of the Amber LIPID17 Force Field, 2019, Dataset (v0.21), Zenodo, https://doi.org/ 10.5281/zenodo.3562014.
- 46 J. Wang, W. Wang, P. A. Kollman and D. A. Case, J. Mol. Graph. Model., 2006, 25, 247–260.
- 47 J. Wang, R. M. Wolf, J. W. Caldwell, P. A. Kollman and D. A. Case, *J. Comput. Chem.*, 2004, 25, 1157–1174.
- 48 S. R. G. Balestra and R. Semino, *J. Chem. Phys.*, 2022, 157, 184502.
- 49 Y.-P. Pang, J. Mol. Model., 1999, 5, 196-202.
- S. Jawahery, N. Rampal, S. M. Moosavi, M. Witman and B. Smit, *J. Chem. Theory Comput.*, 2019, **15**, 3666–3677.
- 51 W. Morris, C. J. Stevens, R. E. Taylor, C. Dybowski, O. M. Yaghi and M. A. Garcia-Garibay, *J. Phys. Chem. C*, 2012, **116**, 13307–13312.
- 52 M. J. Abraham, T. Murtola, R. Schulz, S. Páll, J. C. Smith, B. Hess and E. Lindahl, *SoftwareX*, 2015, 1–2, 19–25.
- 53 B. Hess, H. Bekker, H. J. C. Berendsen and J. G. E. M. Fraaije, *J. Comput. Chem.*, 1997, **18**, 1463–1472.
- 54 S. Páll and B. Hess, Comput. Phys. Commun., 2013, 184, 2641–2650.

- 55 T. Darden, D. York and L. Pedersen, *J. Chem. Phys.*, 1993, **98**, 10089–10092.
- 56 U. Essmann, L. Perera, M. L. Berkowitz, T. Darden, H. Lee and L. G. Pedersen, *J. Chem. Phys.*, 1995, **103**, 8577–8593.
- 57 G. Bussi, D. Donadio and M. Parrinello, J. Chem. Phys., 2007, **126**, 014101.
- 58 H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, A. DiNola and J. R. Haak, *J. Chem. Phys.*, 1984, 81, 3684–3690.
- 59 S. Nosé, Mol. Phys., 1984, 52, 255-268.
- 60 W. G. Hoover, Phys. Rev. A: At., Mol., Opt. Phys., 1985, 31, 1695–1697.
- 61 M. Parrinello and A. Rahman, J. Appl. Phys., 1981, 52, 7182–7190.
- 62 S. Nosé and M. L. Klein, Mol. Phys., 1983, 50, 1055-1076.
- 63 R. J. Gowers, M. Linke, J. Barnoud, T. J. E. Reddy, M. N. Melo, S. L. Seyler, J. Domanski, D. L. Dotson, S. Buchoux, I. M. Kenney and O. Beckstein, *Proc. 15th Python Sci. Conf.*, 2016, pp. 98–105.
- 64 N. Michaud-Agrawal, E. J. Denning, T. B. Woolf and O. Beckstein, *J. Comput. Chem.*, 2011, **32**, 2319–2327.
- 65 W. Humphrey, A. Dalke and K. Schulten, *J. Mol. Graphics*, 1996, **14**, 33–38.
- 66 S. Grimme, A. Hansen, S. Ehlert and J.-M. Mewes, *J. Chem. Phys.*, 2021, **154**, 064103.
- 67 T. Yanai, D. P. Tew and N. C. Handy, *Chem. Phys. Lett.*, 2004, **393**, 51–57.
- 68 F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, 7, 3297–3305.
- 69 S. Kossmann and F. Neese, Chem. Phys. Lett., 2009, 481, 240-243.
- 70 F. Neese, F. Wennmohs, A. Hansen and U. Becker, *Chem. Phys.*, 2009, 356, 98–109.
- 71 R. Izsák and F. Neese, J. Chem. Phys., 2011, 135, 144105.
- 72 F. Weigend, Phys. Chem. Chem. Phys., 2006, 8, 1057-1065.
- 73 J. R. Reimers, Z.-L. Cai, R. Kobayashi, M. Rätsep, A. Freiberg and E. Krausz, *Sci. Rep.*, 2013, **3**, 1–8.
- 74 J. P. Götze, F. Anders, S. Petry, J. F. Witte and H. Lokstein, *Chem. Phys.*, 2022, 559, 111517.
- 75 S. Petry, J. C. Tremblay and J. P. Götze, J. Phys. Chem. B, 2023, 127, 7207–7219.
- 76 A. Sirohiwal, R. Berraud-Pache, F. Neese, R. Izsák and D. A. Pantazis, J. Phys. Chem. B, 2020, 124, 8761–8771.
- 77 A. Sirohiwal, F. Neese and D. A. Pantazis, J. Chem. Theory Comput., 2021, 17, 1858–1873.
- 78 S. Hirata and M. Head-Gordon, Chem. Phys. Lett., 1999, 314, 291–299.
- 79 M. Casanova-Páez and L. Goerigk, J. Chem. Theory Comput., 2021, 17, 5165–5186.
- 80 A. Hellweg, C. Hättig, S. Höfener and W. Klopper, *Theor. Chem. Acc.*, 2007, **117**, 587–597.
- 81 F. Plasser and H. Lischka, J. Chem. Theory Comput., 2012, 8, 2777–2789.
- 82 F. Plasser, M. Wormit and A. Dreuw, J. Chem. Phys., 2014, 141, 024106.
- 83 F. Plasser, J. Chem. Phys., 2020, 152, 084108.

This journal is © the Owner Societies 2024

- 84 S. Grimme and M. Waletzke, J. Chem. Phys., 1999, 111, 5645–5655.
- 85 M. Kleinschmidt, C. M. Marian, M. Waletzke and S. Grimme, *J. Chem. Phys.*, 2009, **130**, 044708.
- 86 C. M. Marian, A. Heil and M. Kleinschmidt, Wiley Interdiscip. Rev.: Comput. Mol. Sci., 2018, 9, e1394.
- 87 C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1988, 37, 785–789.
- 88 A. D. Becke, J. Chem. Phys., 1993, 98, 1372-1377.
- 89 M. Gouterman, G. H. Wagnière and L. C. Snyder, J. Mol. Spectrosc., 1963, 11, 108-127.
- 90 A. Heil, M. Kleinschmidt and C. M. Marian, J. Chem. Phys., 2018, 149, 164106.
- 91 S. Nakagawa, O. Weingart and C. M. Marian, *J. Phys. Chem. B*, 2017, **121**, 9583–9596.
- 92 S. Salzmann, M. R. Silva-Junior, W. Thiel and C. M. Marian, J. Phys. Chem. B, 2009, 113, 15610–15618.
- 93 M. R. Silva-Junior, M. Mansurova, W. Gärtner and W. Thiel, *ChemBioChem*, 2013, 14, 1648–1661.

- 94 D. Bakowies and W. Thiel, J. Phys. Chem., 1996, 100, 10580–10594.
- 95 P. Sherwood, A. H. de Vries, M. F. Guest, G. Schreckenbach, C. R. A. Catlow, S. A. French, A. A. Sokol, S. T. Bromley, W. Thiel, A. J. Turner, S. Billeter, F. Terstegen, S. Thiel, J. Kendrick, S. C. Rogers, J. Casci, M. Watson, F. King, E. Karlsen, M. Sjøvoll, A. Fahmi, A. Schäfer and C. Lennartz, *THEOCHEM*, 2003, 632, 1–28.
- 96 R. Fisher, *Statistical Methods for Research Workers*, Oliver & Boyd, 1925.
- 97 J. W. Tukey, Biometrics, 1949, 5, 99.
- 98 D. L. Theobald, Acta Crystallogr., Sect. A: Found. Crystallogr., 2005, 61, 478-480.
- 99 D. Mester and M. Kállay, J. Chem. Theory Comput., 2022, 18, 1646–1662.
- 100 S. Chandrasekaran, M. Aghtar, S. Valleau, A. Aspuru-Guzik and U. Kleinekathöfer, J. Phys. Chem. B, 2015, 119, 9995–10004.

# Summary and Outlook

This thesis has investigated the crucial influence of environmental effects on photochemical processes through six computational studies.

Chapter 1 explores two photocatalytic reactions, demonstrating how ground state preassemblies between catalysts and substrates can enhance reactivity even with short-lived excited states. These findings significantly expand the potential for novel catalyst design, potentially replacing prevalent precious metal complexes. The first study focuses on naphthalene monoimide-based catalysts for selective  $C(sp^3)$ -O bond cleavage in phosphinated alcohols. Employing an e-PRC approach, a reactive catalyst radical anion is generated electrochemically and subsequently excited with blue light to facilitate single electron transfer to the substrate. This method enables mild, base-free conditions without high electrochemical potentials or energy-intensive light, preserving selectivity across a wide substrate scope. The study reveals the catalyst's ability to dispersively bind substrates in the ground state and characterizes an intramolecular CT state which supports efficient single electron transfer upon photoexcitation. Future work could focus on suppressing the identified non-reactive quartet loss channel in the excited state through targeted substitutions, potentially further increasing catalytic yields. Multireference calculations of energy and spin-orbit coupling elements, possibly followed by excited state dynamics simulations, could aid in such rational catalyst design. The second study in chapter 1 elucidates the operating principle of a novel transition metal photocatalyst, which is composed of earth-abundant 3d-metals and two simple tridentate diiminopyridine ligands. Despite short excited state lifetimes on the order of only a few picoseconds, this complex catalyzes the C-H arylation of pyrroles, aided by ground state preassemblies between the catalyst, amine sacrificial agents, and aryl halides. A conPET mechanism is proposed, where the diiminopyridine ligand facilitates both ground state preassembly and conducts/temporarily stores the transferred electron. This work presents a crucial proof-of-concept that photocatalysis is achievable with inexpensive first-row transition metal catalysts. The detailed mechanistic insights from experiment and theory will enable further optimizations through ligand design. Collectively, the two studies in chapter 1 open new avenues towards economically and ecologically sustainable photocatalysis by exploiting dispersion interactions between molecules in their ground state.

Moving beyond specific critical points on the PES, chapter 2 introduces a novel computational workflow for performing wave packet quantum dynamics in explicit environments. Unlike previous approaches,<sup>[191,192]</sup> this method directly incorporates environmental interactions without prior parameterization. This is achieved by reevaluating the PES for different snapshots from classical MD simulations. Applied to uracil in a solvated RNA strand, the new technique reveals both faster and slower relaxation pathways induced by the environment, emphasizing the importance of including solvent effects. The presented workflow is highly flexible regarding the QM/MM partition scheme and allows simulations in more complex environments than previously possible. Further improvements are imaginable, as the repeated evaluation of the environment potential is becoming more and more affordable with the rise of fast and accurate semiempirical methods.<sup>[78,147,266]</sup> This enables relaxation of the environment at every grid point of the PES, alleviating the approximation of a static environment. For timescales longer than a few picoseconds, the wave packet should additionally be coupled to the motion of the environment to account for decoherence effects. Initial attempts in this direction<sup>[190]</sup> are promising but lack polarization of the electronic wave function by the classical environment, unlike the approach presented here.

Chapter 3 presents three studies investigating key steps towards artificial photosynthesis. The first elucidates protonation sites and reaction mechanisms for hydrogen evolution catalyzed by the [Co(Mabiq)] complex. Combining spectroelectrochemistry with high-level DFT/MRCI calculations, distinct protonation sites on the ligand are identified, leading to different intermediates and influencing the reaction pathway. These insights provide a foundation for future research aimed at suppressing protonation at one site through targeted ligand substitution.

The second study examines excitation energy distribution in cyanobacterial PS I with a detailed computational model. Extensive MD simulations and DFT/MRCI calculations of site energies and excitonic couplings demonstrate that the site energy and exciton distribution in PS I do not resemble an energy funnel towards the reaction center on average. Multiple low-energy sites compete with the reaction center for excitation energy, along with apparent energy barriers. However, thermal fluctuations easily overcome these barriers, contributing to transient energy transfer from the antenna complex to the reaction center. A persistent energy funnel is therefore not required for efficient light-harvesting. This study lays the groundwork for further investigations on exciton dynamics in PS I after initial excitation. Moreover, the excitonic Hamiltonian can be extended with additional pigments, particularly carotenoids, for a more complete picture of the light-harvesting process and potential photoprotective mechanisms.<sup>[267,268]</sup>

The third study explores embedding PS I in the MOF ZIF-8, revealing CT interactions between chlorophylls and the MOF that may explain experimentally observed spectral anomalies. However, the primary function of the photosystem is retained as the reaction center does not interact with the MOF. This understanding paves the way for future research exploring how to optimize the interface between biological systems and MOFs for enhanced functionality.

In conclusion, this thesis demonstrates the versatility and potential of modern theoretical chemistry in advancing photochemistry. Employing a wide array of computational methods across different scales, this research provides deeper insights into the mechanisms of photocatalytic reactions, the photoprotection of the genetic code, and energy transfer processes in photosynthesis. The developed tools and models will enable future research to predict molecular properties in complex environments with greater accuracy, bridging the gap between theoretical predictions and experimental reality. Overall, these results highlight the crucial role of computational methods in accelerating the development of sustainable technologies, from next-generation photocatalysts for organic synthesis to solar energy harvesting for fuel production.

APPENDIX

# Supporting Information to Chapter 1

# A.1 Selective C(sp<sup>3</sup>)–O Cleavages of Phosphinated Alcohols

The complete supporting information to the article "Electro-mediated PhotoRedox Catalysis for Selective  $C(sp^3)$ –O Cleavages of Phosphinated Alcohols to Carbanions" was published 2021 in Angewandte Chemie International Edition and is available at https://doi.org/10. 1002/anie.202105895. An excerpt of the most relevant computational details (section S18 in the original document) is reprinted below. Please note that cross-references to other sections of the supporting information have been kept for the reader's convenience, even though these sections are not reproduced below. They are marked in *italics* to distinguish them from other cross-references within this work.

# A.1.1 General Information

All calculations were performed using Density Functional Theory  $(DFT)^{[269,270]}$  using the Gaussian 16 software package.<sup>[271]</sup> All minima were optimized using the  $\omega$ B97X-D functional<sup>[107]</sup> with the 6-311+G\* basis set.<sup>[272–274]</sup> Solvation effects were included with the integral equation formalism polarizable continuum model (IEFPCM),<sup>[56,275]</sup> with default parameters for acetonitrile, in which preparative e-PRC reactions and spectroscopy were performed. Frequency calculations were performed on all optimized structures in order to characterize minima (zero imaginary frequencies). Spin densities and molecular orbitals depicted in the main article and herein were visualized using VMD 1.9.3<sup>[276]</sup> with an isovalue of 0.004 and 0.02, respectively.

# A.1.2 Bond Dissociation Free Energies

Benchmarks have shown<sup>[277,278]</sup> that the range-separated and dispersion-corrected  $\omega$ B97X-D functional<sup>[107]</sup> is well-suited to main group thermochemistry, while the use of a triplezeta basis set is generally recommended to mitigate basis set incompleteness errors.<sup>[110,279]</sup> To further validate our DFT results, we calculated the bond dissociation energies of selected compounds with the open-shell DLPNO-CCSD(T)<sup>[280,281]</sup> method implemented in  $ORCA \ 4.2.1.^{[282,283]}$  We used the def2-TZVPPD<sup>[247,248]</sup> basis set with the def2-TZVPPD/C correlation basis.<sup>[253,254]</sup> Tight SCF and PNO convergence criteria were applied and solvation effects were treated with the conductor-like polarizable continuum model (C-PCM)<sup>[249,284]</sup> using default parameters for acetonitrile, in which e-PRC reactions and spectroscopy were conducted. The DFT energies are on average  $3.5 \text{ kcal mol}^{-1}$  smaller than those obtained with DLPNO-CCSD(T) (table A.1), but the deviation is systematic and the trend is well reproduced, thus validating the use of DFT in this context.

	( ),	
DFT	DLPNO- CCSD(T)	Difference
-23.44	-28.03	4.59
-19.98	-23.47	3.49
-25.77	-28.86	3.09
-23.87	-27.53	3.66
-11.99	-15.10	3.10
-8.69	-11.33	2.64
	$\begin{array}{c} \textbf{DFT} \\ \hline -23.44 \\ -19.98 \\ -25.77 \\ -23.87 \\ -11.99 \\ -8.69 \end{array}$	$\begin{array}{c c} \mathbf{DFT} & \mathbf{DLPNO-}\\ \mathbf{CCSD(T)} \\ \hline \\ -23.44 & -28.03 \\ -19.98 & -23.47 \\ -25.77 & -28.86 \\ -23.87 & -27.53 \\ -11.99 & -15.10 \\ -8.69 & -11.33 \\ \end{array}$

**Table A.1:** Calculated C–O bond dissociation energies (kcal mol<sup>-1</sup>) without thermodynamic corrections at the  $\omega$ B97X-D/6-311+G\* and DLPNO-CCSD(T)/def2-TZVPPD levels of theory.

Optimized structures were obtained using the theory level ( $\omega$ B97X-D/6-311+G<sup>\*</sup>) and solvent model (IEFPCM) specified in the general part. Bond dissociation free energies  $\Delta$ G were obtained from the frequency analysis at 298.15 K and 1 atm according to:

$$\Delta G = \Delta (E_{\text{elec}} + ZPVE + \Delta G_{\text{trans,rot,vib}} + \Delta G_{\text{solv}}) \tag{A.1}$$

Here,  $E_{\text{elec}}$  denotes the electronic energies, ZPVE is the zero point vibrational energy,  $\Delta G_{\text{trans,rot,vib}}$  includes thermal contributions from translations, rotations and vibrations as well as entropic terms and  $\Delta G_{\text{solv}}$  is the free energy of solvation.

#### A.1.3 Redox Potentials

We investigated the reduction of a phosphinate substrate P by one electron, given by:

$$P + e^- \rightarrow P^{\bullet-}$$

The free energy change  $\Delta G$  of this reaction contains the thermally corrected energies G of reactant and product as well as the thermal contributions of the free electron. There are multiple conventions to include the latter<sup>[285]</sup> and we have chosen the ionic convention where  $G(e^-) = 0 \text{ eV}$ .

$$\Delta G = G(\mathbf{P}^{\bullet-}) - G(\mathbf{P}) - G(e^{-}) \tag{A.2}$$

The absolute redox potential  $E_{abs}^{\circ}$  is related to  $\Delta G$  via:

$$E_{\rm abs}^{\circ} = \frac{-\Delta G}{nF} \tag{A.3}$$

where n is the number of electrons involved in the redox process and F is the Faraday constant. Since we are only considering one-electron processes here, n is 1 in all cases. By supplying the energy in eV, the Faraday constant equals the elementary charge and the value of  $E_{abs}^{\circ}$  is simply the negative change in free energy.  $\Delta G$  is often calculated<sup>[286–291]</sup> by an indirect approach via a thermodynamic cycle. There, the reaction free energy is calculated for the gas phase geometries and the free energy of solvation  $\Delta G_{solv}$  is added separately, possibly at a different level of theory, while neglecting the structural relaxation in solution. The success of this strategy is rooted at least partially in error cancellation effects.<sup>[292,293]</sup>

We therefore decided to use a simpler approach and calculated  $\Delta G$  directly at the optimized geometries of reduced and oxidized species in solution,<sup>[292]</sup> using the theory level ( $\omega$ B97X-D/6311+G<sup>\*</sup>) and solvent model (IEFPCM) specified in the general part. To compare the calculated potential  $E_{abs}^{\circ}$  to experimental results, it must be referenced against a standard potential:

$$E^{\circ} = E^{\circ}_{abs} - E_{ref} \tag{A.4}$$

Here, we used the  $Fc^+/Fc$  couple as an internal standard against the saturated calomel electrode (SCE), whose absolute reduction potential in acetonitrile has been determined computationally as  $4.988 V.^{[294]}$ 



Figure A.1: Correlation between experimental and calculated redox potentials. The dashed black line represents the ideal correlation between experiment and theory (slope 1 and y-intercept 0). The blue points and line denote the raw data obtained from calculations and the orange points illustrate the final potentials reported in the paper. The starred data point (**1a**) was omitted from the fit as an outlier.  $R^2$  of the linear regression is 0.54.

The resulting redox potentials should ideally correlate 1:1 with the experimental ones

(black line in figure A.1). However, because of experimental factors that cannot be reproduced well in calculations, such as conformational variations, as well as systematic errors specific to the chosen DFT functional and solvation model, we can expect a certain deviation from the ideal values. To correct for these deviations, we fitted a linear function with slope 1 to the data set of experimental and calculated potentials (blue line). In addition to the phosphinates in Table 2 of the main paper, we included compound **4a** ( $\Delta E_{exp} = -2.24$  V,  $\Delta E_{calc} = -2.27$  V) in the calibration protocol to enlarge the data set. In contrast, compound **1a** (marked with a star in figure A.1) was removed from the fit as an outlier. The y-intercept of the fit function (-0.67 V) represents the systematic shift of the calculated potentials and is on the higher end of the error margin reported for other DFT calculations.<sup>[286,287,295]</sup>

Taking this into account, the final potentials reported in Table 2 are calculated as:

$$E^{\circ} = E^{\circ}_{abs} - E_{ref} + 0.67 \,\mathrm{V} \tag{A.5}$$

#### A.1.4 DFT/MRCI Calculations

The ground state geometry of **^BuO-NpMI**<sup>•-</sup> was optimized at the  $\omega$ B97X-D/6-311+G<sup>\*</sup> level of theory with *Gaussian 16* (for xyz-coordinates, see section 19). For excited state calculations, we employed the DFT/MRCI method<sup>[296–300]</sup> with the R2018 Hamiltonian.<sup>[299]</sup> Here, the ground state DFT reference was calculated with *ORCA 4.2.1*<sup>[282,283]</sup> using the BHLYP functional.<sup>[301,302]</sup> The def2-TZVPD basis set<sup>[247,248]</sup> was used on all atoms within the resolution-of-the-identity formalism for Coulomb and exchange integrals<sup>[303,304]</sup> (RI-JK) in conjunction with the def2-TZVPD/C<sup>[253]</sup> and def2/JK<sup>[305]</sup> auxiliary basis sets. Solvation effects were accounted for by the C-PCM model<sup>[249,284]</sup> with default parameters for acetonitrile. Symmetry was turned off (keyword NoUseSym) and the SCF convergence threshold was set to  $10 \times 10^{-7}$  E<sub>h</sub> (keyword SCFCONV7). The DFT orbitals for the radical anion were calculated in the unrestricted Kohn-Sham formalism and transformed to quasi-restricted orbitals<sup>[306]</sup> prior to the MRCI calculation. Ten roots were calculated in the MRCI step. The reference space was iteratively optimized using a tight selection threshold of 0.8 E<sub>h</sub> (keywords **\$esel 0.8**, **\$dftparam tight**), until all leading configurations were contained in the reference space.

# A.1.5 CASSCF Calculations

To identify the putative quartet state ES<sub>1</sub>, we performed CASSCF(11,10) calculations<sup>[307–309]</sup> with *Molpro 2021.1*<sup>[310–312]</sup> using the aug-cc-pVTZ<sup>[313,314]</sup> basis set. Density fitting<sup>[315]</sup> was used to approximate the two-electron integrals and speed up the calculations. To further reduce the computational cost, we built a model system for <sup>n</sup>BuO-NpMI<sup>•-</sup> by replacing the O-ether residue in the DFT-optimized structure with hydrogen and symmetrizing the resulting geometry to the  $C_{2v}$  point group. The active space was chosen with the goal of including correlating pairs of  $\pi$  and  $\pi$ \* orbitals as well as including a balanced amount of orbitals localized on the aniline and naphthalene subunits, respectively. The resulting active

space contained 11 electrons in 10 orbitals (figure A.2). State averaging was performed over forty states, namely five doublet and five quartet states in each irreducible representation.



Figure A.2: Active space of the CASSCF(11,10) calculation used to determine the energy of the putative quartet excited state. The naphthalene subunit resides in the yz-plane with the N–C bond aligned along the z-axis. Orbitals were visualized with VMD 1.9.3 using an isovalue of 0.02. The figure depicts the doublet ground state configuration.

The first ten states are summarized in Table S9. Compared to the DFT/MRCI spectrum (see Figure 3, main manuscript), the CASSCF energies are blue-shifted by 1 to 2 eV. This is within the usual range for vertical excitation energies computed with CASSCF, due to the lack of dynamical correlation.<sup>[316]</sup> The tentative charge transfer doublet state, denoted  $D_n$  in the main manuscript is the fifth excited doublet  $D_5$ , in agreement with the DFT/MRCI results. Its vertical excitation energy at the CASSCF(11,10) level of theory is 4.34 eV and its dominant contribution is the single electron excitation  $3-A_2 \rightarrow 4-A_2$ . The transition dipole moment of this state is lower than predicted by DFT/MRCI, which is likely due to the symmetry constraints used in the CASSCF calculation.

The first excited quartet state  $Q_1$  has a vertical excitation energy of 4.18 eV. Taking into account the aforementioned blue-shift of 1 to 2 eV in CASSCF as well as vibrational relaxation in the excited state, this is in reasonable agreement with the new emission band at 540 nm (2.29 eV). The excitation energy of  $Q_1$  is 0.25 eV below that of  $D_5$  and only 0.01 eV below that of  $D_4$ . This indicates that coupling to the quartet domain is a possibility after excitation into one of these doublet states, at least from an energetic point of view. In

State	Sym.	$\Delta E \; [ ext{eV}]^{ ext{a}}$	$ \mu $ [a.u.]	${\bf Dominant \ Transitions}^{\rm b}$
$D_0$	$^{2}A_{2}$	0.00	/	ground state
$D_1$	$^{2}\mathrm{B}_{1}$	2.00	1.4219	$3-A_2 \rightarrow 3-B_1 \ (0.890)$
$D_2$	$^{2}\mathrm{B}_{1}$	2.30	0.0480	$3-A_2 \rightarrow 4-B_1 (0.904)$
$D_3$	$^{2}A_{2}$	3.56	1.2666	$1 - A_2 \rightarrow 3 - A_2 \ (0.868)$
$Q_1$	${}^{4}\mathrm{B}_{1}$	4.18	/	$1 - A_2 \rightarrow 3 - B_1 \ (0.936)$
$D_4$	$^{2}\mathrm{B}_{2}$	4.19	0.0022	$3-A_2 \rightarrow 2-B_2 \ (0.933)$
$D_5$	$^{2}A_{2}$	4.43	0.0611	$3-A_2 \rightarrow 4-A_2 \ (0.927)$
$Q_2$	$^{4}A_{2}$	4.72	/	$1-B_2 \rightarrow 2-B_2 \ (0.708)$
				$2-A_2 \rightarrow 4-A_2 \ (0.624)$
$D_6$	$^{2}A_{2}$	4.73	0.0077	$1-B_2 \rightarrow 2-B_2 \ (0.576)$
_	2-			$2\text{-}A_2 \rightarrow 4\text{-}A_2 \ (0.503)$
$D_7$	$^{2}B_{1}$	4.88	0.5000	$2-B_1 \rightarrow 3-A_2 (0.691)$
				$1-D_1 \rightarrow 3-A_2 (-0.307)$

**Table A.2:** CASSCF(11,10) energies, norm of the transition dipole moments  $|\mu|$  and dominant electronic transitions for the first ten electronic states of the **<sup>n</sup>BuO-NpMI**<sup>•-</sup> model system.

<sup>a</sup> Relative energies and transition moments are reported with respect to the doublet ground state. <sup>b</sup> CI coefficients for each transition are given in parentheses.

light of the luminescence spectra reported in section S14, it is reasonable to assume that the long-lived emitting species is indeed the lowest excited quartet state. This state with B1 symmetry is characterized mainly by the single electron excitation  $1-A_2 \rightarrow 3-B_1$ , which corresponds to an opposite charge transfer from the aniline to the naphthalene subunit. EPR spectra (section S17) and DFT calculations (section S18.6) show that precomplexation of the substrate may occur on the aniline moiety. Therefore, Q<sub>1</sub> being the long-lived emitter state would explain why the luminescence is not quenched upon addition of substrate 1d to the reaction mixture: In a precomplex, the charge would be shifted away from the substrate when the catalyst crosses to Q<sub>1</sub>, thus impeding single electron transfer.

#### A.1.6 Computational Investigation of Preassembly Candidates

The variation of catalyst structure on the reactivity presented in the main article showed increasing yields for the reaction of **1d**, when reducing the steric bulk on the *ortho*-position of the catalyst's N-aniline moiety. Thus we performed DFT calculations to investigate possible arrangements for ground state precomplexation between substrate and the aniline unit of the catalyst radical anion. All calculations were performed at the  $\omega$ B97X-D/6-311+G\* level of theory with *Gaussian 16*.<sup>[271]</sup> Solvation effects were included with the IEFPCM model,<sup>[56,275]</sup> with default parameters for acetonitrile. For the frequency analyses presented in this section, we reduced the two-electron integral accuracy threshold from  $10^{-12}$  to  $10^{-11}$  (keyword int=(acc2e=11)), because the calculations would not converge otherwise. Due to their structural complexity, there are many ways for the phosphinate to dispersively bind to the radical anion catalyst. Assuming that the primary contributors

to the binding mode are  $\pi$ -stacking interactions,<sup>[317,318]</sup> the P-bound phenyl groups as well as the aryl moiety from the benzylic position ("O–CHR-aryl") of the phosphinate may coordinate to the aniline or naphthalene moiety of the radical anion catalyst. Here,  $\pi$ - $\pi$ stacked interactions (face-to-face, parallel displaced) as well as T- $\pi$  shaped interactions (edge-to-face) are conceivable. We expect the strongest dispersive interactions when not just one but two of the substrate's aromatic units coordinate to the N-aniline group in a pincer-like complex. Indeed, the geometry optimizations shown later in this section always converged to an orientation where one of the aromatic units of the substrate coordinates ( $\pi$ - $\pi$ , face-to-face) to the aniline ring and another one to the side (T- $\pi$  edge-to-face), regardless from the starting structure. To assess the accessibility of such a complex starting from isolated molecules, we first performed a series of unrelaxed potential energy scans. The scan coordinate was chosen such that the O–CHR-aryl component of substrate **1d** approaches the catalyst from the side and one of the P-bound phenyl units forms a T- $\pi$  shaped complex with the aniline at small distances (figure A.3).



Figure A.3: Two views on the orientation of **1d** and the catalyst (here **<sup>n</sup>BuO-NpMI**) chosen for potential energy scans. The red arrow indicates the scan coordinate, i.e. the center-of-mass distance between the aniline moiety of the catalyst and the O–CHR-aryl moiety of the substrate. The three interacting aromatic rings are highlighted in bold.

Two energy minima emerge along the scan coordinate (figure A.4, left). Going from large to small distances, the first minimum appears when the P-bound phenyl starts to interact dispersively with the *ortho*-substituent groups. It is followed by an energy barrier when the imide-oxygen and/or the *ortho*-substituent groups come in closer contact with the phenyl unit and repulsive terms presumably start to predominate. As could be expected, this barrier rises with increasing "steric bulk" on the aniline and makes the second minimum entirely inaccessible for NpMI (figure A.4, left). This second energy minimum represents the fully formed pincer-like complex, where the O–CHR-aryl moiety of the substrate is close enough to form dispersive T- $\pi$ -stacking interactions with the aniline unit, which stabilizes the energy.



Figure A.4: Potential energy scans along the approach of substrate 1d towards the aniline unit of the catalyst. The scan coordinate refers to the center-of-mass distance between the O–CHR-aryl moiety and the aniline unit. Left: aniline and naphthalene units orthogonal, this is the ground state minimum of the catalyst. Right: naphthalene unit rotated by 90°, structure not relaxed. The minimum energy is shifted to zero in all scans.



Figure A.5: Relaxed potential energy surface scan for the rotation of the aniline moiety in <sup>n</sup>BuO-NpMI. The four atoms defining the scanned dihedral angle are highlighted as spheres.

For the less sterically hindered catalysts  ${}^{n}BuO-NpMI$  and **5e**, the aniline unit can in principle rotate with respect to the imide group. We calculated the rotational barrier in  ${}^{n}BuO-NpMI^{\bullet-}$  as 16 kcal mol<sup>-1</sup> by performing a relaxed potential energy scan of the respective C–C–N–C dihedral angle between 90° and 180° with a step size of 2° at the same level of theory as before (figure A.5). In effect, the rotation of the aniline group decreases the repulsive "steric" interactions between one the imide oxygens and the P-bound phenyls, thus lowering the energy barrier for precomplexation and stabilizing the complex (figure A.4, right) even more so than the initial dispersive interaction with the *ortho*-substituent.

Assuming that a successful reaction requires formation of a precomplex, based on the arguments presented in the main manuscript:

- (i) known picosecond lifetime of doublet states,<sup>[129,130,319]</sup> apparent anti-Kasha photochemistry,
- (ii) the likely rate-limiting C(sp<sup>3</sup>)–O cleavage and profound influence of catalyst structure on this step,
- (iii) the identical redox (Section 11), UV-vis (Section 13) and emission (Section 14) properties of NpMI and <sup>n</sup>BuO-NpMI that confirm electronic differences cannot explain the success of the latter catalyst for most substrates,

the potential energy scans depicted in figure A.4 could possibly explain the reactivity trend observed in the experimental structure-activity relationship study. Increasing "steric bulk" at the *ortho*-position of the aniline impedes the formation of the most stable and intimate preassembly as the pincer-like  $\pi$ -stacking interaction becomes less accessible. Of course, an unrelaxed potential energy scan for complex molecular assemblies can only convey a rough picture of the real situation. For example, it neglects the internal flexibility of the substituents and the fact that the substrate can re-orient itself upon approaching the catalyst, thus minimizing clashes and stabilizing the complex. To take these effects into account, we optimized several candidate structures for a ground state precomplex. Using different catalysts and relative orientations, we were able to optimize 13 stable ground state preassemblies (figures A.6 to A.10).



Figure A.6: Candidate preassemblies of  $\mathbf{NpMI}^{\bullet-}/\mathbf{1d}$  at the N-aniline moiety.



Figure A.7: Candidate preassemblies of  $\mathbf{5d}^{\bullet-}/\mathbf{1d}$  at the N-aniline moiety.



Figure A.8: Candidate preassemblies of  $5e^{\bullet-}/1d$  at the N-aniline moiety.



Figure A.9: Candidate preassemblies of  ${}^{n}BuO-NpMI^{\bullet-}/1d$  at the N-aniline moiety.



Figure A.10: Candidate preassembly of  ${}^{\mathbf{n}}\mathbf{BuO-NpMI}^{\bullet-}/1d$  at the naphthalene moiety.

Components	Orientation	$\Delta G^{ m compl}$	Intermolecular	Preparative
		$[\text{kcal mol}^{-1}]$	${f distance} \ [{ m \AA}]^{ m a}$	reaction yield
				[% 2d]
NpMI <sup>•-</sup> $(\mathrm{R}{=}i\mathrm{Pr})$ / 1d	1	10.44	4.88 $(T-\pi)^{b}$	n.d.
			4.23 $(\pi - \pi)^{c}$	
	<b>2</b>	3.41	4.86 $(T-\pi)^{c}$	
			4.48 $(\pi - \pi)^{b}$	
	3	5.35	4.98 $(T-\pi)^{c}$	
			$3.84  (\pi - \pi)^{c}$	
	4	11.65	5.65 $(T-\pi)^{D}$	
			4.41 $(\pi - \pi)^{c}$	
5d $^{\bullet-}$ (R $=$ Et) / 1d	1	4.97	$4.52^{b,d}$	40
			$5.37^{ m c,d}$	
	<b>2</b>	4.66	$4.63^{b,d}$	
			$5.23^{c,d}$	
$5e^{-}(R = Me) / 1d$	1	5.88	5.16 $(T-\pi)^{b}$	55
			4.33 $(\pi - \pi)^{c}$	
	<b>2</b>	6.11	5.17 $(T-\pi)^{b}$	
			4.32 $(\pi - \pi)^{c}$	
<sup>n</sup> BuO-NpMI <sup>•-</sup> (R = H) / 1d	1	2.59	4.90 $(T-\pi)^{b}$	75
			4.07 $(\pi - \pi)^{c}$	
	<b>2</b>	-0.18	5.14 $(T-\pi)^{c}$	
			4.26 $(\pi - \pi)^{\rm b}$	
	3	-0.33	4.89 $(T-\pi)^{b}$	
			4.06 $(\pi - \pi)^{c}$	
	4	0.70	5.14 $(T-\pi)^{c}$	
			4.33 $(\pi - \pi)^{\text{b}}$	
	Napthalene	-0.16	4.50 $(T-\pi)^{e}$	
	$\operatorname{complex}$		4.52 $(\pi - \pi)^{r}$	

**Table A.3:** Calculated free energies of complexation  $(\text{kcal mol}^{-1})$  for ground state assemblies of substrate **1d** with various residues R on the *ortho*-position of the N-aniline unit of the catalyst  $(\omega B97X-D/6-311+G^*, \text{IEFPCM}(\text{MeCN})).$ 

n.d., not determined. <sup>a</sup> The distances between the aromatic centerpoints of each aromatic ring of **1d** to the centerpoint of the N-aniline were taken, unless stated otherwise. <sup>b</sup> Interaction between the N-aniline and the O–CHR-Ar arene. <sup>c</sup> Interaction between the N-aniline and the O–P(O)Ph arene. <sup>d</sup> The interaction could not be assigned as  $T-\pi$  or  $\pi-\pi$  and resembled something in between. <sup>e</sup> Distance between the central carbon of the naphthalene moiety and the centerpoint of the O–CHR-Ar arene. <sup>f</sup> Distance between the central carbon of the naphthalene moiety and the centerpoint of the O–P(O)Ph arene.

As a quantitative measure for the stability of the converged structures, we defined the free energy of complexation  $\Delta G^{\text{compl}}$  as the free energy difference between the optimized precomplex and its isolated components (table A.3). For the latter, we calculated the neutral form of phosphinate **1d** and the radical anion of the respective catalyst. In all cases, the optimized structures of isolated radical anion catalysts and preassemblies finds the N-aniline moiety perpendicular to the naphthalene moiety. Multiple stable structures exist for the preassemblies, differing in the relative orientation of the substrate with respect to the catalyst and the calculations presented here are not intended to be comprehensive. However, comparing the relative energies of a few optimized structures is helpful to rationalize the observed structure activity relationship in the context of a potential preassembly. Regardless

of initial input geometries, all optimizations converged to a pincer-like structure where one of the substrate-bound aromatic units coordinates to the side of the aniline and another is oriented parallel to the aniline and coordinates from the top.

Out of all the optimized complexes, the four orientational candidates for <sup>n</sup>BuO-NpMI are consistently the most thermodynamically favorable, again supporting the hypothesis that precomplexation in the ground state is an important aspect in the catalytic process. The trend among the other catalysts is not as clear, however. It is difficult to draw a concrete relationship between increasingly bulky orthosubstituents and thermodynamics, since the substrate can rearrange to coordinate from a different direction. Nonetheless, formation of all complexes with *ortho*-substituted catalysts is endergonic at this level of theory, indicating that steric hindrance on the aniline unit indeed impedes the stacking interaction and destabilizes the complex.

The spin density in all of the optimized precomplex radical anions, where complexation occurs on the N-aniline unit of the catalyst, remains identical to those of the isolated catalysts. In contrast, the spin density of the one precomplex candidate, where the substrate coordinates to the naphthalene moiety of <sup>n</sup>BuO-NpMI, is asymmetrical and thus deviates slightly from that of the isolated catalyst (figure A.11). Such a change in the electronic structure should manifest in a different EPR signal, which we do not observe. This again supports the thesis that if preassociation occurs, it will involve the N-aniline moiety rather than the naphthalene moiety of the catalyst.



**Figure A.11:** Spin densities of **<sup>n</sup>BuO-NpMI**<sup>•-</sup> (left) and an **<sup>n</sup>BuO-NpMI**<sup>•-</sup>/**1d** precomplex structure where the substrate coordinates to the naphthalene moiety of the catalyst (right).

Note that the mere existence of a ground state minimum does not mean that it is catalytically active upon photoexcitation. For example, Barham and co-workers recently proposed the detection of two different triarylaminium radical cation/haloarene precomplex geometries (edge-to-face T- $\pi$  and face-to-face  $\pi$ - $\pi$ ) on the basis of changes in EPR spectra and DFT calculations.<sup>[17]</sup> There, it was proposed the face-to-face  $\pi$ - $\pi$  geometry was "unreactive" upon photoexcitation.

Therefore, the thermodynamics of precomplexation in the ground state is only one aspect to consider in a larger scheme. Our computational results demonstrate that there indeed are stable candidate preassemblies of phosphinate substrate and radical anion catalyst. Moreover, we show that the introduction of substituents at the ortho-position of the Naniline moiety destabilizes these complexes and makes their formation less likely due to a higher kinetic barrier upon approach of the two molecules. Further studies are required to investigate the excited states of our optimized candidate structures and whether certain geometric factors can facilitate SET within preassemblies upon photoexcitation.

# A.2 C–H Arylation of Pyrroles Catalyzed by 3d-Metal Complexes

The complete supporting information to the article "Cobalt-Mediated Photochemical C–H Arylation of Pyrroles" was published 2024 in Angewandte Chemie International Edition and is available at https://doi.org/10.1002/anie.202405780. An excerpt of the most relevant computational details (section S7 in the original document) is reprinted below. Optimized geometries are openly available at https://doi.org/10.5281/zenodo.10528903.

#### A.2.1 General Procedure for Geometry Optimizations and Ground State Energies

Unless otherwise noted, all quantum chemical calculations were performed with the software package  $Orca \ 5.0.3.^{[246,320]}$  Geometries were optimized at the r<sup>2</sup>SCAN-3c<sup>[321]</sup> level of theory and verified as energy minima by the absence of imaginary vibrational frequencies. r<sup>2</sup>SCAN-3c is a recently developed composite method based on the r<sup>2</sup>SCAN density functional and including three empirical corrections. These comprise the atomic charge dependent D4 dispersion correction<sup>[322]</sup> as well as a custom fitted triple- $\zeta$  basis set<sup>[321]</sup> (def2-mTZVPP) and the geometric counterpoise correction<sup>[323]</sup> to correct for the basis set superposition error. r<sup>2</sup>SCAN-3c has proven to yield superior energies and geometries for a wide variety of benchmark sets, including also transition metal complexes, on par with or even surpassing much more expensive hybrid density functional methods with larger basis sets.<sup>[321]</sup> Solvation effects were included with the conductor-like polarizable continuum model<sup>[249]</sup> (C-PCM) using parameters for acetonitrile. The final wave functions were checked for internal and external instabilities. Thermodynamic corrections for enthalpies and Gibbs free energies were extracted from the frequency analyses in the quasi-rigid-rotor-harmonic-oscillator (QRRHO) approximation<sup>[324]</sup> at 295.15 K and 1 atm.

Coupled cluster energies were calculated with the DLPNO-CCSD(T1) method, using an iterative triples correction (T1) which is especially recommended for radicals.<sup>[280,325,326]</sup> Scalar relativistic effects were included in the ZORA formalism<sup>[327,328]</sup> and a quadruple- $\zeta$  basis set with diffuse functions, ma-ZORA-def2-QZVPP,<sup>[247,329]</sup> was employed for these

calculations, in particular to ensure an accurate description of the open-shell and brominecontaining compounds. Tight SCF and PNO criteria were applied and a tighter-than-default integration grid was used (DefGrid3). The RIJCOSX approximation<sup>[250,251,304]</sup> was used with the def2-QZVPPD/C<sup>[253]</sup> and def2/J<sup>[252]</sup> auxiliary basis sets to speed up the Hartree-Fock reference calculation. The C-PCM<sup>[249]</sup> was employed to model solvation in acetonitrile. Molecular visualizations were created with VMD 1.9.3.<sup>[276]</sup>

# A.2.2 Calculated Thermodynamics of Preassemblies between [1-Co]<sup>2+</sup> and Various Amines

Гa	able A	<b>A.4</b> :	Energie	s and	enthalpie	s for	the f	ormatio	n of j	preass	emblies	between	[1-0	$[20]^{2+}$	and
	$\operatorname{amine}$	es, re	lative to	the o	energies of	the	isolat	ed mole	cules	$(r^2SC)$	AN-3c)	. Distanc	es re	efer to	the
	N-H	dista	ance for	assem	blies betw	een [	1-Co]	$^{2+}$ and	amin	les (see	figure	A.21).			

Substr.	ID	$\Delta E \; [ m kcal  mol^{-1}]$	$\Delta H \; [ ext{kcal mol}^{-1}]$	Dist. [Å]
DMEA	g	-5.75	-4.38	2.43
DIPA	h	-6.57	-5.28	2.63
DIPEA	i	-5.84	-4.22	2.49
DMA	j	-6.57	-5.21	2.91
pyrrolidine	k	-5.47	-4.25	2.33

# A.2.3 Conformer Sampling

Iterative metadynamics (iMTD) calculations were performed at the GFN2-xTB<sup>[147]</sup> level with the *CREST 2.11.2* software package<sup>[76,77]</sup> at a simulated temperature of 298.15 K. Solvation effects were taken into account with the analytical linearized Poisson-Boltzmann (ALPB) model, using parameters for acetonitrile. The non-covalent interaction (NCI)-iMTD algorithm<sup>[77]</sup> was used to prevent dissociation of the preassemblies, which would have resulted in an infinite number of conformers. No other constraints were applied to the geometries during conformer sampling.

A larger fraction of the sampled preassemblies already shown in figure 3 of the main article is provided below in figure A.12. The results of additional control calculations, where both NEt<sub>3</sub> and  $2a_{Br}$  coordinate to the catalyst at the same time, are visualized in figure A.13.



Figure A.12: Sampled conformations of preassemblies between (a)  $[1-Co]^{2+}$  and triethylamine (3423 structures) and (b)  $[1-Co]^+$  and 4-bromobenzonitrile  $2a_{Br}$  (7554 structures) within an energy window of 4 kcal mol<sup>-1</sup> of the respective lowest energy conformer. Sampling was performed at the GFN2-xtb level of theory. Colored spheres indicate the respective substrate, in particular the coordinating N atom in the case of NEt<sub>3</sub> and the center of the aryl unit in the case of  $2a_{Br}$ .



Figure A.13: Sampled conformations of preassemblies between (a)  $[1-Co]^{2+}$ , NEt<sub>3</sub> and 4bromobenzonitrile  $2a_{Br}$  (855 structures) and (b)  $[1-Co]^+$ , NEt<sub>3</sub> and 4-bromobenzonitrile  $2a_{Br}$ (998 structures) within an energy window of 2.5 kcal mol<sup>-1</sup> of the respective lowest energy conformer. Sampling was performed at the GFN2-xtb level of theory. Colored spheres indicate the respective substrate, in particular the coordinating N atom in the case of triethylamine and the center of the aryl unit in the case of  $2a_{Br}$ .

# A.2.4 DFT Orbitals and Spin Densities

The canonical Kohn-Sham orbitals and spin densities for the electronic ground states of  $[1-Fe]^{2+}$  and  $[1-Fe]^{+}$  at the r<sup>2</sup>SCAN-3c level are depicted in figure A.14.



Figure A.14: Canonical Kohn-Sham orbitals and spin densities from unrestricted DFT calculations (r<sup>2</sup>SCAN-3c) on the ground states of  $[1-Fe]^{2+}$  and  $[1-Fe]^+$  (Isovalue: 0.04 for orbitals, 0.002 for densities). The spin densities show the difference between  $\alpha$ - and  $\beta$ -densities, where yellow denotes unpaired  $\alpha$ -spins and blue unpaired  $\beta$ -spins. For completeness, the restricted open-shell spin densities are also shown, along with the energy difference between the unrestricted and the restricted open-shell SCF solution. The expectation value  $\langle S^2 \rangle$  gives a quantitative estimate of the amount of spin contamination.

The unrestricted corresponding orbitals<sup>[330]</sup> and spin densities for the electronic ground states of  $[1-Co]^{2+}$  and  $[1-Co]^{+}$  at the r<sup>2</sup>SCAN-3c level are depicted in figure A.15. As discussed in the main text,  $[1-Co]^{+}$  exhibits a small amount of spin contamination, i.e. unpaired  $\beta$ -spin density on the ligands.



Figure A.15: Unrestricted orbitals and spin densities from DFT calculations (r<sup>2</sup>SCAN-3c) on the ground states of  $[1-Co]^{2+}$  and  $[1-Co]^+$  (Isovalue: 0.04 for orbitals, 0.002 for densities). Virtual orbitals are canonical DFT orbitals.  $\sigma$  denotes the spatial overlap between  $\alpha$ - and  $\beta$ -orbitals. The spin densities show the difference between  $\alpha$ - and  $\beta$ -densities, where yellow denotes unpaired  $\alpha$ -spins and blue unpaired  $\beta$ -spins. For completeness, the restricted open-shell spin densities are also shown, along with the energy difference between the unrestricted and the restricted open-shell SCF solution. The expectation value  $\langle S^2 \rangle$  gives a quantitative estimate of the amount of spin contamination.

# A.2.5 Multireference Calculations on the Ground States of [1-Co]<sup>2+</sup> and [1-Co]<sup>+</sup>

The ground state electronic structure of  $[1-Co]^{2+}$  and  $[1-Co]^+$  was further characterized by CASSCF calculations using *Molpro 2023.2*.<sup>[311,312,331]</sup> The active space contained 12 electrons in 9 orbitals (Figure S49), namely the five d-orbitals and two pairs of  $\pi/\pi^*$ orbitals, one pair on each ligand. State-averaging was performed over seven electronic states of the same multiplicity to stabilize the active space. The def2-TZVP<sup>[247]</sup> basis set was used throughout. Integral evaluation was accelerated by density fitting with the def2-TZVP-JKFIT<sup>[305]</sup> auxiliary basis.



Figure A.16: Active space used in CASSCF and NEVPT2 calculations, exemplary visualized for [1-Co]<sup>+</sup> (Isovalue: 0.04).

Due to the non-negligible amount of spin delocalization, the possibility of a quintet ground state for  $[1-Co]^+$  was also investigated. To this end, the geometry of the quintet was optimized at the BP86<sup>[302,332,333]</sup>/def2-TZVP<sup>[247]</sup> level of theory, using the D3BJ<sup>[334,335]</sup> and gCP<sup>[323]</sup> corrections and modeling implicit solvation in acetonitrile via the C-PCM. Initial optimization attempts at the r<sup>2</sup>SCAN-3c level were not successful due to SCF convergence issues. The energies of both the triplet and the quintet ground states were evaluated with the partially contracted NEVPT2 method<sup>[336–338]</sup> at the respective optimized structures, using the same CASSCF(12,9) protocol as described above for the reference calculations. At both the triplet and the quintet geometry, the triplet is significantly more stable than the quintet (table A.5). The adiabatic energy difference, i.e. the difference at the respective minimum energy structures, is 0.41 eV, suggesting that the ground state of  $[1-Co]^+$  is indeed a triplet rather than a quintet.

# A.2.6 Thermodynamics of a Competing Radical Chain Mechanism

Scheme A.1 illustrates the beginning of a radical chain starting from the amine radical cation obtained in the photoreduction of the  $[1-Co]^{2+}$  complex to  $[1-Co]^{+}$ . First, the

geometry.					
Species	Geometry	Mult.	$E_{\mathrm{CASSCF}}$ [E <sub>h</sub> ]	$E_{\mathrm{PT2}} \; [\mathrm{E_h}]$	$\Delta E_{ m PT2} \; [{ m eV}]$
<b>[1-Co]</b> <sup>2+</sup>	$Doublet-Min.^{a}$	2	-3776.700076	-3786.310081	/
[1-Co]+	Triplet-Min. <sup>a</sup>	$\frac{3}{5}$	$-3776.933910 \\ -3776.925877$	$-3786.615121\\-3786.592655$	/ 0.61
	Quintet-Min. <sup>b</sup>	$\frac{3}{5}$	-3776.898585 -3776.892719	$-3786.615104\\-3786.600010$	/ 0.41

**Table A.5:** Calculated energies of  $[1-Co]^{2+}$  and  $[1-Co]^{+}$  at the CASSCF(12,9) and NEVPT2 level. Energy differences for  $[1-Co]^{+}$  are given with respect to the triplet calculation at the respective geometry.

 $^{\rm a}$  optimized at r²SCAN-3c level;  $^{\rm b}$  optimized at BP86-D3BJ-gCP/def2-TZVP level

radical cation  $NR_3 \cdot {}^+$  is deprotonated by a second amine molecule, yielding an  $\alpha$ -aminoalkyl radical  $NR_3 \cdot .$  In a second step, this radical can abstract a halogen atom (halogen atom transfer XAT) from the substrate (4-bromobenzonitrile,  $2a_{Br}$ ) to form an iminium bromide and an aryl radical which in turn initiates the chain reaction as shown in scheme A.2.



Scheme A.1: Calculated Gibbs free energies for the start of a possible competing radical chain mechanism, starting from a one-electron reduced amine radical cation (level of theory: r<sup>2</sup>SCAN-3c + DLPNO-CCSD(T1)/ma-ZORA-def2-QZVPP). Experimental yields refer to the yield of 4a as reported in table A.4.

The reactants and products of both reaction steps were optimized at the r<sup>2</sup>SCAN-3c level of theory. Electronic single-point energies were subsequently calculated at the DLPNO-CCSD(T1) level, as described in appendix A.2.1. The resulting electronic energies were added to the enthalpy and entropy corrections from harmonic frequency analyses at the r<sup>2</sup>SCAN-3c level to obtain the Gibbs free energies shown in scheme A.1. The product yields obtained with different amines generally follow the Gibbs free energies  $\Delta G_{\rm red}$  of the second reaction step, i.e. the reduction of the aryl bromide. Only DIPEA appears as an outlier. DIPEA can form two different  $\alpha$ -aminoalkyl radicals, either at the <sup>i</sup>Pr-carbon or at the ethyl carbon. In agreement with previous DFT studies,<sup>[339]</sup> the ethyl radical is more stable than the <sup>i</sup>Pr radical, resulting in a less exergonic  $\Delta G_{\rm red}$ . Nevertheless, the reduction of **2a**<sub>Br</sub> by both the ethyl and the <sup>i</sup>Pr DIPEA radicals is exergonic with a significantly negative  $\Delta G_{\rm red}$ , which seemingly contradicts the low experimental product yield (34%). The Gibbs energy of the preceding deprotonation step  $\Delta G_{\rm deprot}$  may explain this discrepancy, as the formation of both possible  $\alpha$ -aminoalkyl radicals from the DIPEA radical cation is not as favorable as for amines with higher product yields.



Scheme A.2: Possible radical chain mechanism initiated by  $\alpha$ -aminoalkyl radicals.<sup>[149,150]</sup>

## A.2.7 Calculated Electronic Absorption Spectra

Absorption spectra were calculated at the TD-DFT level in the Tamm-Dancoff approximation,<sup>[340]</sup> using the range-separated double hybrid functional SCS- $\omega$ PBEPP86.<sup>[148]</sup> The reduced triple- $\zeta$  basis set def2-TZVP(-f)<sup>[247]</sup> was employed on all atoms as the largest computationally feasible basis. To speed up the calculation of Coulomb and exchange integrals, the RIJCOX approximation<sup>[250,251,304]</sup> was used with the def2-TZVP/C<sup>[253]</sup> and def2/J<sup>[252]</sup> auxiliary basis sets. Solvation effects were included by the C-PCM,<sup>[249]</sup> using parameters for acetonitrile. 100 roots were included in the calculations. Additional TD-DFT spectra for different preassemblies were calculated at the r<sup>2</sup>SCAN-3c level of theory,<sup>[321]</sup> including 250 roots. Absorption lines were convoluted with Gaussian functions ( $\sigma = 0.1 \text{ eV}$ ) and summed to compare the spectral shape with experimental data. Excited state characters were evaluated based on the one-electron transition density with *TheoDore 2.4.0*.<sup>[341]</sup>

Additional to the spectra of the preassemblies shown in figure 7 of the main text, the spectra of the isolated complexes are depicted below in figure A.17. Moreover, a comparison of the calculated spectra of all optimized preassemblies is provided in figure A.18, illustrating that there is no significant difference between the various possible preassembly conformations.



**Figure A.17:** Comparison of the calculated absorption spectra (SCS- $\omega$ PBEPP86/def2-TZVP(-f)) for the isolated complexes (a) **[1-Co]**<sup>2+</sup> and (b) **[1-Co]**<sup>+</sup>, to the respective experimental spectrum. The calculated spectrum of **[1-Co]**<sup>2+</sup> was red-shifted by 0.65 eV.

To assign excited state characters, we analyzed the one-electron transition density with the program package *TheoDore*.<sup>[341]</sup> The theoretical background of this analysis is detailed in refs. 342, 343 and only a brief overview shall be given here.

The one-electron transition density matrix (1TDM)  $D^{0I}$  between the ground state  $\Psi_0$ and an excited state  $\Psi_I$  is defined as

$$D_{rs}^{0I} = \langle \Psi_0 | \hat{E}_{rs} | \Psi_I \rangle \tag{A.6}$$

where  $\hat{E}_{rs}$  denotes the transition operator from orbital r to orbital s. In an atomic orbital basis, the 1TDM can be structured into blocks by assigning orbitals to molecular fragments A-N. This allows analyzing the 1TDM in terms of charge transfer numbers  $\Omega^{I}_{AB}$ 



Figure A.18: Comparison of the calculated absorption spectra (r<sup>2</sup>SCAN-3c) for different conformations of preassemblies between (a)  $[1-Co]^{2+}$  and NEt<sub>3</sub> (see figure A.21) and (b)  $[1-Co]^{+}$  and 4-bromobenzonitrile  $2a_{Br}$  (see figure A.22), compared to the respective experimental spectrum of the isolated complexes.

between two fragments A and B by summing over squared elements of the 1TDM after basis orthogonalization using the overlap matrix S:

$$\Omega_{AB}^{I} = \frac{1}{2} \sum_{\mu \in A} \sum_{\nu \in B} \left( S^{\frac{1}{2}} D^{0I} S^{\frac{1}{2}} \right)_{\mu\nu}^{2}.$$
(A.7)

In this notation,  $\mu$  and  $\nu$  denote atomic orbitals located on molecular fragments A and B, respectively. The resulting matrix element  $\Omega_{AB}^{I}$  contains information about the fraction of electron density that is transferred from molecular fragment A to fragment B. For a one-electron transition, the sum over all elements of  $\Omega^{I}$  is 1:

$$\sum_{A} \sum_{B} \Omega^{I}_{AB} = 1.$$
 (A.8)

Summing only over the row or column indices of  $\Omega^{I}$  yields electron and hole populations  $p_{e}$  and  $p_{h}$  of excited state I in terms of the predefined molecular fragments:

$$p_e = \sum_A \Omega^I_{AB} \tag{A.9}$$

$$p_h = \sum_B \Omega^I_{AB} \tag{A.10}$$

These descriptors allow the characterization of a large amount of excited states, bypassing the need for visual inspection of molecular orbital transitions or CI coefficients. The significance of the resulting populations hinges on the definition of meaningful molecular fragments. In the present work, the complex was divided into seven fragments and an eighth fragment was added for the respective substrate.

The electron and hole populations for the first 100 excited states of  $[1-Co]^{2+}$  and  $[1-Co]^{+}$  are depicted in figure A.19. Those for the preassemblies of  $[1-Co]^{2+}$  with triethylamine
and of  $[1-Co]^+$  with 4-bromobenzonitrile  $2a_{Br}$  are shown in figure A.20. The excited state energy increases along the x-axis from left to right. The y-axis shows the electron and hole populations for each excited state in terms of the color-coded molecular fragments. An excited state can be characterized as a CT state if the hole and electron are located on different fragments.



Figure A.19: Electron-hole correlation plots of (a)  $[1-Co]^{2+}$  and (b)  $[1-Co]^{+}$  (SCS- $\omega$ PBEPP86/def2-TZVP(-f)).



Figure A.20: Electron-hole correlation plots of the preassemblies of (a)  $[1-Co]^{2+}$  and NEt<sub>3</sub> and (b)  $[1-Co]^{+}$  and  $2a_{Br}$  (SCS- $\omega$ PBEPP86/def2-TZVP(-f)). The CT states relevant for the catalytic mechanism are highlighted with arrows.

#### A.2.8 Optimized Geometries

All optimized geometries are openly available at https://doi.org/10.5281/zenodo.10528904. A comparison between calculated and experimental structures of  $[1-Co]^{2+}$  and  $[1-Co]^{+}$  via selected bond lengths and angles is shown in table A.6 and table A.7. Overall, the calculated geometries agree within the second decimal place with the experimental reference. Optimized structures of ground state preassemblies are shown in figure A.21 and figure A.22.

**Table A.6:** Selected bond parameters of  $[1-Co]^{2+}$  and  $[1-Co]^+$  in Å as optimized in this work, compared to the respective crystal structures.<sup>[344]</sup> The crystal structures of  $[1-Co]^{2+}$  and  $[1-Co]^+$  differ in their atom numbering in that  $[1-Co]^+$  is inverted on one of the horizontal pseudo-mirror planes. Thus, the atom numbers in parentheses refer to the corresponding atom in the crystal structure of  $[1-Co]^+$ . Calculated structures share the same order of atoms.

				$[1-Co]^2$	2+		[1-Co]	+
Туре	Bond (ref.)	Bond (calc.)	ref.	calc.	dev.	ref.	calc.	dev.
Co-N <sub>py</sub>	N2–Co	N10–Co	1.852	1.836	-0.016	1.986	1.989	0.003
10	N5–Co	N7–Co	$1.911^{\rm a}$	1.906	-0.005	1.994	1.989	-0.004
Co-N <sub>im</sub>	N1–Co	N11–Co	2.009	2.001	-0.008	2.153	2.158	0.005
	N3–Co	N9–Co	2.021	2.000	-0.021	2.158	2.154	-0.004
	N6(4)–Co	N8–Co	2.165	2.173	0.008	2.136	2.155	0.019
	N4(6)-Co	N6–Co	2.145	2.187	0.042	2.134	2.163	0.029
$\overline{\mathrm{C}_{\mathrm{im}}-\mathrm{N}_{\mathrm{im}}}$	N1–C8	N11-C85	1.298	1.305	0.007	1.294	1.300	0.006
	N3-C15	N9–C72	1.305	1.305	0.000	1.300	1.301	0.001
	N6(4)-C45(38)	N8-C39	1.289	1.294	0.005	1.307	1.302	-0.005
	N4(6)-C38(45)	N6-C26	1.289	1.293	0.004	1.310	1.300	-0.010
C <sub>py</sub> –C <sub>im</sub>	C8-C10	C84–C85	1.472	1.464	-0.008	1.477	1.468	-0.009
	C14–C15	C72–C77	1.476	1.464	-0.012	1.456	1.468	0.012
	C44(38) - C45(40)	C38–C39	1.487	1.477	-0.010	1.455	1.467	0.012
	C38(44) - C40(45)	C26-C31	1.485	1.478	-0.007	1.470	1.468	-0.002
N <sub>py</sub> -C <sub>py</sub>	N2-C10	N10-C77	1.347	1.349	0.002	1.353	1.352	-0.001
	N2-C14	N10-C84	1.350	1.349	-0.001	1.363	1.351	-0.012
	N5-C44(40)	N7-C38	1.350	1.349	-0.001	1.348	1.351	0.003
	N5-C40(44)	N7-C31	1.347	1.348	0.001	1.364	1.352	-0.012
$\overline{\mathrm{C}_{\mathrm{py}}-\mathrm{C}_{\mathrm{py}}}$	C10-C11	C82–C84	1.387	1.393	0.006	1.384	1.395	0.011
	C11–C12	C80 - C82	1.389	1.392	0.003	1.377	1.393	0.016
	C12–C13	C78–C80	1.385	1.392	0.007	1.396	1.392	-0.004
	C13–C14	C77–C78	1.393	1.392	-0.001	1.391	1.396	0.005
	C44(40)-C43(41)	C38 - C36	1.393	1.394	0.001	1.399	1.396	-0.003
	C43(41)-C42	C36-C34	1.387	1.389	0.002	1.377	1.392	0.015
	C42 - C41(43)	C34-C32	1.389	1.389	0.000	1.379	1.392	0.013
	C41(43)-C40(44)	C32 - C31	1.381	1.394	0.013	1.385	1.395	0.010

<sup>a</sup> 1.991 Å in ref. [344] but 1.911 Å in the crystal structure

Table A.7: Selected angle parameters of  $[1-Co]^{2+}$  and  $[1-Co]^+$  in ° as optimized in this work, compared to the respective crystal structures.<sup>[344]</sup> The crystal structures of  $[1-Co]^{2+}$  and  $[1-Co]^+$  differ in their atom numbering in that  $[1-Co]^+$  is inverted on one of the horizontal pseudo-mirror planes. Thus, the atom numbers in parentheses refer to the corresponding atom in the crystal structure of  $[1-Co]^+$ . Some angles are not affected by this, because the ligands are tilted in opposite directions in the two crystal structures. Calculated structures share the same order of atoms.

				[1-Co] <sup>2</sup>	2+		[1-Co]	+
Туре	Angle (ref.)	Angle (calc.)	ref.	calc.	dev.	ref.	calc.	dev.
N-Co-N	N1–Co–N2	N11-Co-N10	80.17	80.73	0.56	74.9	75.9	1.01
	N1–Co–N3	N11–Co–N9	160.56	161.52	0.96	151.0	151.8	0.81
	N1-Co-N6(4)	N11–Co–N8	97.79	97.11	-0.68	98.2	99.8	1.56
	N1–Co–N5	N11-Co-N7	98.52	100.00	1.48	97.7	100.6	2.86
	N1-Co-N4(6)	N11–Co–N6	87.60	86.04	-1.56	87.3	87.1	-0.19
	N2–Co–N3	N10-Co-N9	80.42	80.79	0.37	76.2	76.0	-0.25
	$N2-Co-N4^{a}$	N10–Co–N8	100.97	100.64	-0.33	110.7	107.5	-3.23
	N2–Co–N5	N10-Co-N7	178.48	178.65	0.17	170.7	175.3	4.62
	$N2-Co-N6^{a}$	N10-Co-N6	103.46	103.29	-0.17	98.4	100.7	2.32
	N3-Co-N6(4)	N9–Co–N8	85.73	86.66	0.93	89.8	87.2	-2.58
	N3–Co–N5	N9–Co–N7	100.91	98.49	-2.43	111.3	107.6	-3.67
	N3-Co-N4(6)	N9–Co–N6	97.11	97.85	0.74	99.2	99.6	0.39
	$N4-Co-N5^{a}$	N8–Co–N7	78.16	78.16	0.00	75.4	76.0	0.59
	N4–Co–N6	N8–Co–N6	155.54	156.07	0.53	150.8	151.8	1.01
	$N5-Co-N6^{a}$	N7–Co–N6	77.45	77.93	0.48	75.4	75.9	0.48

<sup>a</sup> angle not affected by the pseudo-mirror inversion



Figure A.21: Optimized structures of ground state preassemblies between  $[1-Co]^{2+}$  and different amines with relevant hydrogen bond lengths in Angstrom.



Figure A.22: Optimized structures of ground state preassemblies between  $[1-Co]^+$  and 4-bromobenzonitrile  $2a_{Br}$  with relevant distances to the center of the  $2a_{Br}$  aryl unit in Angstrom. Hydrogen atoms were omitted for clarity.

#### A.2.9 Calculated Absolute Energies

Energies and thermodynamic properties obtained at the  $r^2$ SCAN-3c level of theory are provided in table A.8. Absolute energies obtained from coupled-cluster calculations are listed in table A.9.

**Table A.8:** Absolute energies, enthalpies and Gibbs free energies of optimized structures (r<sup>2</sup>SCAN-3c level of theory). The expectation value  $\langle S^2 \rangle$  gives an estimate for the amount of spin contamination in the open-shell species.

Species	Chrg. /	$E^{ m SCF} \left[ { m E_h}  ight]$	$H [\mathrm{E_h}]$	$G \left[ \mathrm{E_{h}} \right]$	$\left< S^2 \right>$	$\langle S^2  angle,$
	Mult.					$\mathbf{ideal}$
[1-Co] <sup>2+</sup>	$+2 \ / \ 2$	-3792.120655	-3791.236934	-3791.369719	0.7746	0.75
[1-Co] <sup>+</sup>	$+1 \ / \ 3$	-3792.257800	-3791.377057	-3791.511521	2.3765	2.00
[1-Fe] <sup>2+</sup>	$+2 \ / \ 1$	-3673.079674	-3672.195038	-3672.325517	0.0000	0.00
<b>[1-Fe]</b> <sup>+</sup>	$+1 \ / \ 2$	-3673.202685	-3672.322924	-3672.455060	0.7554	0.75
NEt <sub>3</sub>	0 / 1	-292.313707	-292.099476	-292.142924	0.0000	0.00
- $\alpha$ -radical	0 / 2	-291.668536	-291.467510	-291.511662	0.7538	0.75
- cation	$+1 \ / \ 2$	-292.132993	-291.918243	-291.962771	0.7546	0.75
DMEA	0 / 1	-213.710156	-213.555112	-213.592152	0.0000	0.00
- $\alpha$ -radical	0 / 2	-213.064418	-212.922581	-212.960776	0.7538	0.75
- cation	$+1 \ / \ 2$	-213.526505	-213.371437	-213.411219	0.7547	0.75
DIPA	0 / 1	-292.328790	-292.114743	-292.157768	0.0000	0.00
- $\alpha$ -radical	0 / 2	-291.683311	-291.482413	-291.526777	0.7539	0.75
- cation	$+1 \ / \ 2$	-292.137142	-291.923070	-291.968887	0.7543	0.75
DIPEA	0 / 1	-370.916218	-370.644057	-370.692897	0.0000	0.00
- $\alpha$ -radical (iPr)	0 / 2	-370.271359	-370.012708	-370.063110	0.7544	0.75
- $\alpha$ -radical (ethyl)	0 / 2	-370.273023	-370.013989	-370.064077	0.7538	0.75
- cation	$+1 \ / \ 2$	-370.741860	-370.468540	-370.518519	0.7545	0.75
DMA	0 / 1	-366.117034	-365.935319	-365.977864	0.0000	0.00
- $\alpha$ -radical	0 / 2	-365.471826	-365.303560	-365.346401	0.7566	0.75
- cation	$+1 \ / \ 2$	-365.933858	-365.751636	-365.796198	0.7738	0.75
Pyrrolidine	0 / 1	-212.522389	-212.387528	-212.421520	0.0000	0.00
- $\alpha$ -radical	0 / 2	-211.873848	-211.753485	-211.788122	0.7544	0.75
- cation	$+1 \ / \ 2$	-212.329626	-212.196734	-212.230967	0.7547	0.75
4-bromobenzonitrile	0 / 1	-2897.961267	-2897.864456	-2897.906374	0.0000	0.00
- radical	0 / 2	-323.738311	-323.645848	-323.683862	0.7582	0.75
$Br-NEt_3$	0 / 1	-2865.902152	-2865.694806	-2865.744934	0.0000	0.00
Br-DMEA	0 / 1	-2787.294815	-2787.146808	-2787.191851	0.0000	0.00
Br-DIPA	0 / 1	-2865.917700	-2865.710807	-2865.761299	0.0000	0.00
Br-DIPEA (iPr)	0 / 1	-2944.512268	-2944.246505	-2944.301846	0.0000	0.00
Br-DIPEA (ethyl)	0 / 1	-2944.506529	-2944.240990	-2944.296696	0.0000	0.00
Br-DMA	0 / 1	-2939.681138	-2939.506821	-2939.554417	0.0000	0.00

Continued on next page

Species	Chrg. /	$E^{ m SCF} \left[ { m E_h}  ight]$	$H [E_h]$	$G \left[ \mathrm{E_{h}}  ight]$	$\left< S^2 \right>$	$\langle S^2  angle,$
	Mult.					ideal
Br-Pyrrolidine	0 / 1	-2786.104134	-2785.977357	-2786.017907	0.0000	0.00
H-NEt <sub>3</sub> <sup>+</sup>	+1 / 1	-292.783253	-292.552763	-292.596301	0.0000	0.00
H-DMEA <sup>+</sup>	$+1 \ / \ 1$	-214.177603	-214.006084	-214.043361	0.0000	0.00
H-DIPA <sup>+</sup>	$+1 \ / \ 1$	-292.797620	-292.567885	-292.611211	0.0000	0.00
H-DIPEA <sup>+</sup>	$+1 \ / \ 1$	-371.387039	-371.098425	-371.147032	0.0000	0.00
H-DMA <sup>+</sup>	$+1 \ / \ 1$	-366.567163	-366.369979	-366.412088	0.0000	0.00
$\operatorname{H-Pyrrolidine}^+$	$+1 \ / \ 1$	-212.989671	-212.839369	-212.873357	0.0000	0.00
<b>[1-Co]</b> <sup>2+</sup> · NEt <sub>3</sub> (a)	$+2 \ / \ 2$	-4084.445020	-4083.345081	-4083.499910	0.7751	0.75
$[1-Co]^{2+} \cdot NEt_3$ (b)	$+2 \ / \ 2$	-4084.441804	-4083.342021	-4083.498022	0.7743	0.75
$[1-Co]^{2+} \cdot NEt_3 (c)$	$+2 \ / \ 2$	-4084.444632	-4083.344593	-4083.499410	0.7749	0.75
$[1-Co]^{2+} \cdot NEt_3 (d)$	$+2 \ / \ 2$	-4084.445504	-4083.345310	-4083.499727	0.7745	0.75
$[1-Co]^{2+} \cdot NEt_3$ (e)	$+2 \ / \ 2$	-4084.444891	-4083.344551	-4083.498778	0.7746	0.75
$[1-Co]2+ \cdot \text{NEt}_3 (f)$	$+2 \ / \ 2$	-4084.441622	-4083.341746	-4083.498186	0.7746	0.75
<b>[1-Co]</b> <sup>2+</sup> · DMEA (g)	$+2 \ / \ 2$	-4005.839979	-4004.799023	-4004.948254	0.7748	0.75
<b>[1-Co]</b> <sup>2+</sup> · DIPA (h)	$+2 \ / \ 2$	-4084.459908	-4083.360097	-4083.514840	0.7748	0.75
<b>[1-Co]</b> <sup>2+</sup> · DIPEA (i)	$+2 \ / \ 2$	-4163.046173	-4161.887722	-4162.046294	0.7750	0.75
<b>[1-Co]</b> <sup>2+</sup> · DMA (j)	$+2 \ / \ 2$	-4158.248157	-4157.180560	-4157.334846	0.7748	0.75
$[1-Co]^{2+}$ · Pyrrolidine (k	) $+2 \ / \ 2$	-4004.651759	-4003.631233	-4003.778603	0.7746	0.75
<b>[1-Co]</b> <sup>+</sup> · <b>2a</b> <sub>Br</sub> (l)	$+1 \ / \ 3$	-6690.231725	-6689.252087	-6689.406866	2.3774	2.00
<b>[1-Co]</b> <sup>+</sup> · <b>2a</b> <sub>Br</sub> (m)	$+1 \ / \ 3$	-6690.231114	-6689.251673	-6689.405836	2.3788	2.00
<b>[1-Co]</b> <sup>+</sup> · <b>2a</b> <sub>Br</sub> (n)	$+1 \ / \ 3$	-6690.232397	-6689.253299	-6689.408968	2.3727	2.00
<b>[1-Co]</b> <sup>+</sup> · <b>2a</b> <sub>Br</sub> (o)	$+1 \ / \ 3$	-6690.232770	-6689.253086	-6689.406857	2.3761	2.00
<b>[1-Co]</b> <sup>+</sup> · <b>2a</b> <sub>Br</sub> (p)	$+1 \ / \ 3$	-6690.232142	-6689.252767	-6689.407616	2.3775	2.00
<b>[1-Co]</b> <sup>+</sup> · <b>2a</b> <sub>Br</sub> (q)	$+1 \ / \ 3$	-6690.230057	-6689.250757	-6689.405786	2.3627	2.00

Table A.8: continued.

**Table A.9:** Absolute HF and DLPNO-CCSD(T1) energies with the ma-ZORA-def2-QZVPP basis set. The expectation value  $\langle S2 \rangle$  (linearized) gives an estimate for the amount of spin contamination in the open-shell species. The T1 diagnostic allows to judge the quality of the single-reference ansatz. A value  $\langle 0.02 \rangle$  is typically considered reliable.<sup>[345]</sup>

Species	Chrg. $/$	$E_{ m HF}~[ m E_{h}]$	$E_{\mathrm{CCSD(T1)}} [\mathrm{E_h}]$	$\mathbf{T1}$	$\left< S^2 \right>$	$\left< S^2 \right>$ ,
	Mult.					ideal
$NEt_3$	0 / 1	-290.699586	-292.177180	0.0091	0.0000	0.00
- α-radical	0 / 2	-290.079817	-291.520813	0.0140	0.7502	0.75
- cation	$+1 \ / \ 2$	-290.560049	-291.982341	0.0140	0.7503	0.75
DMEA	0 / 1	-212.549151	-213.621096	0.0090	0.0000	0.00
- α-radical	0 / 2	-211.929792	-212.965134	0.0156	0.7502	0.75
- cation	$+1 \ / \ 2$	-212.406396	-213.423992	0.0149	0.7503	0.75
DIPA	0 / 1	-290.711861	-292.190151	0.0089	0.0000	0.00

Continued on next page

	Table 11.9. continued.					
Species	Chrg. /	$E_{ m HF} \; [ m E_{ m h}]$	$E_{\rm CCSD(T1)}$ [E <sub>h</sub> ]	$\mathbf{T1}$	$\langle S^{2}  angle$	$\langle S^2  angle,$
	Mult.				. ,	ideal
- α-radical	0 / 2	-290.093232	-291.533566	0.0134	0.7502	0.75
- cation	$+1 \ / \ 2$	-290.561260	-291.984365	0.0144	0.7503	0.75
DIPEA	0 / 1	-368.845690	-370.731914	0.0091	0.0000	0.00
- $\alpha$ -radical (iPr)	0 / 2	-368.225883	-370.074481	0.0131	0.7502	0.75
- $\alpha$ -radical (ethyl)	0 / 2	-368.227719	-370.077532	0.0131	0.7502	0.75
- cation	$+1 \ / \ 2$	-368.712168	-370.543537	0.0133	0.7503	0.75
DMA	0 / 1	-364.188298	-365.906021	0.0109	0.0000	0.00
- α-radical	0 / 2	-363.570650	-365.250661	0.0132	0.7507	0.75
- cation	$+1 \ / \ 2$	-364.054623	-365.714135	0.0176	0.7545	0.75
Pyrrolidine	0 / 1	-211.392080	-212.426030	0.0090	0.0000	0.00
- α-radical	0 / 2	-210.770214	-211.766384	0.0149	0.7502	0.75
- cation	$+1 \ / \ 2$	-211.239353	-212.219221	0.0158	0.7503	0.75
4-bromobenzonitrile	0 / 1	-2944.966694	-2946.969988	0.0107	0.0000	0.00
- radical	0 / 2	-322.160797	-323.536415	0.0141	0.7512	0.75
$\operatorname{Br-NEt}_3$	0 / 1	-2912.929906	-2914.963768	0.0102	0.0000	0.00
Br-DMEA	0 / 1	-2834.774149	-2836.404233	0.0106	0.0000	0.00
Br-DIPA	0 / 1	-2912.944789	-2914.976139	0.0997	0.0000	0.00
Br-DIPEA (iPr)	0 / 1	-2991.082583	-2993.525940	0.0100	0.0000	0.00
Br-DIPEA (ethyl)	0 / 1	-2991.078061	-2993.520857	0.0099	0.0000	0.00
Br-DMA	0 / 1	-2986.380983	-2988.667727	0.0114	0.0000	0.00
Br-Pyrrolidine	0 / 1	-2833.616626	-2835.206202	0.0105	0.0000	0.00
$H$ -TEA $^+$	$+1 \ / \ 1$	-291.178441	-292.647526	0.0084	0.0000	0.00
$\operatorname{H-DMEA^{+}}$	+1 / 1	-213.026422	-214.090319	0.0082	0.0000	0.00
$\operatorname{H-DIPA^{+}}$	+1 / 1	-291.189609	-292.659015	0.0083	0.0000	0.00
$\operatorname{H-DIPEA^{+}}$	$+1 \ / \ 1$	-369.324172	-371.203324	0.0086	0.0000	0.00
$H-DMA^+$	$+1 \ / \ 1$	-364.651813	-366.360847	0.0093	0.0000	0.00
$\operatorname{H-Pyrrolidine}^+$	$+1 \ / \ 1$	-211.869448	-212.894008	0.0083	0.0000	0.00

Table A.9: continued.

# APPENDIX B

### Supporting Information to Chapter 2

In the following, the supporting information to the article "RNA Environment Is Responsible for Decreased Photostability of Uracil", published 2018 in *Journal of the Americal Chemical Society*, is reprinted in full. The supporting information as well as animations of the quantum dynamical propagations discussed in the article are available at https://doi.org/10.1021/ jacs.8b02962.

#### Optimized structures and coordinate vectors

This section lists the optimized molecular geometries of the Franck-Condon (FC) point, the S<sub>2</sub> minimum and the S<sub>2</sub>/S<sub>1</sub> CoIn of uracil adopted from previous works.<sup>[203,346]</sup> The software package *COLUMBUS*<sup>[347–349]</sup> had been used to optimize the structures on the MRCI(12,9)/cc-pVDZ level of theory. A two-dimensional coordinate space used in the quantum dynamical simulations of this work can be constructed from the normalized vector  $q_{\rm FC\to CoIn}$ , pointing from the FC point to the CoIn and the orthonormalized vector  $q_{\rm FC\to S_2-min}$  pointing from the FC point to the S<sub>2</sub>-minimum.<sup>[183]</sup>

$\mathbf{Gr}$	Ground state minimum structure				minimum s	tructure	
Ν	-0.949104	-0.054982	0.000 000	Ν	-0.926348	-0.085981	0.035097
Ν	0.983694	1.198645	0.000000	Ν	0.972975	1.190911	0.041305
$\mathbf{C}$	-0.389225	1.200077	0.000000	$\mathbf{C}$	-0.389514	1.190311	0.000145
$\mathbf{C}$	1.734922	0.051763	0.000000	$\mathbf{C}$	1.817058	0.113236	-0.029692
$\mathbf{C}$	1.165253	-1.172332	0.000000	$\mathbf{C}$	1.155229	-1.212691	-0.065028
$\mathbf{C}$	-0.292517	-1.286427	0.000000	$\mathbf{C}$	-0.200258	-1.252228	0.007623
Ο	-0.909614	-2.314371	0.000000	0	-1.011447	-2.288678	0.013046
Ο	-1.038471	2.209750	0.000000	Ο	-1.066201	2.186465	-0.044068
Η	-1.950663	-0.078792	0.000000	Η	-1.924115	-0.166824	0.089539
Η	1.416417	2.097983	0.000000	Η	1.364363	2.112580	0.096968
Η	2.804600	0.196935	0.000000	Η	2.787327	0.270215	0.428083
Η	1.752062	-2.075605	0.000000	Η	1.730164	-2.117779	-0.148483

$\mathbf{S}_{2}$	$S_2/S_1$ CoIn structure			q	$q_{ m FC  ightarrow  m CoIn}$ coordinate vector				
Ν	-0.875590	-0.061424	-0.438801	Ν	J	0.057502	-0.005039	0.343227	
Ν	0.992269	1.175157	0.169818	Ν	J	0.006707	-0.018372	-0.132830	
С	-0.398243	1.138717	0.002335	(	2	-0.007054	-0.047996	-0.001826	
$\mathbf{C}$	1.749110	0.128037	-0.224914	(	2	0.011098	0.059661	0.175926	
$\mathbf{C}$	1.145232	-1.192330	0.081665	(	2	-0.015660	-0.015642	-0.063878	
$\mathbf{C}$	-0.232660	-1.279499	-0.051994	(	3	0.046820	0.005419	0.040670	
0	-0.995549	-2.232124	0.209019	(	)	-0.067218	0.064333	-0.163493	
0	-1.050462	2.133167	0.172808	(	)	-0.009380	-0.059903	-0.135169	
Η	-1.875903	-0.102508	-0.487059	I	I	0.058477	-0.018551	0.380974	
Η	1.358342	2.108083	0.253583	I	I	-0.045426	0.007900	-0.198351	
Η	2.762919	0.307878	-0.544136	I	I	-0.032603	0.086779	0.425620	
Η	1.654763	-1.868903	0.752027	I	ł	-0.076106	0.161681	-0.588230	

$q_{\rm FC}$	$c \rightarrow s_2 - min$ co	ordinate ve	ctor
Ν	0.009693	-0.068540	-0.177225
Ν	-0.030079	-0.004179	0.196680
$\mathbf{C}$	0.004651	0.013444	0.001717
$\mathbf{C}$	0.183304	0.098417	-0.202115
$\mathbf{C}$	-0.011570	-0.082378	-0.103531
$\mathbf{C}$	0.179959	0.075719	-0.012915
0	-0.186903	0.011389	0.153882
0	-0.057633	-0.009116	-0.000792
Η	0.017807	-0.191438	-0.078670
Η	-0.087184	0.028100	0.376049
Η	-0.015696	0.105498	0.677693
Η	0.006355	-0.220491	0.097587

## Electric dipole moments and electrostatic potentials of uracil in different excited states

This section contains visualizations of the electric dipole moments and the electrostatic potentials of uracil in the first few excited states, each computed at both the (TD)DFT/CAM-B3LYP/6-31G(d) and the (TD)DFT/M06-2X/6-311++G(d,p) levels of theory with the *Gaussian 16*<sup>[271]</sup> program package. The ground state structure was optimized with the respective quantum chemical method and verified with a frequency analysis prior to the excited state calculations.

The two methods yield a different ordering of the higher excited states  $S_{n>3}$  (tables B.1 and B.2) but the bright  $\pi\pi^*$  state, which is the focus of this paper, is the  $S_2$  state in both cases. It is clearly visible from figures B.1 and B.2 that the dipole moment of this state is very close to the one of the electronic ground state in both direction and magnitude, while the other excited states can differ significantly from the ground state. The same is true for the electrostatic potential depicted in figures B.3 and B.4. It is therefore reasonable to assume that the electrostatic interaction of the environment with uracil in the bright  $S_2$  state will be very similar to that in the ground state. Thus, while not generally applicable, the approach to compute the environmental potential  $\hat{V}_{env}$  in the ground state and subsequently add a high-level excited state potential  $\hat{V}_{mol}$  is a valid approximation in our case.

Table B.1: Character, vertical excitation energies and oscillator strength of the first five singlet excited states of uracil (TD-DFT/CAM-B3LYP/6-31G(d)). The bright second excited state is the main focus of this study and highlighted in red.

state	character	$E_{ m vert}$ [eV]	$E_{\mathrm{vert}}$ [nm]	f
S1	$n \to \pi^*$	5.09	243.4	0.00
S2	$\pi \to \pi^*$	5.65	219.5	0.17
S3	$n \to \pi^*$	6.40	193.6	0.00
S4	$\pi \to \pi^*$	6.73	184.3	0.04
S5	$\pi \to \pi^*$	7.18	172.7	0.14

**Table B.2:** Character, vertical excitation energies and oscillator strength of the first five singlet excited states of uracil (TD-DFT/M06-2X/6-311++G(d,p)). The bright second excited state is the main focus of this study and highlighted in red.

state	character	$E_{ m vert} \; [{ m eV}]$	$E_{ m vert}$ [nm]	f
S1	$n \to \pi^*$	5.01	247.5	0.00
S2	$\pi \to \pi^*$	5.55	223.5	0.20
$\mathbf{S3}$	$\pi \to \mathrm{Ry}^*$	5.97	207.5	0.02
S4	$n \to \pi^*$	6.28	197.5	0.00
S5	$\pi \to \pi^*$	6.73	184.3	0.04



Figure B.1: Electric dipole moments of the ground state and the first five excited states of uracil on the (TD)DFT/CAM-B3LYP/6-31G(d) level of theory. Note that the dipole moments of the ground state and the second excited state, that this study focuses on, are very similar in direction and magnitude.



Figure B.2: Electric dipole moments of the ground state and the first five excited states of uracil on the (TD)DFT/M06-2X/6-311++G(d,p) level of theory. Note that the dipole moments of the ground state and the second excited state, that this study focuses on, are very similar in direction and magnitude.



Figure B.3: Electrostatic potential mapped onto the electron density (Isovalue 0.05) of uracil in the ground state and the first five excited states, computed at the (TD)DFT/CAM-B3LYP/6-31G(d) level of theory. Note that the ground state and the second excited state exhibit the same charge distribution across the nucleobase.



Figure B.4: Electrostatic potential mapped onto the electron density (Isovalue 0.05) of uracil in the ground state and the first five excited states, computed at the (TD)DFT/M06-2X/6-311++G(d,p) level of theory. Note that the ground state and the second excited state exhibit the same charge distribution across the nucleobase.

#### Potential energy scans in three-dimensions

Modeling the photorelaxation of uracil in two reactive coordinates is necessarily an approximation. For the isolated base, the validity of the described 2D coordinate space to describe the photorelaxation of uracil has been established in a previous investigation.<sup>[183]</sup> However, it could be conceived that the presence of an atomistic environment opens new relaxation pathways in a different coordinate. In such a case, the potential energy would be stabilized along the aditional dimension.

To check for the necessity of additional coordinates in our simulations, we extended the existing 2D space to three dimensions by adding five normal modes from different spectral regions that cover most of the molecular movement of uracil. Specifically, we chose an N-H ( $q_{\rm NH_s}$ ), a C-H ( $q_{\rm CH_s}$ ) and a C-O ( $q_{\rm CO_s}$ ) stretching mode as well as a C-H bending mode ( $q_{\rm CH_b}$ ) and an out-of-plane deformation ( $q_{\rm oop}$ ) as shown in table B.3. The Cartesian coordinates of these modes are compiled on the following pages.

**Table B.3:** Chosen normal modes to represent molecular movement of uracil in a third dimension. Vibrational frequencies were calculated with M06-2X/6-311++G(d,p) and scaled by a factor of 0.947. The normal modes cover a broad spectral range and include most molecular degrees of freedom not already covered by the 2D coordinate space.

Mode	$\tilde{\nu} \ [\mathrm{cm}^{-1}]$
$q_{\rm NH_s}$	3423
$q_{\rm CH_s}$	3051
$q_{\rm CO_s}$	1762
$q_{\rm CH_b}$	1170
$q_{\rm oop}$	723

$q_{ m oop}$ : $ ilde{ u}=723{ m cm}^{-1}$				$q_{ m C}$	$q_{ m CH_b} \colon  ilde{ u} = 1170{ m cm^{-1}}$			$q_{ m CO_s} \colon \tilde{ u} = 1762{ m cm^{-1}}$			
Ν	0.00	0.00	-0.24	Ν	0.09	-0.02	0.00	Ν	-0.09	0.03	0.00
Ν	0.00	0.00	-0.22	Ν	-0.04	0.08	0.00	Ν	-0.08	0.08	0.00
$\mathbf{C}$	0.00	0.00	0.82	$\mathbf{C}$	-0.06	-0.10	0.00	С	0.59	-0.31	0.00
$\mathbf{C}$	0.00	0.00	0.04	С	0.11	-0.03	0.00	С	0.00	-0.01	0.00
$\mathbf{C}$	0.00	0.00	-0.10	С	0.01	-0.03	0.00	С	0.03	0.04	0.00
$\mathbf{C}$	0.00	0.00	0.09	С	-0.12	0.15	0.00	С	-0.19	-0.16	0.00
Ο	0.00	0.00	-0.03	0	0.00	-0.02	0.00	С	0.13	0.09	0.00
Ο	0.00	0.00	-0.25	0	-0.01	0.00	0.00	С	-0.33	0.18	0.00
Н	0.00	0.00	0.26	Η	0.34	-0.02	0.00	Η	0.26	0.03	0.00
Η	0.00	0.00	0.06	Η	-0.15	0.29	0.00	Η	0.20	-0.42	0.00
Н	0.00	0.00	0.00	Η	0.34	-0.04	0.00	Η	0.02	-0.01	0.00
Η	0.00	0.00	0.27	Η	-0.36	-0.67	0.00	Η	-0.04	-0.08	0.00

$q_{\mathrm{CH}_{\mathrm{s}}}$ : $\tilde{\nu} = 3051\mathrm{cm}^{-1}$			$q_{\mathbf{N}}$	$_{\mathrm{H}_{\mathrm{s}}}:\tilde{\nu}=$	$3423\mathrm{cm}$	<sub>1</sub> –1	
Ν	0.00	0.00	0.00	Ν	0.00	-0.07	0.0
Ν	0.00	0.00	0.00	Ν	0.00	0.00	0.0
$\mathbf{C}$	0.00	0.00	0.00	С	0.00	0.00	0.0
$\mathbf{C}$	0.01	0.09	0.00	С	0.00	0.00	0.0
$\mathbf{C}$	0.01	-0.01	0.00	С	0.00	0.00	0.
С	0.00	0.00	0.00	С	0.00	0.00	0.
0	0.00	0.00	0.00	0	0.00	0.00	0.
0	0.00	0.00	0.00	0	0.00	0.00	0.
Η	0.00	0.00	0.00	Η	-0.02	1.00	0.
Η	0.00	0.01	0.00	Η	0.01	0.00	0.
Η	-0.07	-0.97	0.00	Η	0.00	0.00	0.
Η	-0.17	0.10	0.00	Η	0.00	0.00	0.

We rastered the parts of the 2D space that are accessible to the wave packet with a grid of 14 points (figure B.5). After orthonormalizing the respective normal mode to the 2D space, we performed a potential energy scan at each of these grid points in both directions of the new coordinate, using the same QM/MM methodology as described in the main article.

To account for different environmental conformations, we computed these scans for five MD snapshots, thus giving a total of 25 three-dimensional potentials. For a new relaxation pathway to form in a third dimension, the interaction energy  $\hat{V}_{env}$  would need to compensate the harmonic potential of the respective coordinate and cause stabilization close to the 2D space we considered in our simulations. Therefore, the sum of  $\hat{V}_{env}$  and the normal mode potentials in their harmonic representation is plotted in figures B.6 to B.10. Each subplot shows a set of one-dimensional energy scans along the respective normal mode coordinate, corresponding to the grid points in figure B.5. All the scans remain harmonic in the third dimension under environmental influence. We therefore conclude that this space is well-suited to describe the photorelaxation of uracil and no new relaxation pathways can be expected in a third dimension.



Figure B.5: Grid points overlaid on the 2D-PES of uracil. At each of these points, a potential energy scan was performed along a normal mode coordinate to check for possible new relaxation pathways in a third dimension.



Figure B.6: Sum of the harmonic potential of the respective normal mode and the environmental interaction energy  $\hat{V}_{env}$  in one MD snapshot for the base sequence 5'-GAGUAGG-3'. Each green line represents a one-dimensional potential energy scan along the normal mode coordinate, starting from one of the grid points in figure B.5.



**Figure B.7:** Sum of the harmonic potential of the respective normal mode and the environmental interaction energy  $\hat{V}_{env}$  in one MD snapshot for the base sequence 5'-GAGUAGG-3'. Each green line represents a one-dimensional potential energy scan along the normal mode coordinate, starting from one of the grid points in figure B.5.



Figure B.8: Sum of the harmonic potential of the respective normal mode and the environmental interaction energy  $\hat{V}_{env}$  in one MD snapshot for the base sequence 5'-GAGUAGG-3'. Each green line represents a one-dimensional potential energy scan along the normal mode coordinate, starting from one of the grid points in figure B.5.



**Figure B.9:** Sum of the harmonic potential of the respective normal mode and the environmental interaction energy  $\hat{V}_{env}$  in one MD snapshot for the base sequence 5'-GAGUAGG-3'. Each green line represents a one-dimensional potential energy scan along the normal mode coordinate, starting from one of the grid points in figure B.5.



Figure B.10: Sum of the harmonic potential of the respective normal mode and the environmental interaction energy  $\hat{V}_{env}$  in one MD snapshot for the base sequence 5'-GAGUAGG-3'. Each green line represents a one-dimensional potential energy scan along the normal mode coordinate, starting from one of the grid points in figure B.5.

# APPENDIX

### Supporting Information to Chapter 3

#### C.1 Hydrogen Evolution via CoMabiq

The complete supporting information to the article " $H_2$  Evolution from Electrocatalysts with Redox-Active Ligands: Mechanistic Insights from Theory and Experiment Vis-à-Vis Co-Mabiq" was published 2021 in *Inorganic Chemistry* and is available at https://doi.org/10.1021/acs.inorgchem.1c01157. An excerpt of the most relevant computational details is reprinted below.

#### C.1.1 Structural Distortions upon Protonation of [Co<sup>II</sup>(Mabiq<sup>•</sup>)]<sup>0</sup>



Figure C.1: Optimized structures of possible intermediates after the protonation step, depicted in top and side views of the molecule. Cobalt is depicted in ocher, carbon in gray, nitrogen in blue, hydrogen in white. The added proton is marked in red. Protonation at both diketiminate sites leads to strong distortion from the planar geometry and breaking of ligand aromaticity. Protonation at the cobalt center only causes slight pyramidalization and the imine product remains planar.

#### C.1.2 TD-DFT Absorption Spectrum of (Co<sup>II</sup>(Mabiq<sup>•</sup>))<sup>0</sup>

In our early tests, we calculated a TD-DFT absorption spectrum for the  $[Co^{II}(Mabiq^{\bullet})]$  complex using the same level of theory that was used for optimization (see Computational Details in the main article). The only difference at this early stage was that both the geometry optimization and the TD-DFT calculation was conducted in the gas phase without solvation effects.





[TD-DFT absorption spectrum of [Co<sup>II</sup>(Mabiq<sup>•</sup>)] in comparison to the experimental spectrum. The line spectrum was convoluted with an FWHM of 0.24 eV and the convoluted spectrum was scaled such that the highest absorption is 1. Note that the experimental band at 411 nm cannot be assigned unambiguously in the TD-DFT spectrum. The double peak structure of the band around 520 nm is also not reproduced in the calculation.

C.1.3 DFT/MRCI Spectrum of (Co<sub>Mbq</sub>-H<sub>Im</sub>)<sup>+</sup>



Figure C.3: DFT/MRCI absorption spectrum for the cation  $Co_{Mbq}$ - $H^{Im+}$ , where the proton attaches to one of the imine sites of the ligand.



#### C.1.4 Spin Densities of Cationic and Reduced Intermediate Species

Figure C.4: Broken-symmetry DFT spin densities, i.e. difference between  $\alpha$ - and  $\beta$ -electron densities, of the optimized cationic (1-electron-1-proton) and reduced (2-electron-1-proton) intermediates (Isovalue = 0.002). Reduction happens where the unpaired spin-density changes from the cation to the neutral species. Thus, the second electron is added to the ligand, if the proton attaches to either of the diketiminate sites or the cobalt center, whereas reduction occurs on the metal if the proton attaches to the imine site.



#### C.1.5 Calculated Energy Levels of Intermediates

Figure C.5: Calculated Gibbs free energy levels of DFT optimized intermediates, relative to  $[Co^{II}(Mabiq^{\bullet})]^0$ . Energies of protonation steps include the acid contributions (cf. eq. 2 in the main article). Reduction energies are given for the respective half-reaction. For brevity, the notations H-DK1 and H-Im are used to denote  $Co_{Mbq}$ -H<sup>DK1</sup> and  $Co_{Mbq}$ -H<sup>Im</sup>. TS is the transition state for interconversion between the two species.

#### C.1.6 Electrostatic Potentials and Selected Atomic Charges of (Co<sub>Mbq</sub>-H<sub>2</sub><sup>Im,Co</sup>)<sup>+</sup> and (Co<sub>Mbq</sub>-H<sub>2</sub><sup>Im,Co</sup>)

The charge distribution of the doubly protonated complexes can provide insights into the reactivity towards hydrogen evolution. There are different ways to obtain atomic charges from quantum chemical calculations. In this work, we chose to inspect the electrostatic potential (ESP) rather than common population analyses as it reflects the actual charge distribution in the complex without resorting to arbitrary electron localization schemes. Merz-Singh-Kollman charges<sup>[350]</sup> (table C.1) are derived from the ESP by fitting the potential at various points in space.



Figure C.6: Broken-symmetry DFT derived electrostatic potential (ESP) of  $(Co_{Mbq}-H_2^{Im,Co})^+$ and its reduced form  $(Co_{Mbq}-H_2^{Im,Co})$ , mapped onto a surface plot of the electron density (Isovalue: 0.02). The Co-bound proton carries a visibly smaller positive charge than the other protons in the complex.

	Со	Co-bound H
$(\mathrm{Co}_\mathrm{Mbq} ext{-}\mathrm{H}^\mathrm{Im})^+$	1.16	/
$ m Co_{Mbq} ext{-}H^{Im}$	0.18	/
$(\mathrm{Co}_{\mathrm{Mbq}} ext{-}\mathrm{H}^{\mathrm{Im}})^-$	0.01	/
$(\mathrm{Co}_{\mathrm{Mbq}} ext{-}\mathrm{H}_{2}^{\mathrm{Im,Co}})^{+}$	1.20	-0.14
$(\mathrm{Co}_{\mathrm{Mbq}} ext{-}\mathrm{H_2}^{\mathrm{Im,Co}})$	1.21	-0.17
$(\mathrm{Co}_{\mathrm{Mbq}} ext{-}\mathrm{H}^{\mathrm{DK1}})^+$	1.18	/
$ m Co_{Mbq}$ - $ m H^{DK1}$	1.15	/
$(\mathrm{Co}_{\mathrm{Mbq}} ext{-}\mathrm{H}^{\mathrm{DK1}})^-$	0.52	/
$\mathrm{Co}_{\mathrm{Mbq}} ext{-}\mathrm{H}_{2}^{\mathrm{DK1,Im}}$	0.53	/

Table C.1: Selected Merz-Singh-Kollman charges, derived from broken-symmetry DFT, for the intermediate species along the two possible pathways starting from  $(Co_{Mbq}-H^{Im})^+$  and  $(Co_{Mbq}-H^{DK1})^+$ .

#### C.1.7 Energies of Optimized Geometries

Table C.2 lists the SCF energies  $E_{SCF}$ , enthalpies H (Gaussian Output: Sum of electronic and thermal Enthalpies) and Gibbs free energies G (Gaussian Output: Sum of electronic and thermal Free Energies) of the DFT optimized geometries. The Cartesian coordinates are available in the complete Supporting Information at https://doi.org/10.1021/acs. inorgchem.1c01157.

Species	Chrg. / Mult.	$E_{ m SCF} \left[ { m E_h}  ight]$	$H [{ m E_h}]$	$G [\mathrm{E_h}]$
pCA D-pCA	$egin{array}{cccc} 1 & / & 1 \ 0 & / & 1 \end{array}$	$-380.091264\\-379.671408$	$\begin{array}{r} -379.949961 \\ -379.545770 \end{array}$	$\begin{array}{r} -379.990478 \\ -379.586008 \end{array}$
$[\mathrm{Co}^{\mathrm{II}}(\mathrm{Mabiq}^{\bullet})]^0$	0 / 1	-1859.692794	-1859.038305	-1859.136648
$egin{aligned} &(\mathrm{Co}_{\mathrm{Mbq}}\mathrm{-}\mathrm{H}^{\mathrm{DK1}})^{+}\ &(\mathrm{Co}_{\mathrm{Mbq}}\mathrm{-}\mathrm{H}^{\mathrm{DK2}})^{+}\ &(\mathrm{Co}_{\mathrm{Mbq}}\mathrm{-}\mathrm{H}^{\mathrm{Co}})^{+}\ &(\mathrm{Co}_{\mathrm{Mbq}}\mathrm{-}\mathrm{H}^{\mathrm{Im}})^{+} \end{aligned}$	$egin{array}{cccc} 1 & / & 1 \ 1 & / & 1 \ 1 & / & 1 \ 1 & / & 1 \ 1 & / & 1 \ 1 & / & 1 \ \end{array}$	$\begin{array}{r} -1860.114199\\ -1860.119786\\ -1860.123039\\ -1860.150164\end{array}$	$\begin{array}{r} -1859.448828\\ -1859.453626\\ -1859.458900\\ -1859.483461\end{array}$	$\begin{array}{r} -1859.546706\\ -1859.551293\\ -1859.557196\\ -1859.582583\end{array}$
$\begin{array}{c} {\rm Co}_{\rm Mbq}\text{-}{\rm H}^{\rm DK1}\\ {\rm Co}_{\rm Mbq}\text{-}{\rm H}^{\rm DK2}\\ {\rm Co}_{\rm Mbq}\text{-}{\rm H}^{\rm Co}\\ {\rm Co}_{\rm Mbq}\text{-}{\rm H}^{\rm Im} \end{array}$	$egin{array}{cccc} 0 & / & 2 \ 0 & / & 2 \ 0 & / & 2 \ 0 & / & 2 \ 0 & / & 2 \end{array}$	$\begin{array}{r} -1860.311779 \\ -1860.319865 \\ -1860.255891 \\ -1860.262527 \end{array}$	$\begin{array}{r} -1859.645479\\ -1859.653614\\ -1859.594802\\ -1859.597357\end{array}$	$\begin{array}{r} -1859.743799\\ -1859.752064\\ -1859.694555\\ -1859.696523\end{array}$
$\frac{(\mathrm{Co}_{\mathrm{Mbq}}\mathrm{-}\mathrm{H}^{\mathrm{DK1}})^{-}}{(\mathrm{Co}_{\mathrm{Mbq}}\mathrm{-}\mathrm{H}^{\mathrm{Im}})^{-}}$	-1 / 1 -1 / 1	-1860.354755 -1860.353736	-1859.690039 -1859.688750	-1859.787915 -1859.788357
$(\mathrm{Co}_{\mathrm{Mbq}} ext{-}\mathrm{H_2}^{\mathrm{Im,Co}})^+ \ \mathrm{Co}_{\mathrm{Mbq}} ext{-}\mathrm{H_2}^{\mathrm{Im,Co}} \ \mathrm{Co}_{\mathrm{Mbq}} ext{-}\mathrm{H_2}^{\mathrm{DK1,Im}}$	$egin{array}{cccc} 1 & / & 2 \ 0 & / & 1 \ 0 & / & 1 \ \end{array}$	$\begin{array}{r} -1860.698986 \\ -1860.815777 \\ -1860.886272 \end{array}$	$-1860.023402\\-1860.143616\\-1860.208529$	$\begin{array}{r} -1860.122443\\ -1860.243379\\ -1860.306596\end{array}$
$\label{eq:combar} \begin{array}{c} \mbox{Transition state} \\ \mbox{Co}_{\mathbf{Mbq}}\mbox{-}\mbox{H}^{\mathbf{Im}} \rightarrow \mbox{Co}_{\mathbf{Mbq}}\mbox{-}\mbox{H}^{\mathbf{DK1}} \end{array}$	0/2	-1860.196014	-1859.536157	-1859.634925

**Table C.2:** Charge, spin multiplicity, SCF energies  $E_{SCF}$ , enthalpies H and Gibbs free energies G of optimized geometries.

#### C.2 The Light-Harvesting Network of Photosystem I

The supporting information to the article "Thermal site energy fluctuations in photosystem I: new insights from MD/ QM/MM calculations" was published 2023 in *Chemical Science* and is available at https://doi.org/10.1039/d2sc06160k. It is reprinted in full below; raw and processed data is openly available at https://doi.org/10.5281/zenodo.6576313.

#### C.2.1 Details on Structure Preparation

Table C.3 lists all amino acids that were missing in the crystal structure of cyanobacterial PS I and were added manually with the *Modeller* interface<sup>[351]</sup> to *UCSF Chimera*.<sup>[352]</sup> The residue ID refers to the original numbering in the crystal structure. Partially resolved phytyl chains of the chlorophyll residues were replaced with methyl groups and the affected residues renamed from CLA to CLX, to distinguish them later in the MD simulations. Other missing side chains were replaced manually. Figure C.7 illustrates all modifications on the chlorophyll residues in the crystal structure.

chain	res. ID	res. name
А	1 to 12 263 to 265	MET, THR, ILE, SER, PRO, PRO, GLU, ARG, GLU, PRO, LYS, VAL GLY, VAL, ILE
В	740	GLY
Е	70 to 75	PRO, PRO, LYS, LYS, GLY, LYS
F	-22 to 0	MET, ARG, ARG, PHE, LEU, ALA, LEU, LEU, LEU, VAL, LEU, THR, LEU, TRP, LEU, GLY, PHE, THR, PRO, LEU, ALA, SER, ALA
К	1 to 19	MET, VAL, LEU, ALA, THR, LEU, PRO, ASP, THR, THR, TRP, THR, PRO, SER, VAL, GLY, LEU, VAL, VAL
	33	ALA
	44 to $54$	PRO, ILE, ALA, LEU, PRO, ALA, LEU, PHE, GLU, GLY, PHE
	78 to 83	GLN, TYR, ALA, GLY, ALA, LEU
L	1 to 3	ALA, GLU, GLU
X	1 to 6	ALA, THR, LYS, SER, ALA, LYS

**Table C.3:** Amino acids added to the crystal structure of 1JB0. Residue IDs are given according to the original numbering of the pdb file.



Figure C.7: Chlorophyll *a* residue types after modification, as used in the MD simulations. IDs in parentheses refer to the standard chlorophyll numbering, the other notation indicates the chain and residue given in the crystal structure PDB (1JB0).<sup>[244]</sup> Red: Intact chlorophylls, blue: phytyl chain replaced with  $-CH_3$ , magenta:  $-COOCH_3$  and  $-CH=CH_2COOCH_3$  added to residue J1303 and phytyl chain replaced with  $-CH_3$ , green:  $-COOCH_3$  added to residue A1402 and phytyl chain replaced with  $-CH_3$ .

#### C.2.2 Molecular Dynamics Validation

Proper equilibration of the MD simulations was confirmed by checking the convergence of temperature (T), total energy (E), pressure (p), density  $(\rho)$  and the box vectors (fig. C.8). Average values of T, p,  $\rho$  and E are provided in tab. C.4.



Figure C.8: Key thermodynamic parameters during MD trajectories.

Table C.4: Thermodynamic averages and standard deviations during the MD simulations.

Traj.	$\langle T  angle ~ [{ m K}]$	$\langle p  angle$ [bar]	$\langle  ho  angle ~ [{ m g}  { m L}^{-1}]$	$\langle E  angle ~ [{ m kJmol^{-1}}]$
1	$300.0\pm0.5$	$1 \pm 39$	$1043.5 \pm 0.6$	$(-8.278 \pm 0.007) \times 10^{6}$
2	$300.0\pm0.5$	$1 \pm 37$	$1043.5\pm0.6$	$(-8.277 \pm 0.007) \times 10^{6}$
3	$300.0\pm0.5$	$1 \pm 38$	$1043.6\pm0.6$	$(-8.277 \pm 0.007) \times 10^{6}$
4	$300.0\pm0.5$	$1 \pm 38$	$1043.6\pm0.6$	$(-8.277 \pm 0.007) \times 10^{6}$
5	$300.0\pm0.5$	$1 \pm 37$	$1043.5\pm0.6$	$(-8.277 \pm 0.007) \times 10^{6}$

To assess the quality of the trajectories, we evaluated the mass-weighted RMSD of the protein  $C\alpha$  backbone, the porphyrin units of the CLA/CLX residues and the BCR and PQN cofactors with respect to the crystal structure. Each frame of the trajectory was aligned to the protein  $C\alpha$  atoms of the reference. Hydrogen atoms and all atoms missing in the crystal structure were excluded from the analysis. In all production simulations, the RMSD of the protein backbone as well as that of the cofactors is converged (figure C.9). The time-averaged RMSD (figure C.10) is between 1 Å and 2 Å, which is below the 2.5 Å resolution of the crystal structure, thus validating the sampled geometries.

We also calculated the area per lipid of the POPC membrane (table C.5, figure C.11) using the *FATSLiM 0.2.2* toolbox<sup>[353]</sup> and applying a cutoff distance of 2.9 nm for leaflet identification. Membrane leaflets were identified by the phosphatidylcholine headgroups, while protein and cofactors were used as interacting groups. The average area per lipid across both membrane leaflets  $\langle A \rangle$  is  $0.642 \text{ nm}^2$ , which is in good agreement with previously reported values for POPC bilayers ( $0.604 \text{ nm}^2$ ,  $^{[354]}$   $0.655 \text{ nm}^2$ ,  $^{[355]}$   $0.631 \text{ nm}^2$ ,  $^{[356]}$ ). The time-averaged lipid bilayer thickness  $\langle D \rangle$  (figure C.12), defined as the distance between the P atom layers in the upper and lower leaflet, converged to 3.67 nm after equilibration, which also corresponds well with previous theoretical (3.725 nm,  $^{[355]}$  3.75 nm,  $^{[356]}$ ) and experimental reports (3.7 nm,  $^{[357]}$ ).

Traj.	$\langle A  angle ~ [{ m nm^2}]$	$\langle A_L  angle ~ [{ m nm}^2]$	$\langle A_U  angle ~ [{ m nm}^2]$	$\langle D  angle ~[{ m nm}]$
1	$0.642 \pm 0.003$	$0.630 \pm 0.005$	$0.655 \pm 0.006$	$3.68\pm0.02$
2	$0.642 \pm 0.005$	$0.634 \pm 0.006$	$0.651 \pm 0.006$	$3.67\pm0.02$
3	$0.642 \pm 0.004$	$0.630 \pm 0.006$	$0.655\pm0.014$	$3.67\pm0.02$
4	$0.641\pm0.004$	$0.628 \pm 0.006$	$0.654 \pm 0.005$	$3.67\pm0.01$
5	$0.640 \pm 0.004$	$0.630 \pm 0.006$	$0.650 \pm 0.005$	$3.67\pm0.01$

**Table C.5:** Bilayer thickness  $\langle D \rangle$  and average area per lipid at 300 K in the full membrane ( $\langle A \rangle$ ), the lower (stromal) leaflet ( $\langle A_L \rangle$ ) and the upper (lumenal) leaflet ( $\langle A_U \rangle$ ).



**Figure C.9:** RMSD of different residue groups vs. the crystal structure in each production trajectory over time. CLA: Chlorophyll porphyrin units; BCR:  $\beta$ -carotene, PQN: phylloquinone.



**Figure C.10:** Time-averaged RMSD of different residue groups vs. the crystal structure in each production trajectory. Error bars signify the standard deviation across the trajectory. CLA: Chlorophyll porphyrin units; BCR:  $\beta$ -carotene, PQN: phylloquinone.



Figure C.11: Area per lipid in each production trajectory over time.



Figure C.12: Bilayer thickness in each production trajectory over time.

#### C.2.3 QM Method Assessment



#### Further Chlorophyll Absorption Spectra in Diethyl Ether

**Figure C.13:** a) Absorption spectra of a single chlorophyll molecule, axially coordinated by two diethyl ether ligands and implicitly solvated in diethyl ether at different levels of theory, compared to an experimental spectrum. Stick spectra were convoluted by Gaussians ( $\sigma = 0.05 \text{ eV}$ ). Excited states with an oscillator strength < 0.1 are indicated by dotted lines. b) Optimized structure (r<sup>2</sup>SCAN-3c) used for these benchmark calculations. Hydrogens are omitted for clarity.
### **Truncation of the Phytyl Chain**

The effects of truncating the phytyl chain at various lengths in the QM region were tested in one MD snapshot for chlorophyll eC-A1. The rest of the phytyl chain and the protein environment were described by point charges and the QM calculations were performed at the DFT/MRCI level as described in the main article. These test calculations were conducted with the basis set def2-SV(P) as the largest QM region was not computationally feasible otherwise. As the phytyl chain is not involved in the excitation, the site energies are nearly identical for different truncation schemes (table C.6) and thus allow a truncation after the first carbon.

	C	C1	C	C6	C12	
State	$E \; [eV]$	f	$\overline{E \; [\mathrm{eV}]}$	f	$E \; [eV]$	f
1	1.872	0.33578	1.870	0.33873	1.869	0.34035
2	2.075	0.07015	2.077	0.07000	2.074	0.06990
3	2.849	0.40940	2.853	0.42848	2.850	0.41902
4	3.009	0.25724	3.017	0.25709	3.013	0.24418

**Table C.6:** DFT/MRCI site energies and oscillator strengths in one MD snapshot for chlorophyll eC-A1 with the phytyl chain truncated after the first (C1), sixth (C6) and twelfth (C12) carbon.



Figure C.14: Site energies for each chlorophyll residue, ordered by ascending arithmetic mean (blue triangles) in 40 MD snapshots. Black lines signify the median, red lines its bootstrapped 95% confidence interval. The green boxes extend from the beginning of the second to the end of the third quartile, whiskers extend to the minimum and maximum values of the data or to 1.5 times the interquartile range in case of outliers (gray diamonds).

Table C.7: Arithmetic mean and median of the site energy distributions for each chlorophyll with (subscript env) and without (subscript vac) point charge environment in 40 MD snapshots. Table rows are sorted in ascending order by the mean of the site energy  $E_{\rm env}^{\rm mean}$ , same as in fig. 8 of the main paper. The column *ID (MD)* refers to the residue ID used in our MD simulations, while *Name* denotes the standard residue numbering scheme in PS I<sup>[244,255]</sup> and ID (x-ray) is the residue ID used in the crystal structure PDB (1JB0).<sup>[244]</sup>

index	ID (MD)	Name	ID (x-ray)	$E_{\rm env}^{\rm mean}$ [eV]	$E_{\rm vac}^{\rm mean}$ [eV]	$\Delta E_{ m struct}^{ m mean}$ [eV]	$\Delta E_{\rm elec}^{\rm mean} ~[{\rm eV}]$	$E_{ m env}^{ m med}$ [eV]	$E_{\rm vac}^{\rm med}$ [eV]	$\Delta E_{ m struct}^{ m med}$ [eV]	$\Delta E_{ m elec}^{ m med} \ [ m eV]$
0	2407	B22	1222	1.853455	1.879903	-0.035949	-0.009847	1.85000	1.87425	-0.041602	-0.00880
1	2417	B32	1232	1.864715	1.904375	-0.011477	-0.023060	1.86125	1.90520	-0.010652	-0.02040
2	2349	A10	1110	1.868052	1.891107	-0.024744	-0.006455	1.86435	1.89500	-0.020852	-0.00785
3	2390	B5	1205	1.868535	1.921047	0.005196	-0.035912	1.87155	1.92025	0.004398	-0.03350
4	2386	B1	1201	1.871347	1.903722	-0.012129	-0.015775	1.86785	1.90600	-0.009852	-0.01585
5	2374	A35	1135	1.873417	1.902643	-0.013209	-0.012625	1.87375	1.90500	-0.010852	-0.01185
6	2403	B18	1218	1.875532	1.911070	-0.004782	-0.018937	1.87815	1.91530	-0.000552	-0.01565
7	2392	B7	1207	1.876372	1.905655	-0.010197	-0.012682	1.87115	1.90300	-0.012852	-0.01295
8	2359	A20	1120	1.878215	1.901123	-0.014729	-0.006307	1.87310	1.90055	-0.015302	-0.00680
9	2409	B24	1224	1.878295	1.899550	-0.016302	-0.004655	1.88140	1.90030	-0.015552	-0.00480
10	2415	B30	1230	1.880343	1.903687	-0.012164	-0.006745	1.88195	1.90460	-0.011252	-0.00875
11	2366	A27	1127	1.880590	1.922427	0.006576	-0.025237	1.87870	1.92430	0.008448	-0.02605
12	2406	B21	1221	1.881983	1.918415	0.002563	-0.019832	1.87350	1.91455	-0.001302	-0.01860
13	2382	PL1	1801	1.882463	1.911225	-0.004627	-0.012162	1.88210	1.91410	-0.001752	-0.01370
14	2373	A34	1134	1.883987	1.901632	-0.014219	-0.001045	1.87855	1.90890	-0.006952	0.00045
15	2342	A3	1103	1.885278	1.907900	-0.007952	-0.006022	1.88865	1.90915	-0.006702	-0.00545
16	2389	B4	1204	1.885675	1.916680	0.000828	-0.014405	1.88980	1.91905	0.003198	-0.01395
17	2378	A39	1139	1.886075	1.916050	0.000198	-0.013375	1.87785	1.91280	-0.003052	-0.01310
18	2354	A15	1115	1.886747	1.907238	-0.008614	-0.003890	1.87765	1.90600	-0.009852	-0.00470
19	2367	A28	1128	1.886975	1.909623	-0.006229	-0.006047	1.89170	1.91175	-0.004102	-0.00395
20	2398	B13	1213	1.887160	1.900198	-0.015654	0.003563	1.88080	1.89745	-0.018402	0.00140
21	2351	A12	1112	1.887660	1.911280	-0.004572	-0.007020	1.89635	1.91160	-0.004252	-0.00980
22	2365	A26	1126	1.887768	1.914357	-0.001494	-0.009990	1.88235	1.91430	-0.001552	-0.01250
23	2337	eC-A1	1011	1.888330	1.901138	-0.014714	0.003793	1.88025	1.89670	-0.019152	0.00325
24	2425	J2	1302	1.889665	1.917935	0.002083	-0.011670	1.88575	1.91325	-0.002602	-0.00775
25	2422	B38	1238	1.889822	1.910750	-0.005102	-0.004327	1.88605	1.91080	-0.005052	-0.00615
26	2427	K1	1401	1.890318	1.904300	-0.011552	0.002618	1.89625	1.90960	-0.006252	0.00370
27	2418	B33	1233	1.891440	1.900678	-0.015174	0.007363	1.89255	1.89590	-0.019952	0.00890
28	2377	A38	1138	1.891883	1.916625	0.000773	-0.008142	1.88820	1.90995	-0.005902	-0.00785
29	2431	M1	1601	1.892145	1.914368	-0.001484	-0.005622	1.88950	1.92235	0.006498	-0.00160
30	2353	A14	1114	1.892545	1.909417	-0.006434	-0.000272	1.89315	1.91350	-0.002352	0.00130
31	2430	L3	1503	1.894138	1.913080	-0.002772	-0.002342	1.90385	1.91655	0.000698	-0.00525
32	2416	B31	1231	1.894322	1.912292	-0.003559	-0.001370	1.89275	1.90910	-0.006752	-0.00140
33	2405	B20	1220	1.894405	1.913845	-0.002007	-0.002840	1.88835	1.91235	-0.003502	-0.00260
34	2347	A8	1108	1.894467	1.909172	-0.006679	0.001895	1.89460	1.91625	0.000398	0.00280
35	2393	B8	1208	1.894478	1.923815	0.007963	-0.012737	1.89720	1.93460	0.018748	-0.01475
36	2404	B19	1219	1.896085	1.924205	0.008353	-0.011520	1.90680	1.93340	0.017548	-0.01180
37	2338	eC-A2	1022	1.897437	1.902822	-0.013029	0.011215	1.89485	1.89735	-0.018502	0.01175
38	2412	B27	1227	1.897847	1.924983	0.009131	-0.010535	1.89450	1.91955	0.003698	-0.01080
39	2411	B26	1226	1.898017	1.910083	-0.005769	0.004535	1.90785	1.91685	0.000998	0.00450
40	2375	A36	1136	1.898157	1.923840	0.007988	-0.009082	1.90490	1.93095	0.015098	-0.00455
41	2410	B25	1225	1.898637	1.930700	0.014848	-0.015462	1.89610	1.92665	0.010798	-0.01495
42	2345	A6	1106	1.898895	1.916257	0.000406	-0.000762	1.89740	1.91895	0.003098	-0.00180

C.2 The Light-Harvesting Network of Photosystem I

continued on next page

index	ID (MD)	Name	ID (x-ray)	$E_{\rm env}^{\rm mean}$ [eV]	$E_{\rm vac}^{\rm mean}$ [eV]	$\Delta E_{ m struct}^{ m mean}$ [eV]	$\Delta E_{ m elec}^{ m mean}$ [eV]	$E_{ m env}^{ m med}$ [eV]	$E_{\rm vac}^{\rm med}$ [eV]	$\Delta E_{ m struct}^{ m med} \; [{ m eV}]$	$\Delta E_{ m elec}^{ m med} \ [ m eV]$
43	2341	A2	1102	1.899 025	1.911435	-0.004417	0.004 190	1.89980	1.91345	-0.002402	0.002 90
44	2363	A24	1124	1.899347	1.910568	-0.005284	0.005380	1.89210	1.90565	-0.010202	0.00745
45	2364	A25	1125	1.899860	1.914992	-0.000859	0.001468	1.90525	1.92215	0.006298	0.00375
46	2395	B10	1210	1.899963	1.909255	-0.006597	0.007308	1.89910	1.90850	-0.007352	0.00400
47	2358	A19	1119	1.899990	1.923783	0.007931	-0.007192	1.90235	1.92805	0.012198	-0.00715
48	2371	A32	1132	1.900000	1.923892	0.008041	-0.007292	1.89365	1.91495	-0.000902	-0.00355
49	2372	A33	1133	1.900048	1.918360	0.002508	-0.001712	1.89730	1.91955	0.003698	-0.00260
50	2414	B29	1229	1.900293	1.900165	-0.015687	0.016728	1.89235	1.89380	-0.022052	0.01635
51	2381	K2	1402	1.900640	1.903497	-0.012354	0.013743	1.89280	1.89495	-0.020902	0.01250
52	2376	A37	1137	1.902035	1.920567	0.004716	-0.001932	1.89370	1.91190	-0.003952	-0.00140
53	2380	B37	1237	1.902203	1.937223	0.021371	-0.018420	1.90285	1.93750	0.021648	-0.02170
54	2420	B35	1235	1.902540	1.929632	0.013781	-0.010492	1.90075	1.92495	0.009098	-0.00945
55	2340	A1	1101	1.903197	1.914115	-0.001737	0.005683	1.89890	1.91095	-0.004902	0.00565
56	2384	eC-B2	1012	1.903217	1.908553	-0.007299	0.011265	1.91300	1.92015	0.004298	0.01020
57	2394	B9	1209	1.904045	1.919852	0.004001	0.000793	1.90680	1.91695	0.001098	-0.00070
58	2352	A13	1113	1.904180	1.917625	0.001773	0.003155	1.90705	1.91805	0.002198	0.00345
59	2370	A31	1131	1.904322	1.907128	-0.008724	0.013795	1.89750	1.90560	-0.010252	0.01190
60	2355	A16	1116	1.905285	1.928820	0.012968	-0.006935	1.90920	1.93720	0.021348	-0.00125
61	2356	A17	1117	1.905665	1.918992	0.003141	0.003273	1.89605	1.90460	-0.011252	0.00580
62	2397	B12	1212	1.905957	1.926785	0.010933	-0.004227	1.90250	1.92595	0.010098	-0.00645
63	2426	J3	1303	1.905977	1.925720	0.009868	-0.003142	1.90380	1.92390	0.008048	-0.00345
64	2344	A5	1105	1.905982	1.919150	0.003298	0.003433	1.90475	1.91565	-0.000202	0.00365
65	2357	A18	1118	1.906210	1.919397	0.003546	0.003413	1.90670	1.92210	0.006248	0.00390
66	2387	B2	1202	1.906287	1.921128	0.005276	0.001760	1.90095	1.92060	0.004748	0.00170
67	2428	L1	1501	1.906370	1.916643	0.000791	0.006328	1.90890	1.91910	0.003248	0.00750
68	2348	A9	1109	1.906925	1.918485	0.002633	0.005040	1.91365	1.92270	0.006848	0.00500
69	2391	B6	1206	1.907240	1.924843	0.008991	-0.001002	1.89950	1.92360	0.007748	0.00190
70	2383	eC-B1	1021	1.908070	1.917340	0.001488	0.007330	1.90215	1.92280	0.006948	0.00755
71	2362	A23	1123	1.908513	1.910687	-0.005164	0.014425	1.90500	1.90355	-0.012302	0.01465
72	2429	L2	1502	1.908653	1.924425	0.008573	0.000828	1.91415	1.92875	0.012898	0.00230
73	2369	A30	1130	1.908765	1.920622	0.004771	0.004743	1.91015	1.92150	0.005648	0.00490
74	2343	A4	1104	1.909773	1.912655	-0.003197	0.013718	1.90770	1.90795	-0.007902	0.01220
75	2360	A21	1121	1.909940	1.917733	0.001881	0.008808	1.91550	1.91685	0.000998	0.00660
76	2419	B34	1234	1.910905	1.917778	0.001926	0.009728	1.90875	1.91445	-0.001402	0.01045
77	2421	B36	1236	1.911068	1.919745	0.003893	0.007923	1.90750	1.91250	-0.003352	0.00830
78	2400	B15	1215	1.911920	1.926585	0.010733	0.001935	1.90230	1.91895	0.003098	0.00295
79	2396	B11	1211	1.912047	1.924960	0.009108	0.003688	1.91555	1.92525	0.009398	0.00710
80	2399	B14	1214	1.913243	1.922330	0.006478	0.007513	1.90670	1.92305	0.007198	0.00830
81	2385	eC-B3	1023	1.914633	1.901227	-0.014624	0.030005	1.91480	1.89380	-0.022052	0.03080
82	2423	B39	1239	1.914892	1.926077	0.010226	0.005415	1.91195	1.92310	0.007248	0.00785
83	2401	B16	1216	1.916793	1.928077	0.012226	0.005315	1.91105	1.92530	0.009448	0.00450
84	2432	X1	1701	1.918455	1.922808	0.006956	0.012248	1.92350	1.92270	0.006848	0.01230
85	2368	A29	1129	1.918708	1.926020	0.010168	0.009288	1.91675	1.92590	0.010048	0.01065
86	2346	A7	1107	1.921690	1.920180	0.004328	0.018110	1.92790	1.92585	0.009998	0.01760
87	2408	B23	1223	1.921953	1.925617	0.009766	0.012935	1.92700	1.92660	0.010748	0.01320
88	2424	J1	1301	1.922465	1.923923	0.008071	0.015143	1.92060	1.92065	0.004798	0.01645
89	2361	A22	1122	1.923098	1.931405	0.015553	0.008293	1.91965	1.92830	0.012448	0.00875

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index	ID (MD)	Name	ID (x-ray)	$E_{\rm env}^{\rm mean}$ [eV]	$E_{\rm vac}^{\rm mean} \ [{\rm eV}]$	$\Delta E_{ m struct}^{ m mean}$ [eV]	$\Delta E_{\rm elec}^{\rm mean} \; [{\rm eV}]$	$E_{ m env}^{ m med}$ [eV]	$E_{\rm vac}^{\rm med}  [{\rm eV}]$	$\Delta E_{ m struct}^{ m med} \ [eV]$	$\Delta E_{ m elec}^{ m med}$ [eV]
90	2402	B17	1217	1.923480	1.922458	0.006606	0.017623	1.91955	1.91950	0.003648	0.01715
91	2379	A40	1140	1.925195	1.924612	0.008761	0.017183	1.92930	1.92395	0.008098	0.01895
92	2413	B28	1228	1.927463	1.932893	0.017041	0.011170	1.92815	1.93645	0.020598	0.00980
93	2388	B3	1203	1.927652	1.924952	0.009101	0.019300	1.92865	1.92045	0.004598	0.01755
94	2350	A11	1111	1.928800	1.939572	0.023721	0.005828	1.93405	1.94195	0.026098	0.00475
95	2339	eC-A3	1013	1.929500	1.925275	0.009423	0.020825	1.92450	1.92815	0.012298	0.02185

Table C.7: continued.



Figure C.15: Site energies for the RC chlorophylls, ordered by ascending arithmetic mean (blue triangles) in 200 MD snapshots. Black lines signify the median, red lines its bootstrapped 95% confidence interval. The green boxes extend from the beginning of the second to the end of the third quartile, whiskers extend to the minimum and maximum values of the data or to 1.5 times the interquartile range in case of outliers (gray diamonds).

**Table C.8:** Arithmetic mean and median of the site energy distributions for the reaction center chlorophylls including the point charge environment in 200 MD snapshots. The column *ID (MD)* refers to the residue ID used in our MD simulations, while *Name* denotes the standard residue numbering scheme in PS I<sup>[244,255]</sup> and *ID (x-ray)* is the residue ID used in the crystal structure PDB (1JB0).<sup>[244]</sup>

index	ID (MD)	Name	ID (x-ray)	$E_{\rm env}^{\rm mean}$ [eV]	$E_{ m env}^{ m med} \ [ m eV]$
0	2384	eC-B2	1012	1.892429	1.89065
1	2338	eC-A2	1022	1.893950	1.89290
2	2337	eC-A1	1011	1.896057	1.89335
3	2383	eC-B1	1021	1.906744	1.90615
4	2385	eC-B3	1023	1.915238	1.91550
5	2339	eC-A3	1013	1.915286	1.91185

### C.2.5 Statistical Considerations



#### Site Energy Convergence with the Number of Snapshots

Figure C.16: Convergence of the mean site energy for each chlorophyll with the number of snapshots.

#### **ANOVA and HSD Analysis**

The raw results of the statistical analysis are provided as csv-files at 10.5281/zenodo.6576313.

A one-way ANOVA was performed to assess the significance of the mean site energies. The analysis showed that there is a statistically significant difference in the site energies between at least two chlorophylls (F(95, 3744) = 4.175, p = 0.000). Tukey's Honestly Significant Difference (HSD) test for multiple comparisons found that the mean site energies were significantly different for 165 pairs of chlorophylls, based on p < 0.05. They correspond to the extreme cases of red and blue chlorophylls discussed in the main manuscript.

An ANOVA analysis for the site energies of the RC chlorophylls in 200 MD snapshots also revealed significant differences (F(5, 1194) = 10.148, p = 0.000). Tukey's HSD test found seven out of 15 pairs of RC chlorophylls with significantly different mean site energies, based on p < 0.05.

Concerning the structural site energy shifts, an ANOVA analysis shows significant differences in at least two pairs of chlorophylls (F(95, 3744) = 2.043, p = 0.000). The same holds for the electrostatic shifts (F(95, 3744) = 19.413, p = 0.000). Tukey's HSD test reveals significant differences in  $\Delta E_{\text{struct}}$  in 29 out of 4560 possible pairs of chlorophylls. For  $\Delta E_{\text{elec}}$ , 1479 pairs of chlorophylls with statistically significant differences are found.



#### C.2.6 Comparison with Literature Data

Figure C.17: Correlation of previously published site energies with the present work. Adolphs *et al.*<sup>[49]</sup> employed the charge density coupling (CDC) method for the protein in standard (st) and non-standard (ns) protonation states. Damjanovic *et al.*<sup>[358]</sup> and Yin *et al.*<sup>[259]</sup> performed semi-empirical and first quantum chemical calculations. Brüggemann *et al.*<sup>[257]</sup> Byrdin *et al.*<sup>[255]</sup> and Vaitekonis *et al.*<sup>[258]</sup> performed fits of optical spectra. Energies are given in eV. The diagonal plots illustrate the kernel density estimate (KDE) of each data set.

# C.2.7 Dimer Excited States



Figure C.18: Selected chlorophyll pairs to compute excited states at the QM( $\omega$ B97X-D4/def2-TZVP)/MM level of theory.



Figure C.19: Natural transition orbitals and excitation energies for the first and second excited state of selected chlorophyll pairs in PS I at the QM( $\omega$ B97X-D4/def2-TZVP)/MM level (isovalue: 0.02). The name above the figures refers to the chlorophyll, on which the excitation is localized. Numbers next to the arrows denote the singular value of the transition.



Figure C.19 (cont.): Natural transition orbitals and excitation energies for the first and second excited state of selected chlorophyll pairs in PS I at the QM( $\omega$ B97X-D4/def2-TZVP)/MM level (isovalue: 0.02). The name above the figures refers to the chlorophyll, on which the excitation is localized. Numbers next to the arrows denote the singular value of the transition.



#### C.2.8 Excitonic Red-Shift of the Triad B31-B32-B33

Figure C.20: Natural transition orbitals for the  $Q_y$  states of the triad B31-B32-B33 in PS I at the QM( $\omega$ B97X-D4/def2-TZVP)/MM level (isovalue: 0.02). Numbers next to the arrows denote the weight of the transition. In the left column the entire triad was treated quantum mechanically, in the right column only one of the monomers was included in the QM region. The resulting difference in the excitation energies can be attributed to excitonic coupling including both shortand long-range effects. The results show that the excited states remain localized on one of the monomers (cf. also fig. C.19) and that excitonic coupling shifts the collective absorption band of this chlorophyll triad further to the red.

### C.2.9 Exciton Energies and Fluctuations

**Table C.9:** Mean exciton energies and chlorophyll contributions to each exciton. Chlorophylls were assigned to an exciton domain if their weight  $w_i$  in the excitonic wave function was larger than 0.1. Contribution coefficients  $c_i$  of each chlorophyll to the respective exciton are also provided. Table rows are sorted in ascending order by the exciton energy  $E_{\text{exc}}$ . The column *ID* (*MD*) refers to the residue ID used in our MD simulations, while *Name* denotes the standard residue numbering scheme in PS I<sup>[244,255]</sup> and *ID* (*x-ray*) is the residue ID used in the crystal structure PDB (1JB0).<sup>[244]</sup>

Exciton	$E_{ m exc} \; [{ m eV}]$	name	ID (MD)	ID (x-ray)	$w_i$	$c_i$
0	1.828 042	B31 B32 B33	$2416 \\ 2417 \\ 2418$	1231 1232 1233	$\begin{array}{c} 0.195118\\ 0.649384\\ 0.152557\end{array}$	$-0.441721\\0.805844\\-0.390586$
1	1.848 102	B22	2407	1222	0.932454	-0.965636
2	1.855110	A32 B7	2371 2392	$     \begin{array}{r}       1132 \\       1207     \end{array} $	$\begin{array}{c} 0.300483 \\ 0.637277 \end{array}$	$\begin{array}{c} 0.548163 \\ -0.798296 \end{array}$
3	1.855323	eC-A1 eC-B1	$2337 \\ 2383$	$\begin{array}{c} 1011 \\ 1021 \end{array}$	$\begin{array}{c} 0.494504 \\ 0.378447 \end{array}$	$-0.703210\\0.615181$
4	1.857625	A18 A10	$2357 \\ 2349$	$\begin{array}{c} 1118\\1110\end{array}$	$\begin{array}{c} 0.140398 \\ 0.798581 \end{array}$	$-0.374697\\0.893634$
5	1.858 303	A14 A12	$2353 \\ 2351$	$\begin{array}{c} 1114\\ 1112 \end{array}$	$\begin{array}{c} 0.442904 \\ 0.527440 \end{array}$	$\begin{array}{c} 0.665511 \\ -0.726251 \end{array}$
6	1.861035	K1 A34 A33	$2427 \\ 2373 \\ 2372$	$1401 \\ 1134 \\ 1133$	$\begin{array}{c} 0.243838 \\ 0.503734 \\ 0.146774 \end{array}$	$\begin{array}{c} -0.493799\\ 0.709742\\ -0.383111\end{array}$
7	1.861079	B4 B5	$2389 \\ 2390$	$1204 \\ 1205$	$\begin{array}{c} 0.100653 \\ 0.716660 \end{array}$	$-0.317259\\0.846557$
8	1.863934	A35	2374	1135	0.760822	0.872251
9	1.866 067	B19 B18	$\begin{array}{c} 2404 \\ 2403 \end{array}$	1219 1218	$\begin{array}{c} 0.217122 \\ 0.698064 \end{array}$	$-0.465964\\0.835502$
10	1.867530	A21 A20	$2360 \\ 2359$	$     1121 \\     1120   $	$\begin{array}{c} 0.178706 \\ 0.778045 \end{array}$	$\begin{array}{r} 0.422736 \\ -0.882069 \end{array}$
11	1.868 081	A27 A26	$\begin{array}{c} 2366\\ 2365 \end{array}$	$1127 \\ 1126$	$\begin{array}{c} 0.613017 \\ 0.333531 \end{array}$	$\begin{array}{c} 0.782954 \\ -0.577521 \end{array}$
12	1.868466	B1	2386	1201	0.878091	0.937065
13	1.870 030	B24 B25	$\begin{array}{c} 2409 \\ 2410 \end{array}$	$1224 \\ 1225$	$\begin{array}{c} 0.661983 \\ 0.178490 \end{array}$	$\begin{array}{r} 0.813623 \\ -0.422481 \end{array}$
14	1.870 608	A38 A39	$2377 \\ 2378$	$     1138 \\     1139 $	$\begin{array}{c} 0.365919 \\ 0.581874 \end{array}$	$\begin{array}{c} 0.604912 \\ -0.762807 \end{array}$
15	1.871 598	B37 B38	$2380 \\ 2422$	1237 1238	$\begin{array}{c} 0.357380 \\ 0.596142 \end{array}$	$-0.597813\\0.772102$
16	1.874623	B29 B30	$2414 \\ 2415$	$1229 \\ 1230$	$\begin{array}{c} 0.152928 \\ 0.769399 \end{array}$	$-0.391060\ 0.877154$
17	1.875 401	A15 A28 A3	$2354 \\ 2367 \\ 2342$	$1115 \\ 1128 \\ 1103$	$\begin{array}{c} 0.255024 \\ 0.182773 \\ 0.362707 \end{array}$	$\begin{array}{r} 0.504999 \\ -0.427519 \\ 0.602252 \end{array}$
18	1.875542	K1 A3 A15 A28	$2427 \\ 2342 \\ 2354 \\ 2367$	$1401 \\ 1103 \\ 1115 \\ 1128$	$\begin{array}{c} 0.123142\\ 0.244751\\ 0.376818\\ 0.122904 \end{array}$	$\begin{array}{r} 0.350916\\ 0.494723\\ -0.613855\\ -0.350577\end{array}$
19	1.876628	B20 B21	$2405 \\ 2406$	$1220 \\ 1221$	$\begin{array}{c} 0.161884 \\ 0.708178 \end{array}$	$-0.402348\\0.841533$

continued on next page

Exciton	$E_{\rm exc}$ [eV]	name	ID (MD)	ID (x-ray)	$w_i$	$c_i$
20	1 879 461	PL1	2382	1801	0.280.999	0.530.093
20	1.015401	A37	2376	1137	0.189624	0.435459
		A36	2375	1136	0.165709	-0.407074
21	1 880 295	eC-A2	2338	1022	0 146 223	-0.382391
	1.000 200	PL1	2382	1801	0.567957	0.753629
	1 880 905	eC-B3	2385	1023	0 103 896	0 322 330
22	1.000 505	eC-A2	2338	1023	0.300 868	-0.548514
		A25	2364	1125	0.164430	0.405500
		A16	2355	1116	0.135008	-0.367435
23	1.882831	eC-B2	2384	1012	0.540912	-0.735467
		eC-A3	2339	1013	0.163749	0.404659
24	1.884245	eC-A2	2338	1022	0.160273	-0.400342
		A36	2375	1136	0.165179	-0.406422
		A37	2376	1137	0.173 057	0.416 001
		A16	2355	1116	0.138346	0.371 949
25	1.884562	B33	2418	1233	0.355979	-0.596640
		B31	2416	1231	0.382522	0.618484
		B23	2408	1223	0.106 091	-0.325716
26	1.885946	B13	2398	1213	0.852941	-0.923548
27	1.886643	A28	2367	1128	0.219895	0.468930
		A2	2341	1102	0.177815	-0.421681
		A5	2344	1105	0.109066	0.330252
		A6	2345	1106	0.263407	-0.513231
		J2	2425	1302	0.121208	-0.348149
28	1.887070	J2	2425	1302	0.132203	-0.363597
		A2	2341	1102	0.159052	0.398 813
		A0 128	$2345 \\ 2367$	1100	0.195989	-0.442706 0.535082
	1 997657	D97	2307	1997	0.200.012	0.729.209
29	1.007.007	D21	0200	1227	0.040202	-0.730 390
	1.888 189	B4	2389	1204	0.005488	0.778131
31	1.888 801	B35 B36	2420 2421	1235	0.364311 0.165751	0.603582 0.407125
		D30	2421	1230	0.105751	-0.407 125
32	1.890070	J2 46	2425 2345	$1302 \\ 1106$	0.697440 0.216526	-0.835129 0.465323
		AU	2040	1100	0.210 520	0.403 323
33	1.890 081	B26	2411	1226	0.334362	-0.578240
		B2 B10	2387 2395	1202	0.191483 0.132953	0.437587 -0.364627
	1 000 700	D	2000	1210	0.112 200	0.9491021
34	1.890788	B8 B0	2393	1208	0.117774	-0.343182 0 747153
		B17	$2394 \\ 2402$	$1209 \\ 1217$	0.338238 0.209701	-0.457931
25	1 201 450	1.21	2270	1191	0.421.046	0.656.541
- 20	1.891 430	L3	2370 2430	$1151 \\ 1503$	0.431040 0.234599	-0.050541 0.484354
	1 001 000	 	0491	1000	0.682.020	0.996.200
30	1.691 925	B26	2431 2411	1226	0.082920 0.138329	-0.820390 0.371927
37	1 802 607	A 17	2256	1117	0.274.275	0 522 712
51	1.092 097	A24	∠350 2363	1194	0.214210 0 114487	-0.323713 -0.338350
		A26	2365	1126	0.229358	0.478914
38	1.893645	L3	2430	1503	0.676789	0.822672
30	1 893 818	A19	2358	1119	0 427 088	0 653 520
00	1.000.010	A8	2347	1108	0.307 000	-0.554076
40	1.893838	B8	2393	1208	0.158 821	-0.398523
		B19	2404	1219	0.128308	-0.358202
		B26	2411	1226	0.139354	-0.373302
		B20	2405	1220	0.142135	0.377008

Table C.9: continued.

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Exciton	$E_{\rm exc} \; [{\rm eV}]$	name	ID (MD)	ID (x-ray)	$w_i$	$c_i$
41	1.893865	B20	2405	1220	0.111430	-0.333811
		B8	2393	1208	0.287124	-0.535839
		M1	2431	1601	0.121646	-0.348778
		B10	2395	1210	0.131978	0.363288
42	1.894098	A8	2347	1108	0.557365	0.746569
		A19	2358	1119	0.197224	0.444099
		A23	2362	1123	0.103607	-0.321880
43	1.895421	B23	2408	1223	0.118736	0.344581
		B14	2399	1214	0.240402	-0.490308
		B15	2400	1215	0.173575	0.416623
		B34	2419	1234	0.113378	-0.336717
44	1.896178	A4	2343	1104	0.268726	-0.518388
		A3	2342	1103	0.129138	0.359358
		A9 A9	2348	1109	0.101082 0.227640	-0.318870
		AZ	2341	1102	0.337 040	0.381 008
45	1.897241	A33	2372	1133	0.190437	0.436 391
		A2(	2300	1127	0.153116	0.391301
		A26	2365	1120	0.249 558	0.499 558
46	1.898247	B10	2395	1210	0.100942	-0.317713
		A1	2340	1101	0.232190	0.481 861
		A38	2377	1138	0.132243	-0.363 653
47	1.898388	B10	2395	1210	0.136873	-0.369964
		A1 A38	$2340 \\ 2377$	1101 1138	0.310317 0.178030	-0.557061 0.421936
	1 909 704	100	2011	1100	0.110 554	0.121 990
48	1.898794	A24 B10	2303	$1124 \\ 1210$	0.118554 0.101067	0.344317 0.317910
	1 000 001	D10	2000	1210	0.100.005	0.917.910
49	1.898 831	B10	2395	1210	0.126 285	-0.355366
50	1.899570	A30	2369	1130	0.464012	-0.681184
		A29	2368	1129	0.232 011	0.481676
		K2	2381	1402	0.109151	0.330380
51	1.899850	K2	2381	1402	0.726171	0.852157
52	1.900646	B30	2415	1230	0.109560	0.330999
		J1	2424	1301	0.101269	-0.318228
		B29	2414	1229	0.600378	0.774 840
53	1.903487	B19	2404	1219	0.260007	0.509908
		B16	2401	1216	0.240773	-0.490687
		B20	2405	1220	0.235371	0.485151
		A13	2352	1113	0.128 478	-0.358438
54	1.903513	A13	2352	1113	0.729275	-0.853976
55	1.903947	L1	2428	1501	0.597210	0.772793
		L2	2429	1502	0.337425	-0.580883
56	1.904647	A36	2375	1136	0.106929	-0.327000
		A24	2363	1124	0.101461	0.318529
		A17	2356	1117	0.214894	-0.463566
		A25	2364	1125	0.111551	0.333 992
57	1.904731	B25	2410	1225	0.149997	0.387294
		B12	2397	1212	0.413936	0.643379
		B11	2396	1211	0.135412	-0.367984
58	1.905707	B25	2410	1225	0.235655	0.485443
		B14	2399	1214	0.105429	-0.324698
		B12	2397	1212	0.392341	-0.626371
59	1.906036	A22	2361	1122	0.107270	-0.327520
		J3	2426	1303	0.116709	-0.341628
		A19	2358	1119	0.104776	0.323691
		A23	2302	1123	0.484 (01	0.096204

Table C.9: continued.

Exciton	$E_{\rm org}$ [eV]	name	ID (MD)	ID (x-rav)	117:	C:
60	1 006 002	12	2/26	1303	0.823.700	0.007.620
	1.900 095	10	2420	1303	0.823790	0.907 029
61	1.907 203	A9 A4	$\begin{array}{c} 2348 \\ 2343 \end{array}$	$\frac{1109}{1104}$	0.664706 0.174504	$0.815295 \\ -0.417737$
62	1.908090	A38	2377	1138	0.222040	-0.471211
		A39	$2378 \\ 2340$	$1139 \\ 1101$	0.234728	-0.484487 0 531 822
	1.000 550	AI	2340	1101	0.202.000	-0.331 822
63	1.908 553	A31 B6	2370 2391	1131 1206	0.119445 0.346391	0.345608 -0.588550
		L1	2428	1501	0.101 030	-0.317852
64	1.909289	A5	2344	1105	0.459890	-0.678152
		A7	2346	1107	0.142323	0.377257
		A9	2348	1109	0.137 955	0.371422
65	1.909864	B11 X1	$2396 \\ 2432$	$1211 \\ 1701$	$0.119742 \\ 0.205180$	0.346038 0.543313
		B35	2432 2420	1235	0.295189 0.226218	-0.475624
		B36	2421	1236	0.101370	-0.318387
66	1.911168	L2	2429	1502	0.417685	-0.646285
		B39	2423	1239	0.199829	-0.447022
	1.010.101	Da	2428	1301	0.204 595	-0.432 320
67	1.912181	B0 B30	2391 2423	1206	0.135390 0.277248	0.367954 0.526544
		B2	2387	1202	0.1217210 0.121776	-0.348964
68	1.912666	B39	2423	1239	0.155128	0.393862
		B11	2396	1211	0.337936	-0.581323
69	1.914460	B11	2396	1211	0.130986	-0.361920
		B3 D10	2388	1203	0.145256	0.381125
		B10 B2	$2395 \\ 2387$	1210	0.113752 0.243389	-0.493345
70	1.915 101	A21	2360	1121	0.289830	0.538359
		A18	2357	1118	0.156792	-0.395970
		A22	2361	1122	0.214854	-0.463523
71	1.916 105	A18	2357	1118	0.285 880	0.534678
72	1.916 961	A18	2357	1118	0.265878	0.515634
73	1.918735	$\begin{array}{c} \mathrm{B37}\\\mathrm{B38}\end{array}$	$\begin{array}{c} 2380 \\ 2422 \end{array}$	$\begin{array}{c} 1237 \\ 1238 \end{array}$	$\begin{array}{c} 0.349259 \\ 0.220158 \end{array}$	$\begin{array}{c} 0.590981 \\ 0.469210 \end{array}$
74	1.919690	A4	2343	1104	0.135612	0.368256
		A40	2379	$1140 \\ 1013$	0.289933 0.100.786	-0.538454 0436701
	1 001 197	-C A2	2009	1013	0.1207077	0.400 850
(5	1.921 137	eC-A3 A4	2339 2343	1013 1104	0.167977 0.116551	-0.341395
77	1.921671	B15 B16	$2400 \\ 2401$	$1215 \\ 1216$	$0.139387\ 0.218466$	$0.373346 \\ -0.467404$
78	1 923 /0/	 A14	2353	1114	0.290.541	0.530.010
	1.525454	A12	2351	1114	0.259554	0.509465
79	1.924126	B16	2401	1216	0.121 233	0.348 186
		A1 B23	2432 2408	1701 1223	$0.202728 \\ 0.153157$	0.450253 -0.391.352
		B20 B34	2419	1234	0.171598	-0.414244
80	1.924600	J1	2424	1301	0.540084	-0.734904
81	1.925327	B31	2416	1231	0.103011	-0.320953
		B15 B16	2400 2401	1215 1916	0.148255 0.162.030	0.385039 0.402540
		B32	2417	1232	0.102009 0.121666	-0.348806
		B33	2418	1233	0.123588	-0.351551

Table C.9: continued.

		IC		munucu.		
Exciton	$E_{ m exc} \; [{ m eV}]$	name	ID (MD)	ID (x-ray)	$w_i$	$c_i$
82	1.926 194	A29 B39 eC-B3	$2368 \\ 2423 \\ 2385$	$1129 \\ 1239 \\ 1023$	$\begin{array}{c} 0.180379 \\ 0.114209 \\ 0.292771 \end{array}$	$\begin{array}{r} 0.424710 \\ -0.337949 \\ -0.541083 \end{array}$
83	1.928196	A40	2379	1140	0.212333	-0.460796
84	1.929014	A40 eC-B3	$2379 \\ 2385$	$\begin{array}{c} 1140 \\ 1023 \end{array}$	$\begin{array}{c} 0.195152 \\ 0.108588 \end{array}$	$-0.441760\\-0.329527$
85	1.932087	A11 B28	$2350 \\ 2413$	1111 1228	$\begin{array}{c} 0.236406 \\ 0.166345 \end{array}$	$-0.486216\\-0.407854$
86	1.932273	A11 B36	$2350 \\ 2421$	1111     1236	$\begin{array}{c} 0.156550 \\ 0.133267 \end{array}$	$\begin{array}{r} -0.395664 \\ -0.365057 \end{array}$
87	1.934053	A7 B3 B17	$2346 \\ 2388 \\ 2402$	$1107 \\ 1203 \\ 1217$	$\begin{array}{c} 0.100599\\ 0.243536\\ 0.103352 \end{array}$	$\begin{array}{r} 0.317173 \\ -0.493494 \\ 0.321484 \end{array}$
88	1.934916	B17 B3	2402 2388	$1217 \\ 1203$	$\begin{array}{c} 0.123412 \\ 0.174263 \end{array}$	$\begin{array}{c} 0.351300 \\ -0.417448 \end{array}$
89	1.937186	A22	2361	1122	0.124780	-0.353243
90	1.938129	B17	2402	1217	0.214266	0.462889
91	1.939676	B17 B3	$\begin{array}{c} 2402 \\ 2388 \end{array}$	$1217 \\ 1203$	$\begin{array}{c} 0.136998\\ 0.131734 \end{array}$	$\begin{array}{c} 0.370132 \\ 0.362952 \end{array}$
92	1.940546	B28	2413	1228	0.362478	-0.602061
93	1.947943	eC-B1	2383	1021	0.117403	-0.342641
94	1.954418	eC-A1 eC-B1	2337 2383	$\begin{array}{c} 1011 \\ 1021 \end{array}$	$\begin{array}{c} 0.206972 \\ 0.264167 \end{array}$	$\begin{array}{c} 0.454942 \\ 0.513972 \end{array}$
95	1.962741	B23 B31	$2408 \\ 2416$	$1223 \\ 1231$	$0.270108 \\ 0.131710$	$-0.519719 \\ -0.362919$

Table C.9: continued.



Figure C.21: Exciton energies in three selected MD frames, analogous to Fig. 8 of the main article. Each dot signifies a chlorophyll and is colored by the lowest energy exciton domain that this chlorophyll belongs to  $(w_i > 0.1)$ . Connecting lines represent the coupling strength  $(V_{ij} > 1 \text{ meV})$  with thicker lines denoting stronger coupling. The energy axis is centered around the mean of all exciton energies.

# C.3 Intermonomer Coupling in Photosystem I

	Donor			Accepto	r		
Name	ID (MD)	ID (x-ray)	Name	ID (MD)	ID (x-ray)	r [Å]	$V_{ij}~[{ m eV}]$
A21	2360	1121	B8	4854	1208	19.7	0.001139
A21	2360	1121	M1	4892	1601	22.8	0.001037
A22	2361	1122	M1	4892	1601	21.0	0.001722
A29	2368	1129	M1	4892	1601	15.0	0.001138
A30	2369	1130	M1	4892	1601	13.9	0.005855
A37	2376	1137	M1	4892	1601	18.6	0.001929
B37	2380	1237	L1	7350	1501	26.8	0.001185
PL1	2382	1801	B8	4854	1208	16.4	0.002887
PL1	2382	1801	M1	4892	1601	11.8	0.002417
B8	2393	1208	A20	7281	1120	23.8	0.001097
B8	2393	1208	A21	7282	1121	18.6	0.001856
B8	2393	1208	PL1	7304	1801	15.7	0.003226
B11	2396	1211	A33	7294	1133	26.8	0.001091
B38	2422	1238	L1	7350	1501	22.7	0.001197
L1	2428	1501	B37	4841	1237	26.8	0.001172
L1	2428	1501	B38	4883	1238	22.9	0.001105
M1	2431	1601	A21	7282	1121	24.1	0.001147
M1	2431	1601	A22	7283	1122	21.7	0.001728
M1	2431	1601	A29	7290	1129	15.1	0.001153
M1	2431	1601	A30	7291	1130	13.6	0.005724
M1	2431	1601	A37	7298	1137	17.7	0.001871
M1	2431	1601	PL1	7304	1801	13.3	0.001815
M1	2431	1601	L1	7350	1501	23.5	0.001074
A20	4820	1120	B8	7315	1208	23.0	0.001738
A21	4821	1121	B8	7315	1208	19.0	0.002042
A21	4821	1121	M1	7353	1601	24.7	0.001520
A22	4822	1122	M1	7353	1601	21.9	0.001934
A29	4829	1129	M1	7353	1601	14.9	0.001478
A30	4830	1130	M1	7353	1601	13.0	0.004265
A33	4833	1133	B11	7318	1211	27.2	0.001121
A34	4834	1134	B11	7318	1211	19.9	0.001211
A37	4837	1137	M1	7353	1601	18.5	0.001047
PL1	4843	1801	B8	7315	1208	16.5	0.002708
PL1	4843	1801	B9	7316	1209	25.2	0.001029
PL1	4843	1801	M1	7353	1601	13.4	0.002020
L1	4889	1501	B37	7302	1237	26.8	0.001182
L1	4889	1501	B38	7344	1238	22.5	0.001217
L1	4889	1501	M1	7353	1601	23.1	0.001479

Table C.10: Chlorophylls contributing to intermonomer coupling in PS I. Only values larger than 1 meV are printed.

# C.4 Stabilizing Photosystem I in a MOF

The supporting information to the article "Molecular Interactions of Photosystem I and ZIF-8 in Bio-Nanohybrid Materials" was published 2024 in *Phys. Chem. Chem. Phys.* and is available at https://doi.org/10.1039/d4cp03021d. It is reprinted in full below; Parameter files for the Gromacs port of *nb-ZIF-FF* are available at https://doi.org/10.5281/zenodo. 12546403, raw and processed data used in this work are available at https://doi.org/10.5281/zenodo. 5281/zenodo.13120983.

#### C.4.1 Gromacs Port of nb-ZIF-FF

nb-ZIF-FF models the interactions between the ZIF-8 building blocks as non-bonded interactions between dummy atoms (figure C.22). The general form of the force field is given by eq. (C.1). For bonds,  $k_b$  describes the bond stretching constant, b the bond length and  $b_0$  the equilibrium bond length. Valence angles are described by the sum of a harmonic potential and a Urey-Bradley term, where  $k_{\theta}$  is the harmonic force constant,  $\theta$  is the angle and  $\theta_0$  denotes the equilibrium angle. Analogously,  $k_{UB}$  denotes the Urey-Bradley force constant, r the 1–3 distance and  $r_0$  the equilibrium 1–3 distance. Dihedral angles are modeled by periodic cosine potentials, where  $k_{\phi}$  is the force constant,  $\phi$  is the dihedral, nis the frequency of the cosine and, in the case of torsions, d denotes the phase. Non-bonded dispersive interactions are described by Lennard-Jones (LJ) 12–6 potentials, where  $\sigma_{ij}$  is the distance at which the two-particle potential is zero,  $\epsilon_{ij}$  is the dispersion energy and  $r_{ij}$ is the distance between two particles. Electrostatic interactions are described by Coulomb potentials, where  $q_i$  and  $q_j$  are the partial charges of the interacting particles and  $\varepsilon_0$  denotes the electric field constant.

$$E = \sum_{bonds} k_b (b - b_0)^2 +$$

$$\sum_{angles} k_\theta (\theta - \theta_0)^2 + k_{UB} (r - r_0)^2 +$$

$$\sum_{torsions} k_\phi [1 + \cos(n\phi - d)] +$$

$$\sum_{impropers} k_\phi [1 - \cos(n\phi)] +$$

$$\sum_{i} \sum_{j=i+1}^N \left( 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \right)$$
(C.1)



**Figure C.22:** Scheme of the cationic and anionic dummy-atom models for Zn<sup>2+</sup> and MIm<sup>-</sup> (gray: C, blue: N, white: H, purple: Zn, orange: Zn dummy atoms, pink: N dummy atoms).<sup>[359]</sup>

The original implementation of nb-ZIF-FF is published for use with LAMMPS,<sup>[359,360]</sup> but the calculations in the present work were conducted with *Gromacs*, which uses a different system of units. Therefore, the force constants were converted using the conversion factors provided in table C.11. The ported force field parameter files are openly available at https://doi.org/10.5281/zenodo.12546403

s used for both	dihedrals and in	mproper dih	edrals.	
$\mathbf{Type}$	Parameter	Factor	LAMMPS	Gromacs
Bonded	$b_0$	0.1	Å	nm
	$r_{13}$	0.1	Å	nm
	$k_b$	836.8	$0.5 \text{ kcal mol}^{-1} \text{ Å}^{-2}$	$kJ \mathrm{mol}^{-1} \mathrm{nm}^{-2}$
	$k_{UB}$	836.8	$0.5 \text{ kcal mol}^{-1} \text{\AA}^{-2}$	$kJ \mathrm{mol}^{-1} \mathrm{nm}^{-2}$
	$k_{ heta}$	8.368	$0.5 \text{ kcal mol}^{-1} \text{ rad}^{-2}$	$kJ \mathrm{mol}^{-1} \mathrm{rad}^{-2}$
	$k_{\phi}$	4.184	$ m kcalmol^{-1}$	${ m kJmol^{-1}}$
Non-bonded	$\sigma$	0.1	Å	nm
	$\epsilon$	96.4869	eV	${ m kJmol^{-1}}$

Table C.11: Conversion factors used to convert the nb-ZIF-FF force-field parameters from LAMMPS format (source file forcefield.lmp) into Gromacs format. The units were converted by multiplication with the corresponding conversion factor. The same conversion factor was used for both dihedrals and improper dihedrals.

In the original implementation, the interactions between  $\text{Zn}^{2+}$  and  $\text{MIm}^-$  are modeled by a Morse potential, which is not available in *Gromacs*. Simple application of the Lorentz-Berthelot mixing rules to the  $\sigma_{ij}$  and  $\epsilon_{ij}$  parameters of the two atom types does not fit the original Morse potential well (figure C.23). Therefore, a custom 12–6-LJ potential was fitted to describe the  $\text{Zn}^{2+}/\text{MIm}^-$  interaction, resulting in the following parameters:

$$\sigma_{ij} = 0.2442 \,\mathrm{nm}$$
  
$$\epsilon_{ij} = 0.1678 \,\mathrm{kJ} \,\mathrm{mol}^{-1}.$$



**Figure C.23:** Fit of the non-bonded interactions between  $\text{Zn}^{2+}$  and  $\text{MIm}^-$  in nb-ZIF-FF with a LJ potential. For comparison, the LJ potential resulting from application of the Lorentz-Berthelot mixing rules to the original  $\sigma$  and  $\epsilon$  parameters is also shown.

Moreover, 1–4 Coulomb interactions are scaled by a factor of 0.6874 in the original force field.<sup>[359]</sup> However, the PS I model<sup>[361]</sup> employs a scaling factor of 0.8333, compatible with the Amber force field. As the main interest of this work is in the photosystem we retained and used the factor of 0.8333 in all simulations.

To validate the ported force field, we performed a series of MD simulations on ZIF-8 in various environments and compared the results to the original work.<sup>[359]</sup> All of these control simulations were conducted with the leap-frog integrator, using a time step of 0.5 fs and constraining bonds to hydrogen atoms with the LINCS algorithm.<sup>[362]</sup> Short-range interactions were evaluated with Verlet lists,<sup>[363]</sup> using a cutoff of 1.4 nm (in methanol) or 1.2 nm (in water), while the smooth particle-mesh Ewald scheme<sup>[364,365]</sup> was used for long-range interactions with a Fourier grid spacing of 0.16 nm and fourth-order interpolation.

In analogy to the reference work,<sup>[359]</sup> we first set up a solution of the ZIF-8 building blocks in methanol, describing the solvent with the TraPPE force field.<sup>[366]</sup> The cubic simulation box had an edge length of 4.6 nm and contained 125 Zn<sup>2+</sup> ions, 250 MIm<sup>-</sup> ions and 825 methanol molecules. The energy of the system was minimized until the maximum force was below 1000 kJ mol<sup>-1</sup> nm<sup>-1</sup> and the system was equilibrated in two phases: First, the temperature was annealed from 10 K to 300 K over 1 ns and propagated for another 200 ps in an NVT ensemble controlled by the V-rescale thermostat<sup>[367]</sup> using a time constant  $\tau_T$  of 0.1 ps. Subsequently, the pressure was equilibrated to 1 bar in an NPT ensemble controlled by the Berendsen barostat,<sup>[368]</sup> using a time constant  $\tau_p$  of 2.5 ps and an isothermal compressibility of  $6.02 \times 10^{-5}$  bar<sup>-1</sup> for methanol,<sup>[369]</sup> while keeping the thermostat settings from the previous step. The production MD was conducted for 15 ns in the same NPT ensemble, while raising the temperature from 300 K to the 400 K discussed in the reference work<sup>[359]</sup> within the first 1.5 ns. From figure C.24 it is obvious that the methanol solution of Zn<sup>2+</sup> and MIm<sup>-</sup> ions undergoes spontaneous self-assembly and forms an amorphous phase, just like with the original force field.<sup>[359]</sup>



**Figure C.24:** Control MD simulation of ZIF-8 building blocks in methanol. Starting from the initial configuration before equilibration (left), the building blocks undergo self-assembly to form an amorphous phase (right). H-atoms omitted for clarity.

Next, we set up two ZIF-8 crystals, solvated in methanol and in water, respectively. The cubic simulation boxes had an edge length of 3.63 nm (methanol) and 3.44 nm (water) after equilibration and contained 96  $\text{Zn}^{2+}$  ions, 192 MIm<sup>-</sup> ions and 379 (methanol) or 541 (water) solvent molecules. Both were equilibrated according to the same protocol: First, the energy was minimized until the maximum force was below  $1000 \,\mathrm{kJ}\,\mathrm{mol}^{-1}\,\mathrm{nm}^{-1}$ . Next, the temperature was raised from 10 K to 300 K over 2 ns in an NVT ensemble, controlled by the V-rescale thermostat<sup>[367]</sup> ( $\tau_T = 0.1 \,\mathrm{ps}$ ). The system was propagated in the same ensemble at constant temperature for another 1 ns. In the second step, the system was equilibrated for 2 ns in an NPT ensemble at 1 bar, controlled by the Berendsen barostat<sup>[368]</sup>  $(\tau_p = 2.5 \,\mathrm{ps})$ . The isothermal compressibility was set to  $6.02 \times 10^{-5} \,\mathrm{bar}^{-1}$  for methanol<sup>[369]</sup> and  $4.5 \times 10^{-5}$  bar<sup>-1</sup> for water.<sup>[370]</sup> The temperature was kept stable at 300 K using the same settings as before. Production MD simulations were conducted for 1 ns in the same ensemble. The  $Zn^{2+}-Zn^{2+}$  radial distribution function (RDF) were evaluated in both simulations (figure C.25) and found to agree well with that of the original force field implementation<sup>[359]</sup> and an experimentally determined<sup>[371]</sup> RDF. For comparison, figure C.25 also depicts the RDF for the PS I@ZIF-8 simulation, which also agrees well with the reference.



**Figure C.25:** Normalized Zn<sup>2+</sup>-Zn<sup>2+</sup> radial distribution function in various control simulations compared to literature values.<sup>[359,371]</sup> Satellite peaks in the experimentally determined RDF are most likely due to defects in the crystal structure. The RDF from the present work is averaged over the entire trajectory and thus smoother than the calculated reference RDF.

### C.4.2 Structural Changes of PS I in Water



**Figure C.26:** RMSD of key PS I components in water.  $C_{\alpha}$ : Protein backbone, CLA: chlorophyll *a*, BCR:  $\beta$ -carotene, PQN: phylloquinone. The jump in the  $\beta$ -carotene RMSD at 32 ns is due to the reorientation of a peripheral carotenoid, as shown on the right, where the motion of the carotenoids over 100 ns is illustrated with respect to the first frame of the trajectory (view from the stromal side).

#### C.4.3 MD of PS I in Solution with MImH and MImH<sub>2</sub><sup>+</sup>

To investigate the effects of the linker alone, without  $\text{Zn}^{2+}$  ions, we performed an MD simulation and investigated the coordination of the chlorophylls. To this end, the PS I model was placed in a triclinic box with dimensions  $23 \times 23 \times 18$  nm and solvated by 297 327 water molecules. The pKa values of 2-methylimidazole are 7.7 (MImH<sub>2</sub><sup>+</sup>/MImH) and 14.7 (MImH/MIm<sup>-</sup>), so that the concentration of MIm<sup>-</sup> in a buffered solution around pH 9 is negligible. Thus, water molecules were randomly replaced by 4300 MImH molecules and 4300 MImH<sub>2</sub><sup>+</sup> ions.

Parameters for MImH and MImH<sub>2</sub><sup>+</sup> were generated with *antechamber*<sup>[372]</sup> using the GAFF2 force field.<sup>[373]</sup> Charge neutralization was achieved by adding 4285 Cl<sup>-</sup> ions. The final system contained 900 460 atoms and was equilibrated using the same protocol as for the MD in amorphous ZIF-8, described in the main article. A production simulation was carried out for 100 ns. Even though the MImH<sub>2</sub><sup>+</sup> cation is over-represented in the simulation, it does expectedly not coordinate to the also positively charged chlorophyll centers. In contrast, the neutral MImH coordinates often to the Mg<sup>2+</sup> ions of the peripheral chlorophylls in PS I (figure C.27). Neither MImH, nor MImH<sub>2</sub><sup>+</sup> induce a CT to the chlorophylls, as shown in appendix C.4.5.



Figure C.27: Coordination of chlorophylls by ZIF-8 building blocks at neutral pH. Coordination is defined as any ligand atom closer than 4.0 Å to the respective Mg<sup>2+</sup> ion. Labels denote chlorophylls which are coordinated for more than 40% of the trajectory.



### C.4.4 Further Structural Analysis of PS I@ZIF-8

**Figure C.28:** Coordination of chlorophylls by MIm<sup>-</sup> residues over the course of the PS I@ZIF-8 trajectory inside the ZIF-8 crystal (left) and in amorphous ZIF-8 (right). Coordination is defined as any ligand atom closer than 4.0 Å to the respective Mg<sup>2+</sup> ion. Labels denote chlorophylls which are coordinated for more than 40% of the trajectory.



Figure C.29: Difference in the N-terminal loop orientations of chain K (right) and F (top) over the course of the 100 ns trajectories of PS I in amorphous ZIF-8 (red) compared to PS I in water (blue). View from the lumenal side.



**Figure C.30:** Permeation of the protein matrix by  $Zn^{2+}$  (magenta) and MIm<sup>-</sup> (yellow) ions during the 100 ns trajectory of PS I in amorphous ZIF-8.  $Zn^{2+}$  and MIm<sup>-</sup> positions are accumulated over all time steps in this illustration. (a) View from the stromal side and (b) rotated by 90° around x with respect to (a).

### C.4.5 Excited States

# Neutral and anionic chlorophyll a

state	$\Delta E \; [\mathrm{eV}]$	f	CI weight	CI transition
$S_1$	1.97	0.3495	0.731	$\pi_1 \to \pi_1^*$
$S_2$	2.22	0.0337	0.574	$\pi_2 \to \pi_1^*$
			0.247	$\pi_1 \to \pi_2^*$
$S_3$	3.07	0.0667	0.693	$\pi_3 \to \pi_1^*$
$S_4$	3.09	0.8657	0.490	$\pi_1  o \pi_2^*$

Table C.12: Isolated Chl *a*, DFT/MRCI. The respective orbitals are illustrated in figure C.31.

**Table C.13:** Isolated Chl *a*, SCS-ωPBEPP86/def2-TZVP. The respective orbitals are illustrated in figure C.31.

state	$\Delta E \; [\mathrm{eV}]$	f	CI weight	CI transition
$S_1$	1.90	0.3018	0.765	$\pi_1 \rightarrow \pi_1^*$
$S_2$	2.17	0.0254	$0.523 \\ 0.395$	$\pi_2  ightarrow \pi_1^* \ \pi_1  ightarrow \pi_2^*$
$S_3$	3.23	0.4931	$0.211 \\ 0.400$	$\pi_1  ightarrow \pi_2^* \ \pi_4  ightarrow \pi_1^*$
$S_4$	3.33	1.3134	$0.292 \\ 0.232 \\ 0.266$	$\begin{array}{c} \pi_1 \rightarrow \pi_2^* \\ \pi_2 \rightarrow \pi_1^* \\ \pi_4 \rightarrow \pi_1^* \end{array}$
$S_5$	3.37	0.0335	0.595	$\pi_5  ightarrow \pi_1^*$
$S_6$	3.39	1.3591	0.591	$\pi_2 \to \pi_2^*$
$S_7$	3.69	0.2950	0.587	$\pi_6 \to \pi_1^*$
$S_8$	3.71	0.0047	$0.296 \\ 0.335$	$LP_O \to \pi_1^* \\ LP_O \to \pi_3^*$

state	$\Delta E \; [\mathrm{eV}]$	f	CI weight	CI transition
$S_1$	0.80	0.0376	0.767	$\pi_1^* \to \pi_2^*$
$S_2$	1.49	0.0610	0.579	$\pi_1 \to \pi_1^*$
$S_3$	1.58	0.0475	0.701	$\pi_2 \to \pi_1^*$
$S_4$	1.81	0.2095	0.526	$\pi_1^* \to \pi_3^*$

**Table C.14:** Isolated Chl  $a^-$ , DFT/MRCI. Note that the MO  $\pi_1^*$  is singly occupied and can serve as both a donor and acceptor orbital. The respective orbitals are illustrated in figure C.31.

**Table C.15:** Isolated Chl  $a^-$ , SCS- $\omega$ PBEPP86/def2-TZVP. Note that the MO  $\pi_1^*$  is singly occupied and can serve as both a donor and acceptor orbital. The respective orbitals are illustrated in figure C.31.

state	$\Delta E \; [\mathrm{eV}]$	f	CI weight	CI transition
$S_1$	1.26	0.0735	0.708	$\pi_1^* \to \pi_2^*$
$S_2$	1.69	0.0389	0.633	$\pi_1 \to \pi_1^*$
$S_3$	2.24	0.1089	0.277	$\pi_1 \to \pi_2^*$
			0.320	$\pi_2  o \pi_1^*$
$S_4$	2.25	0.1011	0.464	$\pi_1^* \to \pi_3^*$
$S_5$	2.51	0.1402	0.292	$\pi_3 \to \pi_1^*$
$S_6$	2.57	0.0749	0.230	$\pi_2 \to \pi_1^*$
$S_7$	2.78	0.0057	0.215	$\pi_1^* \to \pi_4^*$
$S_8$	2.90	0.4448	0.220	$\pi_2 \to \pi_2^*$



Figure C.31: MOs with labels as in tables C.12 to C.15 (Isovalue: 0.02).

### Chlorophyll *a* ··· Mlm<sup>-</sup> assembly

state	$\Delta E \; [\mathrm{eV}]$	f	CI weight	CI transition
$S_1$	1.94	0.2452	0.383	$\pi_1 \to \pi_1^*$
			0.370	$\pi_{\rm MIm^-,1} \to \pi_1^*$
$S_2$	1.98	0.0900	0.497	$\pi_{\rm MIm^-,1} \to \pi_1^*$
			0.329	$\pi_1  o \pi_1^*$
$S_3$	2.10	0.0483	0.643	$\pi_2 \to \pi_1^*$
$S_4$	2.74	0.0153	0.820	$\pi_{\rm MIm^-,1} \to \pi_2^*$

**Table C.16:** Chl  $a \cdots MIm^-$ , Franck-Condon point, DFT/MRCI. The respective orbitals are illustrated in figure C.32.

**Table C.17:** Chl  $a \cdots MIm^-$ , Franck-Condon point, SCS- $\omega$ PBEPP86/def2-TZVP. The respective orbitals are illustrated in figure C.32.

state	$\Delta E \; [\mathrm{eV}]$	f	CI weight	CI transition
$S_1$	1.86	0.2635	0.736	$\pi_1 \to \pi_1^*$
$S_2$	2.00	0.0362	0.566	$\pi_2 \to \pi_1^*$
			0.315	$\pi_1 \to \pi_2^*$
$S_3$	2.05	0.0013	0.966	$\pi_{\rm MIm^-,1} \to \pi_1^*$
$S_4$	2.94	0.0641	0.777	$\pi_{\rm MIm^-,1} \to \pi_2^*$
$S_5$	3.04	0.8719	0.226	$\pi_2  o \pi_1^*$
			0.498	$\pi_1 \to \pi_2^*$
$S_6$	3.10	0.8911	0.569	$\pi_2 \to \pi_2^*$
$S_7$	3.31	0.7360	0.433	$\pi_4  ightarrow \pi_1^*$
$S_8$	3.33	0.0230	0.353	$\pi_5  ightarrow \pi_1^*$

state	$\Delta E \; [\mathrm{eV}]$	f	CI weight	CI transition
$S_1$	0.53	0.0001	0.887	$\pi_{\mathrm{MIm}^-,1} \to \pi_1^*$
$S_2$	1.58	0.0003	0.820	$\pi_{\rm MIm^-,1} \to \pi_2^*$
$S_3$	1.95	0.4446	0.745	$\pi_1 \to \pi_1^*$
$S_4$	2.05	0.1285	0.711	$\pi_2 \to \pi_1^*$

**Table C.18:** Chl  $a \cdots MIm^-$ , S<sub>1</sub> minimum, DFT/MRCI. The respective orbitals are illustrated in figure C.32.

**Table C.19:** Chl  $a \cdots MIm^-$ , S<sub>1</sub> minimum, SCS- $\omega$ PBEPP86/def2-TZVP. The respective orbitals are illustrated in figure C.32.

state	$\Delta E \; [\mathrm{eV}]$	f	CI weight	CI transition
$S_1$	0.66	0.0001	0.993	$\pi_{\rm MIm^-,1} \to \pi_1^*$
$S_2$	1.83	0.0013	0.985	$\pi_{\rm MIm^-,1} \to \pi_2^*$
$S_3$	1.84	0.3467	0.765	$\pi_1  o \pi_1^*$
$S_4$	1.92	0.1197	0.693	$\pi_2  o \pi_1^*$
$S_5$	2.85	0.1368	0.745	$\pi_{\rm MIm^-,2} \to \pi_1^*$
$S_6$	2.96	0.0391	0.721	$\pi_4  ightarrow \pi_1^*$
$S_7$	3.11	0.8397	0.532	$\pi_1  o \pi_2^*$
$S_8$	3.15	0.4137	0.463	$\pi_5 \to \pi_1^*$



Figure C.32: MOs with labels as in tables C.16 to C.19. The  $\pi$ -orbitals located on the chlorophyll molecule are numbered according to figure C.31 (Isovalue: 0.02).

### Chlorophyll a · · · MImH assembly

	) /		I	
state	$\Delta E \; [\mathrm{eV}]$	f	CI weight	CI transition
$S_1$	1.98	0.3380	0.719	$\pi_1  ightarrow \pi_1^*$
$S_2$	2.18	0.0514	0.622	$\pi_2 \to \pi_1^*$
$S_3$	3.09	0.6190	0.480	$\pi_1 \to \pi_2^*$
$S_4$	3.14	0.3698	0.508	$\pi_4 \to \pi_1^*$

Table C.20: Chl  $a \cdots$  MImH, DFT/MRCI. The respective orbitals are illustrated in figure C.33.

**Table C.21:** Chl  $a \cdots$  MImH, SCS- $\omega$ PBEPP86/def2-TZVP. The respective orbitals are illustrated in figure C.33.

state	$\Delta E \; [\mathrm{eV}]$	f	CI weight	CI transition
$S_1$	1.88	0.2612	0.745	$\pi_1 \rightarrow \pi_1^*$
$S_2$	2.08	0.0386	$0.563 \\ 0.339$	$\begin{array}{c} \pi_2 \rightarrow \pi_1^* \\ \pi_1 \rightarrow \pi_2^* \end{array}$
$S_3$	3.15	0.5842	$0.327 \\ 0.265$	$\begin{array}{c} \pi_1 \rightarrow \pi_2^* \\ \pi_4 \rightarrow \pi_1^* \end{array}$
$S_4$	3.24	1.1210	0.608	$\pi_2 \to \pi_2^*$
$S_5$	3.32	0.9864	$0.221 \\ 0.363$	$\begin{array}{c} \pi_1 \rightarrow \pi_2^* \\ \pi_4 \rightarrow \pi_1^* \end{array}$
$S_6$	3.32	0.0459	0.548	$\pi_5  o \pi_1^*$
$S_7$	3.64	0.2943	0.595	$\pi_6 \to \pi_1^*$
$S_8$	3.67	0.0022	$0.289 \\ 0.297$	$LP_O \to \pi_3^*$ $LP_O \to \pi_1^*$

# Chlorophyll $a \cdots MImH_2^+$ assembly

state	$\Delta E \; [\mathrm{eV}]$	f	CI weight	CI transition
$S_1$	2.04	0.3546	0.757	$\pi_1 \rightarrow \pi_1^*$
$S_2$	2.29	0.0276	$\begin{array}{c} 0.548 \\ 0.260 \end{array}$	$\begin{array}{l} \pi_2 \rightarrow \pi_1^* \\ \pi_1 \rightarrow \pi_2^* \end{array}$
$S_3$	2.99	0.0370	0.713	$\pi_4 \to \pi_1^*$
$S_4$	3.18	0.5882	$0.323 \\ 0.176$	$\begin{array}{c} \pi_1 \to \pi_2^* \\ \pi_5 \to \pi_1^* \end{array}$

**Table C.22:** Chl  $a \cdots \text{MImH}_2^+$ , DFT/MRCI. The respective orbitals are illustrated in figure C.33.

**Table C.23:** Chl  $a \cdots \text{MImH}_2^+$ , SCS- $\omega$ PBEPP86/def2-TZVP. The respective orbitals are illustrated in figure C.33.

state	$\Delta E \; [ ext{eV}]$	f	CI weight	CI transition
$S_1$	1.89	0.2704	0.790	$\pi_1 \rightarrow \pi_1^*$
$S_2$	2.15	0.0160	0.515	$\pi_2 \to \pi_1^*$
			0.416	$\pi_1 \to \pi_2^*$
$S_3$	3.12	0.0956	0.725	$\pi_4  o \pi_1^*$
$S_4$	3.19	1.3081	0.367	$\pi_2 \to \pi_1^*$
			0.452	$\pi_1 \to \pi_2^*$
$S_5$	3.25	0.0516	0.675	$\pi_5  o \pi_1^*$
$S_6$	3.38	1.2031	0.646	$\pi_2  ightarrow \pi_2^*$
$S_7$	3.52	0.0086	0.241	$LP_O \rightarrow \pi_1^*$
			0.257	$LP_O \rightarrow \pi_3^*$
$S_8$	3.55	0.2761	0.654	$\pi_6 \to \pi_1^*$



Gouterman MOs

Figure C.33: MOs with labels as in tables C.20 to C.23. The  $\pi$ -orbitals located on the chlorophyll molecule are numbered according to figure C.31 (Isovalue: 0.02).

## C.4.6 Statistics of QM/MM Sampling

(a) CT number				(b) Energies			
coord.	samples	$\overline{\mathbf{CT}}$	$\sigma$	coord.	samples	$\Delta \overline{\mathrm{E}} \; [\mathrm{eV}]$	$\sigma \; [\mathrm{eV}]$
0	51	0.000	0.000	0	51	1.898	0.054
1	93	0.809	0.279	1	93	1.434	0.320
2	11	0.893	0.102	2	11	1.198	0.563

**Table C.24:** Mean and standard deviation  $\sigma$  among the three types of coordination in the sampled data points.

### C.4.7 Excitons in the Presence of ZIF-8

#### Comparison with Free PS I



Figure C.34: Left: Unperturbed excitonic network in PS I.<sup>[361]</sup> Right: The same network when the highlighted, frequently coordinated chlorophylls are not coupled. Each data point represents one chlorophyll, colored by the lowest-energy exciton it contributes to. Thicker lines signify stronger excitonic coupling. View from the stromal side.

#### List of Excitonic Energies and Pigment Contributions

**Table C.25:** Exciton energies and chlorophyll contributions to each exciton. Chlorophylls are assigned to an exciton domain if their weight  $w_i$  in the excitonic wavefunction is larger than 0.1. Contribution coefficients  $c_i$  of each chlorophyll to the respective exciton are also provided. Table rows are sorted in ascending order by the exciton energy  $E_{\text{exc}}$ . The column *ID* (*MD*) refers to the residue ID used in our MD simulations, while *Name* denotes the standard residue numbering scheme in PS I<sup>[244,255]</sup> and *ID* (*x-ray*) is the residue ID used in the crystal structure PDB (1JB0).<sup>[244]</sup>

Exciton	$E_{ m exc} \; [{ m eV}]$	name	ID (MD)	ID (x-ray)	$w_i$	$c_i$
0	1.828088	B31	2416	1231	0.195925	0.442634
	1.828088	B32	2417	1232	0.648848	-0.805511
	1.828088	B33	2418	1233	0.153045	0.391210
1	1.848102	B22	2407	1222	0.932374	-0.965595
2	1.854704	eC-A1	2337	1011	0.509149	0.713547
	1.854704	eC-B1	2383	1021	0.390128	-0.624602
3	1.855147	B7	2392	1207	0.650815	-0.806731
	1.855147	A32	2371	1132	0.309593	0.556411
4	1.857635	A10	2349	1110	0.799544	0.894172
	1.857635	A18	2357	1118	0.140763	-0.375183
5	1.858305	A12	2351	1112	0.528240	-0.726801
	1.858305	A14	2353	1114	0.443728	0.666129
6	1.861035	A34	2373	1134	0.505303	0.710847
	1.861 035	A33	2372	1133	0.147 228	-0.383703
	1.861 035	KI	2427	1401	0.244 595	-0.494566
7	1.861079	B4	2389	1204	0.101061	-0.317902
	1.861079	B5	2390	1205	0.718982	0.847928
8	1.863935	A35	2374	1135	0.760835	0.872259
9	1.867531	A21	2360	1121	0.178762	-0.422803
	1.867531	A20	2359	1120	0.778031	0.882061
10	1.868089	A26	2365	1126	0.333405	-0.577412
	1.868089	A27	2366	1127	0.612573	0.782670
11	1.868464	B1	2386	1201	0.877538	0.936770
12	1.870032	B25	2410	1225	0.178489	-0.422479
	1.870032	B24	2409	1224	0.661842	0.813537
13	1.870611	A38	2377	1138	0.366831	-0.605665
	1.870611	A39	2378	1139	0.581475	0.762545
14	1.871598	B38	2422	1238	0.596097	0.772073
	1.871598	B37	2380	1237	0.357361	-0.597797
15	1.874772	B30	2415	1230	0.777110	0.881539
	1.874772	B29	2414	1229	0.146486	-0.382734
16	1.875467	A15	2354	1115	0.557350	0.746559
	1.875467	K1	2427	1401	0.178492	-0.422483
17	1.875521	B21	2406	1221	0.678866	-0.823933
	1.875521	B20	2405	1220	0.227798	0.477282
18	1.875533	B18	2403	1218	1.000000	1.000000
19	1.875636	A28	2367	1128	0.279299	-0.528487
10	1.875636	A3	2342	1103	0.525045	0.724600
20	1.879495	A37	2376	1137	0.184 435	-0.429459
-0	1.879495	PL1	2382	1801	0.306 897	-0.553983
	1.879495	A36	2375	1136	0.160531	0.400664
21	1.880 347	PL1	2382	1801	0.579592	-0.761309

continued on next page
Exciton	$E_{\rm exc} [{\rm eV}]$	name	ID (MD)	ID (x-ray)	$w_i$	$c_i$
22	1 881 054	eC-A2	2338	1022	0.356157	-0.596789
	1.881054	A16	2355	1116	0.128.110	-0.357925
	1 881 054	oC B3	2385	1023	0.120110 0.122730	0.350 320
	1 881 054	A 25	2364	1025	0.151840	0.380678
	1.001 004	A20	2304	1120	0.151 649	0.369 018
23	1.882959	eC-B2	2384	1012	0.544657	-0.738009
	1.882959	eC-A3	2339	1013	0.161406	0.401753
24	1 00/ 919	A 16	0255	1116	0 191 999	0 262 225
24	1.004.012	AI0	2000	1110	0.131323 0.177744	0.302303 0.491 507
	1.004.012	eC-A2	2000	1022	0.177744	-0.421097 0.208.171
	1.004.012	A30	2373	1100	0.136340 0.166.979	-0.398171
	1.884312	A37	2370	1137	0.100 873	0.408 501
25	1.884616	B31	2416	1231	0.388471	-0.623274
	1.884616	B33	2418	1233	0.387574	0.622554
	1.000.001	1.0	00.41	1100	0 190 469	0.979.440
26	1.880.691	A2	2341	1102	0.139463	-0.373448
	1.886.691	Ab	2345	1106	0.319840	-0.565544
	1.886.691	A28	2367	1128	0.153778	0.392146
	1.886.691	J2	2425	1302	0.151 099	-0.388715
	1.886691	A5	2344	1105	0.131068	0.362033
27	1.887096	B19	2404	1219	0.167401	-0.409147
	1 887 096	B21	2406	1221	0 153 884	0.392.281
	1 887 096	B20	2405	1221	0.175134	0.418.490
	1.887.096	B20 B27	2405	1220 1227	0.175134 0.378037	-0.614847
	1.007/030	$D_{21}$	2412	1221	0.518 051	-0.014047
28	1.887160	B13	2398	1213	1.000000	-1.000000
29	1.887162	A6	2345	1106	0.139227	-0.373132
	1.887162	A3	2342	1103	0.101675	-0.318865
	1.887162	A28	2367	1128	0.336348	-0.579955
	1.887162	A2	2341	1102	0 210 149	0.458420
	1.887162	.12	2425	1302	0 100 819	-0.317520
				1002		0.011010
30	1.888162	B35	2420	1235	0.121318	0.348307
	1.888162	B4	2389	1204	0.457553	0.676426
31	1.888564	B35	2420	1235	0.275329	-0.524718
01	1.888564	B4	2389	1204	0.212466	0.460.940
	1.888564	B36	$\frac{2000}{2421}$	1236	0.154960	0 393 650
	11000 001				0.101000	0.000 000
32	1.890059	A6	2345	1106	0.151294	0.388966
	1.890059	J2	2425	1302	0.516858	-0.718928
33	1 890 118	B2	2387	1202	0 137 058	0 370 213
00	1 800 118	B26	2411	1202	0.1070000 0.227074	-0.476523
	1 800 118	12	2425	1302	0.183566	-0.428446
	1.050 110	52	2420	1502	0.105 000	0.420 440
34	1.890433	B19	2404	1219	0.148855	0.385817
	1.890433	B9	2394	1209	0.302101	-0.549637
	1.890433	B27	2412	1227	0.166039	-0.407478
	1.890433	B17	2402	1217	0.113012	0.336172
25	1 801 971	B17	2/02	1917	0 128 308	-0 358 397
55	1.091.271	D17 D10	2402	1217	0.126.398	-0.336.327 0.256.155
	1.091.271	D19 D0	2404	1219	0.120.040	0.550155
	1.091.271	D9 D9	2094	1209	0.345745 0.102.065	0.300001 0.210476
	1.691 271	Do	2393	1208	0.102 005	-0.319470
36	1.891988	B7	2392	1207	0.110304	-0.332120
	1.891988	A31	2370	1131	0.493989	0.702843
	1.891988	A32	2371	1132	0.144535	-0.380178
37	1 892 145	M1	2431	1601	1 000 000	1 000 000
	1.002 140		2 101	1117	0.005.405	0.515110
38	1.892732	AT7	2350	1117	0.267405	-0.517112
	1.892732	A24	2363	1124	0.107 370	-0.327674
	1.892732	A26	2365	1126	0.226 199	0.475603
39	1.893462	B26	2411	1226	0.231486	0.481130
	1.893462	$B\tilde{8}$	$239\bar{3}$	1208	0.554302	0.744514
	1.893462	B10	2395	1210	0.129429	-0.359762
		= + v			50 <b>1_</b> 0	0.000,01

Table C.25: continued.

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	Table C.25:     continued.							
Exciton	$E_{ m exc} \; [{ m eV}]$	name	ID (MD)	ID (x-ray)	$w_i$	$c_i$		
40	1.894031	A21	2360	1121	0.109612	0.331077		
	1.894031	A19	2358	1119	0.637051	-0.798155		
	1.894 031	A23	2362	1123	0.147 290	0.383784		
41	1.894138	L3	2430	1503	1.000000	1.000 000		
42	1.894143	A8	2347	1108	0.877256	0.936620		
43	1.894917	B23	2408	1223	0.136893	0.369990		
	1.894917	B34	2419	1234	0.119035	-0.345014		
	1.894917 1.894917	B14 B15	$2399 \\ 2400$	$1214 \\ 1215$	$0.291036 \\ 0.188578$	-0.539477 0.434255		
44	1.896 232	A4	2343	1104	0.268 393	-0.518066		
	1.896232	A3	2342	1103	0.130076	0.360661		
	1.896232	A9	2348	1109	0.106773	-0.326761		
	1.896 232	A2	2341	1102	0.323645	0.568 898		
45	1.897 242	A27	2366	1127	0.153255	-0.391478		
	1.897242 1.897242	A20 A33	2305 2372	1120	0.249707	-0.499767 -0.436649		
	1.007.212	 	2012	1910	0.100.002	0.255.112		
40	1.898239 1.898239	A38	2395 2377	1138	0.120103 0130784	0.355113 0.361641		
	1.898239	A1	2340	1101	0.226349	-0.475761		
47	1.898412	B10	2395	1210	0.193242	-0.439593		
	1.898 412	A38	2377	1138	0.165018	0.406224		
	1.898 412	A1	2340	1101	0.299346	-0.547125		
49	1.898832	A24	2363	1124	0.114051	-0.337714		
	1.898 832	A33	2372	1133	0.100 149	0.316 463		
50	1.899573	A29	2368	1129	0.231297	-0.480934		
	1.899573	A30 K2	2309 2381	$1130 \\ 1402$	0.403129 0.115358	-0.339644		
	1.899.858	K2	2381	1402	0 719 781	-0.848399		
52	1 902 253	B19	2404	1219	0 233 577	-0.483298		
02	1.902253	B10 B20	2401 2405	1210	0.360797	-0.600664		
	1.902253	B16	2401	1216	0.149756	0.386983		
53	1.903326	B29	2414	1229	0.572155	-0.756410		
54	1.903526	A13	2352	1113	0.835026	-0.913798		
55	1.904648	B12	2397	1212	0.170047	-0.412368		
	1.904 648	A17	2356	1117	0.143394	0.378674		
56	1.904701	A17	2356	1117	0.112090	0.334798		
	1.904701	B12	2397	1212	0.263 689	0.513506		
	1.904 /01	B25	2410	1225	0.112739	0.335700		
57	1.905588 1.005 588	B12 B25	$2397 \\ 2410$	$1212 \\ 1225$	0.438807 0.207668	-0.662425 0.455706		
	1.005.078	120	2410	1220	1.000.000	1.000.000		
50	1.905 978	JJ T 1	2420	1503	1.000.000	1.000.000		
	1.900.570		2420	1100	1.000.000	-1.000.000		
60	1.906722 1.906722	A9 A22	$2348 \\ 2361$	1109 1122	0.238936 0.113133	0.488811 0.336352		
	1.906722 1.906722	A23	2362	1122	0.113133 $0.439689$	-0.663090		
61	1 907 346	Δ4	2343	1104	0 212 051	0 460 490		
01	1.907346	A5	2344	1105	0.212001 0.107615	-0.328047		
	1.907346	A9	2348	1109	0.410185	-0.640457		
62	1.907592	L2	2429	1502	0.524420	0.724168		
	1.907592	B6	2391	1206	0.143100	0.378286		
63	1.909 004	A38	2377	1138	0.208253	0.456347		
	1.909004 1.909.004	A39 A 1	2378	$1139 \\ 1101$	0.216828	0.465648 0.400.759		
	1.909.004	<b>A1</b>	2040	1101	0.240 044	0.490708		

Table C 25 

 $continued \ on \ next \ page$ 

		14	<b>DIE 0.20.</b> C	ontinucu.		
Exciton	$E_{ m exc} \; [{ m eV}]$	name	ID (MD)	ID (x-ray)	$w_i$	$c_i$
64	1.909493	L2	2429	1502	0.138602	0.372293
01	1.909 493	A5	2344	1105	0.198904	0.445986
					0.000000	
65	1.909616	A5	2344	1105	0.213995	-0.462596
	1.909616	L2	2429	1502	0.187462	0.432969
	1.909616	B6	2391	1206	0.128049	-0.357839
66	1.910.026	X1	2432	1701	0.195606	-0.442274
00	1.910 026	B35	2420	1235	0.151312	0.388 988
	1.910026	B11	2396	1211	0.118044	-0.343576
67	1.911992	B39	2423	1239	0.399 060	-0.631712
	1.911992	B6	2391	1206	0.105547	-0.324880
	1.911992	B2	2387	1202	0.130006	0.360563
68	1.912639	B11	2396	1211	0.315743	-0.561910
	1.912639	B39	2423	1239	0.161665	0.402075
	1.912639	B2	2387	1202	0.108282	0.329062
69	1.914304	B11	2396	1211	0.158450	0.398058
	1.914304	B10	2395	1210	0.104274	0.322915
	1.914304	B3	2388	1203	0.128770	-0.358845
	1.914304	B2	2387	1202	0.211201	0.459566
70	1.915613	A20	2359	1120	0.103825	0.322219
	1.915613	A21	2360	1121	0.339017	0.582251
	1.915613	A23	2362	1123	0.118541	-0.344298
	1.915613	A22	2361	1122	0.271081	-0.520654
71	1.916176	A18	2357	1118	0.255012	0.504988
	1.916176	A34	2373	1134	0.104146	-0.322717
72	1.917261	A18	2357	1118	0.412792	0.642489
73	1 918 720	B37	2380	1237	0 357 297	0.597744
	1.918720	B38	2422	1238	0.225130	0.474479
74	1.919671	B16	2401	1216	0.399464	0.632032
75	1 010 036	B16	9401	1916	0 118 781	-0.344.646
15	1 010 036	CA3	2330	1013	0.223/04	-0.344040 -0.483212
	1 010 036	A40	2355	11/0	0.235494 0.228207	0.405212 0.477710
70	1.021.104	1110	2010	1110	0.220.201	0.200 FFF
	1.921 194	A37	2370	1137	0.135833	0.308 555
77	1.922410	A4	2343	1104	0.114748	0.338745
78	1.922465	J1	2424	1301	1.000000	-1.000000
79	1.923637	X1	2432	1701	0.223642	-0.472908
	1.923637	B34	2419	1234	0.192104	0.438297
	1.923637	B23	2408	1223	0.143297	0.378547
80	1 924 516	A12	2351	1112	0 197 625	-0.444551
00	1.924516	A14	2353	1114	0.216729	-0.465541
81	1.924 983	B33	2418	1233	0.175255	-0.418635
	1.924983	B31	2416	1231	0.132504	-0.364011
	1.924983	B15	2400	1215	0.169140	0.411267
	1.924983	B32	2417	1232	0.166779	-0.408386
82	1.926521	A29	2368	1129	0.133007	0.364702
	1.926521	eC-B3	2385	1023	0.335708	-0.579403
	1.926521	B39	2423	1239	0.120227	-0.346737
83	1.928397	Α7	2346	1107	0.180694	-0.425081
00	1.928 397	A40	2379	1140	0.287016	0.535739
84	1.928 800	A11	2350	1111	1.000.000	1.000.000
0E	1.020.064	0 D2	2000	1092	0.119.069	0.926.100
00	1.920 904	Δ 40	2000 2270	1020	0.112 900	-0.330100
	1.920.904	A 20	2019 9971	1140	0.149200	-0.000071
	1.920 904	A97	2011	1104	0.104014	0.929441

Table C.25: continued.

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	Table 0.25. continued.						
Exciton	$E_{ m exc} \; [{ m eV}]$	name	ID (MD)	ID (x-ray)	$w_i$	$c_i$	
86	$\begin{array}{c} 1.932066 \\ 1.932066 \\ 1.932066 \end{array}$	X1 B28 B36	$2432 \\ 2413 \\ 2421$	$1701 \\ 1228 \\ 1236$	$\begin{array}{c} 0.130374 \\ 0.241287 \\ 0.173693 \end{array}$	$\begin{array}{c} 0.361074 \\ -0.491210 \\ 0.416765 \end{array}$	
87	$\frac{1.933187}{1.933187}$	A6 A7	$2345 \\ 2346$	$\begin{array}{c} 1106 \\ 1107 \end{array}$	$\begin{array}{c} 0.127127 \\ 0.338049 \end{array}$	$\begin{array}{c} -0.356549 \\ -0.581420 \end{array}$	
88	$\frac{1.934316}{1.934316}$	B3 B17	$2388 \\ 2402$	$1203 \\ 1217$	$\begin{array}{c} 0.360470\\ 0.176799 \end{array}$	$\begin{array}{c} 0.600392 \\ -0.420474 \end{array}$	
89	$\begin{array}{c} 1.936331 \\ 1.936331 \\ 1.936331 \end{array}$	A32 B17 A22	$2371 \\ 2402 \\ 2361$	$1132 \\ 1217 \\ 1122$	$\begin{array}{c} 0.107432 \\ 0.140836 \\ 0.173899 \end{array}$	$\begin{array}{c} -0.327767\\ 0.375281\\ 0.417012\end{array}$	
90	1.937941	B17	2402	1217	0.210714	-0.459036	
91	$\frac{1.939294}{1.939294}$	B17 B3	$\begin{array}{c} 2402 \\ 2388 \end{array}$	$1217 \\ 1203$	$\begin{array}{c} 0.132350 \\ 0.139629 \end{array}$	$\begin{array}{c} -0.363800 \\ -0.373670 \end{array}$	
92	$\frac{1.939766}{1.939766}$	B27 B28	$2412 \\ 2413$	1227 1228	$\begin{array}{c} 0.117600 \\ 0.447904 \end{array}$	$\begin{array}{c} 0.342929 \\ 0.669256 \end{array}$	
93	1.947151	A22	2361	1122	0.109347	-0.330676	
94	$\overline{1.954365}$ 1.954365	eC-A1 eC-B1	$2337 \\ 2383$	$\begin{array}{c} 1011\\ 1021 \end{array}$	$0.233655\\0.296717$	$\frac{0.483379}{0.544717}$	
95	$\frac{1.962355}{1.962355}$	B31 B23	$\begin{array}{c} 2416 \\ 2408 \end{array}$	$1231 \\ 1223$	$\begin{array}{c} 0.130906 \\ 0.273667 \end{array}$	$\begin{array}{c} -0.361810 \\ -0.523132 \end{array}$	

Table C.25: continued.

## List of Abbreviations

$2 \text{-} \text{MIm}^-$	2-methylimidazolate
C-PCM	conductor-like polarizable continuum model
CoIn	conical intersection
$\operatorname{conPET}$	consecutive photoinduced electron transfer
CT	charge-transfer
CV	cyclic voltammetry
e-PRC	electro-mediated photoredox catalysis
ECE	electrochemical-chemical-electrochemical
ECEC	$electrochemical\-chemical\-electrochemical\-chemical$
EPR	electron paramagnetic resonance
ETC	electron transfer chain
FC	Franck-Condon
IC	internal conversion
ISC	intersystem crossing
LJ	Lennard-Jones
MD	molecular dynamics
MOF	metal organic framework
NAC	non-adiabatic coupling elements
$\mathbf{NpMI}$	$2, 6\mbox{-diisopropylphenyl-containing naphthalenemonoimide}$
pAn	<i>p</i> -anisidinium
pBrA	p-bromoanilinium
pCA	p-cyanoanilinium
PES	potential energy surface
PRC	photoredox catalysis
PS I	photosystem I
QM	quantum mechanical
TDSE	time-dependent Schrödinger equation
TISE	time-independent Schrödinger equation
UV	ultraviolet

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#### Bibliography

- [1] G. Ciamician, *Science* **1912**, *36*, 385–394.
- [2] Ancient Egyptian Materials and Technology, (Eds.: P. T. Nicholson, I. Shaw), Cambridge University Press, Cambridge; New York, 2000.
- [3] H. D. Roth, Angew. Chem. Int. Ed. Engl. 1989, 28, 1193–1207.
- [4] H. Trommsdorff, Ann. Pharm. 1834, 11, 190–207.
- [5] W. Heldt, Justus Liebigs Ann. Chem. 1847, 63, 10–83.
- [6] D. S. Price, J. Chem. Soc. 1865, 18, 245–249.
- [7] E. ter Meer, Justus Liebigs Ann. Chem. 1876, 181, 1–22.
- [8] A. Breuer, T. Zincke, Ber. Dtsch. Chem. Ges. 1878, 11, 1403–1407.
- [9] A. Breuer, T. Zincke, Ber. Dtsch. Chem. Ges. 1880, 13, 631–635.
- [10] C. Liebermann, Ber. Dtsch. Chem. Ges. 1895, 28, 1443–1448.
- [11] T. Wedgwood, H. Davy, J. R. Inst. Great Britain 1802, 1, 170–174.
- [12] A. G. Green, C. F. Cross, E. J. Bevan, Ber. Dtsch. Chem. Ges. 1890, 23, 3131– 3133.
- [13] G. Ciamician, P. Silber, Ber. Dtsch. Chem. Ges. 1900, 33, 2911–2913.
- [14] G. Ciamician, P. Silber, Ber. Dtsch. Chem. Ges. 1901, 34, 2040–2046.
- [15] H. Wang, Y.-M. Tian, B. König, *Nat. Rev. Chem.* **2022**, *6*, 745–755.
- [16] A. Lin, S. Lee, R. R. Knowles, Acc. Chem. Res. 2024, 57, 1827–1838.
- [17] S. Wu, J. Żurauskas, M. Domański, P. S. Hitzfeld, V. Butera, D. J. Scott, J. Rehbein, A. Kumar, E. Thyrhaug, J. Hauer, J. P. Barham, Org. Chem. Front. 2021, 8, 1132– 1142.
- [18] M. J. P. Mandigma, J. Kaur, J. P. Barham, *ChemCatChem* **2023**, *15*, e202201542.
- T. Constantin, B. Górski, M. J. Tilby, S. Chelli, F. Juliá, J. Llaveria, K. J. Gillen,
   H. Zipse, S. Lakhdar, D. Leonori, *Science* 2022, 377, 1323–1328.
- [20] F. Juliá, T. Constantin, D. Leonori, Chem. Rev. 2022, 122, 2292–2352.

- [21] J. Großkopf, M. Plaza, A. Seitz, S. Breitenlechner, G. Storch, T. Bach, J. Am. Chem. Soc. 2021, 143, 21241–21245.
- [22] A. Chinchole, M. A. Henriquez, D. Cortes-Arriagada, A. R. Cabrera, O. Reiser, ACS Catal. 2022, 12, 13549–13554.
- R. J. Kutta, J. Großkopf, N. van Staalduinen, A. Seitz, P. Pracht, S. Breitenlechner,
   C. Bannwarth, P. Nuernberger, T. Bach, J. Am. Chem. Soc. 2023, 145, 2354–2363.
- [24] E. Riedle, M. K. Roos, S. Thallmair, C. F. Sailer, N. Krebs, B. P. Fingerhut, R. de Vivie-Riedle, *Chem. Phys. Lett.* **2017**, *683*, 128–134.
- [25] F. Schüppel, M. K. Roos, R. de Vivie-Riedle, *Phys. Chem. Chem. Phys.* 2018, 20, 22753–22761.
- [26] D. P. Schwinger, M. T. Peschel, T. Rigotti, P. Kabaciński, T. Knoll, E. Thyrhaug, G. Cerullo, J. Hauer, R. de Vivie-Riedle, T. Bach, J. Am. Chem. Soc. 2022, 144, 18927–18937.
- [27] R. Wilcken, M. Schildhauer, F. Rott, L. A. Huber, M. Guentner, S. Thumser, K. Hoffmann, S. Oesterling, R. de Vivie-Riedle, E. Riedle, H. Dube, J. Am. Chem. Soc. 2018, 140, 5311–5318.
- [28] G. C. Thaggard, K. C. Park, J. Lim, B. K. P. Maldeni Kankanamalage, J. Haimerl, G. R. Wilson, M. K. McBride, K. L. Forrester, E. R. Adelson, V. S. Arnold, S. T. Wetthasinghe, V. A. Rassolov, M. D. Smith, D. Sosnin, I. Aprahamian, M. Karmakar, S. K. Bag, A. Thakur, M. Zhang, B. Z. Tang, J. A. Castaño, M. N. Chaur, M. M. Lerch, R. A. Fischer, J. Aizenberg, R. Herges, J.-M. Lehn, N. B. Shustova, *Nat. Commun.* **2023**, *14*, 7556.
- [29] P. Kobauri, F. J. Dekker, W. Szymanski, B. L. Feringa, Angew. Chem. Int. Ed. 2023, 62, e202300681.
- [30] W. Domcke, D. Yarkony, H. Köppel, Conical Intersections: Electronic Structure, Dynamics & Spectroscopy, World Scientific, River Edge, N.J., 2004.
- [31] D. Polli, P. Altoè, O. Weingart, K. M. Spillane, C. Manzoni, D. Brida, G. Tomasello, G. Orlandi, P. Kukura, R. A. Mathies, M. Garavelli, G. Cerullo, *Nature* 2010, 467, 440–443.
- [32] R. Improta, F. Santoro, L. Blancafort, Chem. Rev. 2016, 116, 3540-3593.
- [33] M. Kasha, *Discuss. Faraday Soc.* 1950, 9, 14–19.
- [34] A. Hölzl-Hobmeier, A. Bauer, A. V. Silva, S. M. Huber, C. Bannwarth, T. Bach, *Nature* 2018, 564, 240–243.
- [35] B. D. Ravetz, A. B. Pun, E. M. Churchill, D. N. Congreve, T. Rovis, L. M. Campos, *Nature* 2019, 565, 343–346.
- [36] T. Renger, V. May, O. Kühn, *Phys. Rep.* **2001**, *343*, 137–254.

- [37] M. Şener, J. Strümpfer, J. Hsin, D. Chandler, S. Scheuring, C. N. Hunter, K. Schulten, *ChemPhysChem* 2011, 12, 518–531.
- [38] D. Wang, O. C. Fiebig, D. Harris, H. Toporik, Y. Ji, C. Chuang, M. Nairat, A. L. Tong, J. I. Ogren, S. M. Hart, J. Cao, J. N. Sturgis, Y. Mazor, G. S. Schlau-Cohen, *Proc. Natl. Acad. Sci. USA* 2023, 120, e2220477120.
- [39] T. Förster, Ann. Phys. 1948, 437, 55–75.
- [40] D. L. Dexter, J. Chem. Phys. 1953, 21, 836–850.
- [41] D. Keefer, S. Thallmair, J. P. P. Zauleck, R. de Vivie-Riedle, J. Phys. B: At. Mol. Opt. Phys. 2015, 48, 234003.
- [42] D. Keefer, R. de Vivie-Riedle, Adv. Quantum Technol. 2019, 2, 1800099.
- [43] F. F. Graupner, T. T. Herzog, F. Rott, S. Oesterling, R. de Vivie-Riedle, T. Cordes, W. Zinth, *Chem. Phys.* 2018, 515, 614–621.
- [44] K. Stallhofer, M. Nuber, F. Schüppel, S. Thumser, H. Iglev, R. de Vivie-Riedle, W. Zinth, H. Dube, J. Phys. Chem. A 2021, 125, 4390–4400.
- [45] M. T. Peschel, J. Kussmann, C. Ochsenfeld, R. de Vivie-Riedle, *Phys. Chem. Chem. Phys.* 2024, 26, 23256–23263.
- [46] Y. Xu, M. T. Peschel, M. Jänchen, R. Foja, G. Storch, E. Thyrhaug, R. de Vivie-Riedle, J. Hauer, J. Phys. Chem. A 2024, 128, 3830–3839.
- [47] Y. Sempere, M. Morgenstern, T. Bach, M. Plaza, Photochem. Photobiol. Sci. 2022, 21, 719–737.
- [48] L. Wylie, J. P. Barham, B. Kirchner, *ChemPhysChem* **2023**, *24*, e202300470.
- [49] J. Adolphs, F. Müh, M. E.-A. Madjet, M. S. am Busch, T. Renger, J. Am. Chem. Soc. 2010, 132, 3331–3343.
- [50] A. Sirohiwal, F. Neese, D. A. Pantazis, J. Am. Chem. Soc. 2020, 142, 18174–18190.
- [51] A. Sirohiwal, F. Neese, D. A. Pantazis, J. Chem. Theory Comput. 2021, 17, 1858– 1873.
- [52] M. Born, Z. Phys. **1920**, 1, 45–48.
- [53] J. G. Kirkwood, J. Chem. Phys. 1934, 2, 767–781.
- [54] J. G. Kirkwood, J. Chem. Phys. 1939, 7, 911–919.
- [55] L. Onsager, J. Am. Chem. Soc. 1936, 58, 1486–1493.
- [56] J. Tomasi, B. Mennucci, R. Cammi, Chem. Rev. 2005, 105, 2999–3094.
- [57] A. Warshel, M. Levitt, J. Mol. Biol. 1976, 103, 227–249.
- [58] D. Bakowies, W. Thiel, J. Phys. Chem. 1996, 100, 10580–10594.
- [59] F. Maseras, K. Morokuma, J. Comput. Chem. 1995, 16, 1170–1179.

- [60] M. Svensson, S. Humbel, R. D. J. Froese, T. Matsubara, S. Sieber, K. Morokuma, J. Phys. Chem. 1996, 100, 19357–19363.
- [61] H. M. Senn, W. Thiel, Angew. Chem. Int. Ed. 2009, 48, 1198–1229.
- [62] L. W. Chung, W. M. C. Sameera, R. Ramozzi, A. J. Page, M. Hatanaka, G. P. Petrova, T. V. Harris, X. Li, Z. Ke, F. Liu, H.-B. Li, L. Ding, K. Morokuma, *Chem. Rev.* 2015, 115, 5678–5796.
- [63] I. Antes, W. Thiel, J. Phys. Chem. A 1999, 103, 9290–9295.
- [64] D. Das, K. P. Eurenius, E. M. Billings, P. Sherwood, D. C. Chatfield, M. Hodošček,
   B. R. Brooks, J. Chem. Phys. 2002, 117, 10534–10547.
- [65] H. Lin, D. G. Truhlar, J. Phys. Chem. A 2005, 109, 3991–4004.
- [66] G. A. Cisneros, J.-P. Piquemal, T. A. Darden, J. Phys. Chem. B 2006, 110, 13682–13684.
- [67] F. Melaccio, M. Olivucci, R. Lindh, N. Ferré, Int. J. Quantum Chem. 2011, 111, 3339–3346.
- [68] B. T. Thole, *Chem. Phys.* **1981**, *59*, 341–350.
- [69] A. K. Rappe, W. A. Goddard, J. Phys. Chem. 1991, 95, 3358–3363.
- [70] S. W. Rick, S. J. Stuart, Rev. Comput. Chem. 2002, 89–146.
- [71] G. Lamoureux, B. Roux, J. Chem. Phys. 2003, 119, 3025–3039.
- [72] Y. Zhang, H. Lin, D. G. Truhlar, J. Chem. Theory Comput. 2007, 3, 1378–1398.
- [73] C. M. Baker, WIREs Comput. Mol. Sci. 2015, 5, 241–254.
- [74] Z. Jing, C. Liu, S. Y. Cheng, R. Qi, B. D. Walker, J.-P. Piquemal, P. Ren, Annu. Rev. Biophys. 2019, 48, 371–394.
- [75] N. Liguori, R. Croce, S. J. Marrink, S. Thallmair, *Photosynth. Res.* 2020, 144, 273–295.
- [76] S. Grimme, J. Chem. Theory Comput. 2019, 15, 2847–2862.
- [77] P. Pracht, F. Bohle, S. Grimme, *Phys. Chem. Chem. Phys.* 2020, 22, 7169–7192.
- [78] P. Pracht, C. Bannwarth, J. Chem. Theory Comput. 2022, 18, 6370–6385.
- [79] J. M. R. Narayanam, C. R. J. Stephenson, Chem. Soc. Rev. 2010, 40, 102–113.
- [80] M. H. Shaw, J. Twilton, D. W. C. MacMillan, J. Org. Chem. 2016, 81, 6898–6926.
- [81] N. A. Romero, D. A. Nicewicz, Chem. Rev. 2016, 116, 10075–10166.
- [82] D. M. Hedstrand, W. H. Kruizinga, R. M. Kellogg, *Tetrahedron Lett.* 1978, 19, 1255–1258.
- [83] C. Pac, M. Ihama, M. Yasuda, Y. Miyauchi, H. Sakurai, J. Am. Chem. Soc. 1981, 103, 6495–6497.

- [84] K. Hironaka, S. Fukuzumi, T. Tanaka, J. Chem. Soc. Perkin Trans. 2 1984, 1705–1709.
- [85] H. Cano-Yelo, A. Deronzier, *Tetrahedron Lett.* 1984, 25, 5517–5520.
- [86] H. Cano-Yelo, A. Deronzier, J. Chem. Soc. Perkin Trans. 2 1984, 1093–1098.
- [87] K. Okada, K. Okamoto, N. Morita, K. Okubo, M. Oda, J. Am. Chem. Soc. 1991, 113, 9401–9402.
- [88] T. J. Meyer, Acc. Chem. Res. 1989, 22, 163–170.
- [89] K. Kalyanasundaram, M. Grätzel, Coord. Chem. Rev. 1998, 177, 347–414.
- [90] D. A. Nicewicz, D. W. C. MacMillan, *Science* 2008, 322, 77–80.
- [91] M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, J. Am. Chem. Soc. 2008, 130, 12886–12887.
- [92] J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, J. Am. Chem. Soc. 2009, 131, 8756–8757.
- [93] L. Marzo, S. K. Pagire, O. Reiser, B. König, Angew. Chem. Int. Ed. 2018, 57, 10034–10072.
- [94] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363.
- [95] K. Teegardin, J. I. Day, J. Chan, J. Weaver, Org. Process Res. Dev. 2016, 20, 1156–1163.
- [96] Visible Light Photocatalysis in Organic Chemistry, First edition, (Eds.: C. R. J. Stephenson, T. P. Yoon, D. W. C. MacMillan), Wiley-VCH, Weinheim, Germany, 2018.
- [97] L. Candish, K. D. Collins, G. C. Cook, J. J. Douglas, A. Gómez-Suárez, A. Jolit, S. Keess, *Chem. Rev.* 2022, 122, 2907–2980.
- [98] A. Juris, V. Balzani, F. Barigelletti, S. Campagna, P. Belser, A. von Zelewsky, Coord. Chem. Rev. 1988, 84, 85–277.
- [99] L. Flamigni, A. Barbieri, C. Sabatini, B. Ventura, F. Barigelletti in *Photochemistry and Photophysics of Coordination Compounds II*, (Eds.: V. Balzani, S. Campagna), Springer, Berlin, Heidelberg, **2007**, pp. 143–203.
- [100] D. Kim, V. Q. Dang, T. S. Teets, *Chem. Sci.* **2024**, *15*, 77–94.
- [101] L. Capaldo, D. Ravelli, *Eur. J. Org. Chem.* **2020**, *2020*, 2783–2806.
- [102] D. M. Arias-Rotondo, J. K. McCusker, Chem. Soc. Rev. 2016, 45, 5803–5820.
- [103] O. S. Wenger, J. Am. Chem. Soc. 2018, 140, 13522–13533.
- [104] P. Nuss, M. J. Eckelman, *PLOS ONE* **2014**, *9*, e101298.
- [105] E. Speckmeier, T. G. Fischer, K. Zeitler, J. Am. Chem. Soc. 2018, 140, 15353– 15365.

- [106] C. B. Larsen, O. S. Wenger, *Chem. Eur. J.* **2018**, *24*, 2039–2058.
- [107] J.-D. Chai, M. Head-Gordon, Phys. Chem. Chem. Phys. 2008, 10, 6615–6620.
- [108] A. Fabrizio, C. Corminboeuf, J. Phys. Chem. Lett. 2018, 9, 464–470.
- [109] S. Grimme, WIREs Comput. Mol. Sci. 2011, 1, 211–228.
- [110] H. Kruse, L. Goerigk, S. Grimme, J. Org. Chem. 2012, 77, 10824–10834.
- [111] C. R. Bock, J. A. Connor, A. R. Gutierrez, T. J. Meyer, D. G. Whitten, B. P. Sullivan, J. K. Nagle, J. Am. Chem. Soc. 1979, 101, 4815–4824.
- [112] S. K. Pagire, N. Kumagai, M. Shibasaki, Org. Lett. 2020, 22, 7853–7858.
- [113] K. Dedeian, P. I. Djurovich, F. O. Garces, G. Carlson, R. J. Watts, *Inorg. Chem.* 1991, 30, 1685–1687.
- [114] J. Mortensen, J. Heinze, Angew. Chem. Int. Ed. Engl. 1984, 23, 84–85.
- [115] L. Pause, M. Robert, J.-M. Savéant, J. Am. Chem. Soc. 1999, 121, 7158-7159.
- [116] H. G. Roth, N. A. Romero, D. A. Nicewicz, *Synlett* **2016**, *27*, 714–723.
- [117] A. J. Birch, J. Chem. Soc. 1944, 430–436.
- [118] R. F. Nystrom, S. W. Chaikin, W. G. Brown, J. Am. Chem. Soc. 1949, 71, 3245– 3246.
- [119] D. K. Joshi, J. W. Sutton, S. Carver, J. P. Blanchard, Org. Process Res. Dev. 2005, 9, 997–1002.
- [120] I. Ghosh, T. Ghosh, J. I. Bardagi, B. König, *Science* 2014, 346, 725–728.
- [121] C. Kerzig, X. Guo, O. S. Wenger, J. Am. Chem. Soc. 2019, 141, 2122–2127.
- [122] C. Kerzig, O. S. Wenger, *Chem. Sci.* **2019**, *10*, 11023–11029.
- [123] J. Liu, L. Lu, D. Wood, S. Lin, ACS Cent. Sci. 2020, 6, 1317–1340.
- [124] J. P. Barham, B. König, Angew. Chem. Int. Ed. 2020, 59, 11732–11747.
- [125] H. Huang, K. A. Steiniger, T. H. Lambert, J. Am. Chem. Soc. 2022, 144, 12567– 12583.
- [126] H. Kim, H. Kim, T. H. Lambert, S. Lin, J. Am. Chem. Soc. 2020, 142, 2087–2092.
- [127] N. G. W. Cowper, C. P. Chernowsky, O. P. Williams, Z. K. Wickens, J. Am. Chem. Soc. 2020, 142, 2093–2099.
- [128] A. Rieth, M. Gonzalez, B. Kudisch, M. Nava, D. Nocera, J. Am. Chem. Soc. 2021, 143, 14352–14359.
- [129] D. Gosztola, M. P. Niemczyk, W. Svec, A. S. Lukas, M. R. Wasielewski, J. Phys. Chem. A 2000, 104, 6545–6551.
- [130] C. Lu, M. Fujitsuka, A. Sugimoto, T. Majima, J. Phys. Chem. C 2016, 120, 12734–12741.
- [131] J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177–2250.

- [132] J. D. Hayler, D. K. Leahy, E. M. Simmons, *Organometallics* 2019, 38, 36–46.
- [133] A. Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards, L. I. Frye, O. L. Garry, M. N. Lavagnino, B. X. Li, Y. Liang, E. Mao, A. Millet, J. V. Oakley, N. L. Reed, H. A. Sakai, C. P. Seath, D. W. C. MacMillan, *Chem. Rev.* 2022, 122, 1485–1542.
- [134] T. Duchanois, T. Etienne, C. Cebrián, L. Liu, A. Monari, M. Beley, X. Assfeld, S. Haacke, P. C. Gros, *Eur. J. Inorg. Chem.* 2015, 2015, 2469–2477.
- [135] L. Liu, T. Duchanois, T. Etienne, A. Monari, M. Beley, X. Assfeld, S. Haacke, P. C. Gros, *Phys. Chem. Chem. Phys.* **2016**, *18*, 12550–12556.
- [136] A. Francés-Monerris, P. C. Gros, M. Pastore, X. Assfeld, A. Monari, *Theor. Chem. Acc.* 2019, 138, 86.
- [137] K. D. Vogiatzis, M. V. Polynski, J. K. Kirkland, J. Townsend, A. Hashemi, C. Liu,
   E. A. Pidko, *Chem. Rev.* 2019, 119, 2453–2523.
- [138] J. K. McCusker, *Science* **2019**, *363*, 484–488.
- [139] B. M. Hockin, C. Li, N. Robertson, E. Zysman-Colman, *Catal. Sci. Technol.* 2019, 9, 889–915.
- [140] S. Kaufhold, K. Wärnmark, *Catalysts* **2020**, *10*, 132.
- [141] S. H. Kyne, G. Lefèvre, C. Ollivier, M. Petit, V.-A. R. Cladera, L. Fensterbank, *Chem. Soc. Rev.* 2020, 49, 8501–8542.
- [142] R. Lauenstein, S. L. Mader, H. Derondeau, O. Z. Esezobor, M. Block, A. J. Römer, C. Jandl, E. Riedle, V. R. I. Kaila, J. Hauer, E. Thyrhaug, C. R. Hess, *Chem. Sci.* 2021, 12, 7521–7532.
- [143] T. Mandal, N. Katta, H. Paps, O. Reiser, ACS Org. Inorg. Au 2023, 3, 171–176.
- [144] A. Y. Chan, A. Ghosh, J. T. Yarranton, J. Twilton, J. Jin, D. M. Arias-Rotondo, H. A. Sakai, J. K. McCusker, D. W. C. MacMillan, *Science* 2023, *382*, 191–197.
- [145] P. Pyykko, *Chem. Rev.* **1988**, *88*, 563–594.
- [146] M. Kaupp, J. Comput. Chem. 2007, 28, 320–325.
- [147] C. Bannwarth, S. Ehlert, S. Grimme, J. Chem. Theory Comput. 2019, 15, 1652– 1671.
- [148] M. Casanova-Páez, L. Goerigk, J. Chem. Theory Comput. 2021, 17, 5165–5186.
- [149] T. Constantin, M. Zanini, A. Regni, N. S. Sheikh, F. Juliá, D. Leonori, *Science* 2020, 367, 1021–1026.
- [150] T. Constantin, F. Juliá, N. S. Sheikh, D. Leonori, *Chem. Sci.* 2020, 11, 12822– 12828.
- [151] S. Matsika, P. Krause, Annu. Rev. Phys. Chem. 2011, 62, 621–643.
- [152] F. Agostini, B. F. E. Curchod, WIREs Comput. Mol. Sci. 2019, 9, e1417.

- [153] J. C. Tully, R. K. Preston, J. Chem. Phys. 1971, 55, 562–572.
- [154] J. C. Tully, *Faraday Discuss.* **1998**, *110*, 407–419.
- [155] M. Barbatti, WIREs Comput. Mol. Sci. 2011, 1, 620–633.
- [156] S. Mai, P. Marquetand, L. González, WIREs Comput. Mol. Sci. 2018, 8, e1370.
- [157] J. P. Zobel, M. Heindl, F. Plasser, S. Mai, L. González, Acc. Chem. Res. 2021, 54, 3760–3771.
- [158] M. Ruckenbauer, M. Barbatti, T. Müller, H. Lischka, J. Phys. Chem. A 2010, 114, 6757–6765.
- [159] D. Avagliano, M. Bonfanti, M. Garavelli, L. González, J. Chem. Theory Comput. 2021, 17, 4639–4647.
- [160] M. Bondanza, B. Demoulin, F. Lipparini, M. Barbatti, B. Mennucci, J. Phys. Chem. A 2022, 126, 6780–6789.
- [161] E. Brunk, U. Rothlisberger, Chem. Rev. 2015, 115, 6217–6263.
- [162] M. Bondanza, M. Nottoli, L. Cupellini, F. Lipparini, B. Mennucci, *Phys. Chem. Chem. Phys.* 2020, 22, 14433–14448.
- [163] F. Santoro, J. A. Green, L. Martinez-Fernandez, J. Cerezo, R. Improta, *Phys. Chem. Chem. Phys.* **2021**, 23, 8181–8199.
- [164] J. M. Toldo, M. T. do Casal, E. Ventura, S. A. do Monte, M. Barbatti, *Phys. Chem. Chem. Phys.* 2023, 25, 8293–8316.
- [165] D. J. Tannor, Introduction to Quantum Mechanics: A Time-Dependent Perspective, University Science Books, Sausalito, California, 2007.
- [166] S. Reiter, D. Keefer, R. de Vivie-Riedle in *Quantum Chemistry and Dynamics of Excited States*, (Eds.: L. González, R. Lindh), John Wiley & Sons Ltd, **2020**, pp. 355–381.
- [167] E. Schrödinger, Ann. Phys. 1926, 384, 361–376.
- [168] E. Schrödinger, Ann. Phys. 1926, 384, 489–527.
- [169] E. Schrödinger, Ann. Phys. 1926, 385, 437–490.
- [170] E. Schrödinger, Ann. Phys. **1926**, 386, 109–139.
- [171] C. Leforestier, R. H. Bisseling, C. Cerjan, M. D. Feit, R. Friesner, A. Guldberg, A. Hammerich, G. Jolicard, W. Karrlein, H. .-. Meyer, N. Lipkin, O. Roncero, R. Kosloff, J. Comput. Phys. 1991, 94, 59–80.
- [172] H. Tal-Ezer, R. Kosloff, J. Chem. Phys. 1984, 81, 3967–3971.
- [173] M. Kowalewski, R. de Vivie-Riedle, QDng: A Grid Based Molecular Quantum Dynamics Package, version 1.0.0, Zenodo, 2024.
- [174] A. Hofmann, R. de Vivie-Riedle, J. Chem. Phys. 2000, 112, 5054–5059.

- [175] J. P. P. Zauleck, S. Thallmair, M. Loipersberger, R. de Vivie-Riedle, J. Chem. Theory Comput. 2016, 12, 5698–5708.
- [176] J. P. P. Zauleck, R. de Vivie-Riedle, J. Chem. Theory Comput. 2018, 14, 55–62.
- [177] B. Podolsky, *Phys. Rev.* **1928**, *32*, 812–816.
- [178] E. B. Wilson, J. C. Decius, P. C. Cross, Molecular Vibrations: The Theory of Infrared and Raman Vibrational Spectra, Dover Publications, New York, 1980.
- [179] L. J. Schaad, J. Hu, J. Mol. Struct.: THEOCHEM 1989, 185, 203–215.
- [180] M. Kowalewski, J. Mikosch, R. Wester, R. de Vivie-Riedle, J. Phys. Chem. A 2014, 118, 4661–4669.
- [181] S. Thallmair, M. K. Roos, R. de Vivie-Riedle, J. Chem. Phys. 2016, 144, 234104.
- [182] C. Eckart, *Phys. Rev.* **1935**, *47*, 552–558.
- [183] D. Keefer, S. Thallmair, S. Matsika, R. de Vivie-Riedle, J. Am. Chem. Soc. 2017, 139, 5061–5066.
- [184] M. T. d. N. Varella, Y. Arasaki, H. Ushiyama, V. McKoy, K. Takatsuka, J. Chem. Phys. 2006, 124, 154302.
- [185] P. von den Hoff, I. Znakovskaya, M. F. Kling, R. de Vivie-Riedle, *Chem. Phys.* 2009, 366, 139–147.
- [186] D. Picconi, V. Barone, A. Lami, F. Santoro, R. Improta, *ChemPhysChem* 2011, 12, 1957–1968.
- [187] M. K. Roos, S. Reiter, R. de Vivie-Riedle, *Chem. Phys.* 2018, 515, 586–595.
- [188] J. Kim, C. H. Kim, C. Burger, M. Park, M. F. Kling, D. E. Kim, T. Joo, J. Phys. Chem. Lett. 2020, 755–761.
- [189] S. Reiter, L. Bäuml, J. Hauer, R. de Vivie-Riedle, Phys. Chem. Chem. Phys. 2022, 24, 27212–27223.
- [190] J. P. P. Zauleck, M. T. Peschel, F. Rott, S. Thallmair, R. de Vivie-Riedle, J. Phys. Chem. A 2018, 122, 2849–2857.
- [191] S. Thallmair, M. Kowalewski, J. P. P. Zauleck, M. K. Roos, R. de Vivie-Riedle, J. Phys. Chem. Lett. 2014, 5, 3480–3485.
- [192] S. Thallmair, J. P. P. Zauleck, R. de Vivie-Riedle, J. Chem. Theory Comput. 2015, 11, 1987–1995.
- [193] M. Barbatti, A. J. A. Aquino, J. J. Szymczak, D. Nachtigallová, P. Hobza, H. Lischka, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 21453–21458.
- [194] C. Sagan, J. Theor. Biol. 1973, 39, 195–200.
- [195] A. A. Beckstead, Y. Zhang, M. S. de Vries, B. Kohler, *Phys. Chem. Chem. Phys.* 2016, 18, 24228–24238.

- [196] M. M. Brister, M. Pollum, C. E. Crespo-Hernández, *Phys. Chem. Chem. Phys.* 2016, 18, 20097–20103.
- [197] W. L. de Laat, N. G. J. Jaspers, J. H. J. Hoeijmakers, *Genes Dev.* 1999, 13, 768–785.
- [198] D. B. Bucher, C. L. Kufner, A. Schlueter, T. Carell, W. Zinth, J. Am. Chem. Soc. 2016, 138, 186–190.
- [199] S. Faraji, D. Zhong, A. Dreuw, Angew. Chem. Int. Ed. 2016, 55, 5175–5178.
- [200] D. L. Jones, B. K. Baxter, Front. Microbiol. 2017, 8, 1882.
- [201] Z. Liu, C. Tan, X. Guo, Y.-T. Kao, J. Li, L. Wang, A. Sancar, D. Zhong, Proc. Natl. Acad. Sci. USA 2011, 108, 14831–14836.
- [202] L. B. Clark, G. G. Peschel, I. Tinoco, J. Phys. Chem. 1965, 69, 3615–3618.
- [203] S. Matsika, J. Phys. Chem. A 2004, 108, 7584–7590.
- [204] P. D. Frischmann, K. Mahata, F. Würthner, Chem. Soc. Rev. 2013, 42, 1847–1870.
- [205] W. Zhang, A. R. Mohamed, W.-J. Ong, Angew. Chem. Int. Ed. 2020, 59, 22894– 22915.
- [206] D. G. Nocera, Acc. Chem. Res. 2012, 45, 767–776.
- [207] T. Keijer, T. Bouwens, J. Hessels, J. N. H. Reek, Chem. Sci. 2021, 12, 50-70.
- [208] P. M. Stanley, J. Haimerl, N. B. Shustova, R. A. Fischer, J. Warnan, Nat. Chem. 2022, 14, 1342–1356.
- [209] K. Nguyen, B. D. Bruce, Biochim. Biophys. Acta Bioenerg. 2014, 1837, 1553– 1566.
- [210] K. A. Brown, P. W. King, *Photosynth. Res.* **2020**, *143*, 193–203.
- [211] J. Z. Zhang, E. Reisner, *Nat. Rev. Chem.* **2020**, *4*, 6–21.
- [212] A. N. Webber, W. Lubitz, *Biochim. Biophys. Acta Bioenerg.* 2001, 1507, 61–79.
- [213] O. G. Poluektov, S. V. Paschenko, L. M. Utschig, K. V. Lakshmi, M. C. Thurnauer, J. Am. Chem. Soc. 2005, 127, 11910–11911.
- [214] S. Santabarbara, P. Heathcote, M. C. W. Evans, *Biochim. Biophys. Acta Bioenerg.* 2005, 1708, 283–310.
- [215] M. G. Müller, C. Slavov, R. Luthra, K. E. Redding, A. R. Holzwarth, Proc. Natl. Acad. Sci. USA 2010, 107, 4123–4128.
- [216] S. Santabarbara, L. Galuppini, A. P. Casazza, J. Integr. Plant Biol. 2010, 52, 735–749.

- [217] S. M. Keable, A. Kölsch, P. S. Simon, M. Dasgupta, R. Chatterjee, S. K. Subramanian, R. Hussein, M. Ibrahim, I.-S. Kim, I. Bogacz, H. Makita, C. C. Pham, F. D. Fuller, S. Gul, D. Paley, L. Lassalle, K. D. Sutherlin, A. Bhowmick, N. W. Moriarty, I. D. Young, J. P. Blaschke, C. de Lichtenberg, P. Chernev, M. H. Cheah, S. Park, G. Park, J. Kim, S. J. Lee, J. Park, K. Tono, S. Owada, M. S. Hunter, A. Batyuk, R. Oggenfuss, M. Sander, S. Zerdane, D. Ozerov, K. Nass, H. Lemke, R. Mankowsky, A. S. Brewster, J. Messinger, N. K. Sauter, V. K. Yachandra, J. Yano, A. Zouni, J. Kern, *Sci. Rep.* 2021, *11*, 21787.
- [218] R. A. Grimme, C. E. Lubner, D. A. Bryant, J. H. Golbeck, J. Am. Chem. Soc. 2008, 130, 6308–6309.
- [219] S. M. Kaniber, M. Brandstetter, F. C. Simmel, I. Carmeli, A. W. Holleitner, J. Am. Chem. Soc. 2010, 132, 2872–2873.
- [220] L. M. Utschig, N. M. Dimitrijevic, O. G. Poluektov, S. D. Chemerisov, K. L. Mulfort,
   D. M. Tiede, J. Phys. Chem. Lett. 2011, 2, 236–241.
- [221] T. Noji, T. Suzuki, M. Kondo, T. Jin, K. Kawakami, T. Mizuno, H. Oh-oka, M. Ikeuchi, M. Nango, Y. Amao, N. Kamiya, T. Dewa, *Res. Chem. Intermed.* 2016, 42, 7731–7742.
- [222] K. P. Sokol, W. E. Robinson, A. R. Oliveira, J. Warnan, M. M. Nowaczyk, A. Ruff,
   I. A. C. Pereira, E. Reisner, J. Am. Chem. Soc. 2018, 140, 16418–16422.
- [223] K. P. Sokol, W. E. Robinson, J. Warnan, N. Kornienko, M. M. Nowaczyk, A. Ruff, J. Z. Zhang, E. Reisner, *Nat. Energy* 2018, 3, 944–951.
- [224] P. Wang, A. Frank, J. Appel, M. Boehm, N. Strabel, M. M. Nowaczyk, W. Schuhmann, F. Conzuelo, K. Gutekunst, Adv. Energy Mater. 2023, 13, 2203232.
- [225] F. Fu, C. Wang, Q. Wang, A. M. Martinez-Villacorta, A. Escobar, H. Chong, X. Wang, S. Moya, L. Salmon, E. Fouquet, J. Ruiz, D. Astruc, J. Am. Chem. Soc. 2018, 140, 10034–10042.
- [226] T. F. Jaramillo, K. P. Jørgensen, J. Bonde, J. H. Nielsen, S. Horch, I. Chorkendorff, Science 2007, 317, 100–102.
- [227] Y. Li, H. Wang, L. Xie, Y. Liang, G. Hong, H. Dai, J. Am. Chem. Soc. 2011, 133, 7296–7299.
- [228] Q. Liu, Y. Guo, Z. Chen, Z. Zhang, X. Fang, Appl. Catal. B: Environ. 2016, 183, 231–241.
- [229] S. Singla, S. Sharma, S. Basu, N. P. Shetti, T. M. Aminabhavi, Int. J. Hydrog. Energy 2021, 46, 33696–33717.
- [230] J. L. Dempsey, B. S. Brunschwig, J. R. Winkler, H. B. Gray, Acc. Chem. Res. 2009, 42, 1995–2004.
- [231] C. H. Lee, D. K. Dogutan, D. G. Nocera, J. Am. Chem. Soc. 2011, 133, 8775–8777.

- [232] B. H. Solis, S. Hammes-Schiffer, *Inorg. Chem.* 2011, 50, 11252–11262.
- [233] J. R. McKone, S. C. Marinescu, B. S. Brunschwig, J. R. Winkler, H. B. Gray, *Chem. Sci.* 2014, 5, 865–878.
- [234] H. Lei, A. Han, F. Li, M. Zhang, Y. Han, P. Du, W. Lai, R. Cao, *Phys. Chem. Chem. Phys.* 2014, 16, 1883–1893.
- [235] S. Roy, A. Bhunia, N. Schuth, M. Haumann, S. Ott, Sustain. Energy Fuels 2018, 2, 1148–1152.
- [236] G. C. Tok, A. T. S. Freiberg, H. A. Gasteiger, C. R. Hess, *ChemCatChem* 2019, 11, 3973–3981.
- [237] M. G. Papanikolaou, A. Elliott, J. McAllister, J. K. Gallos, A. D. Keramidas, T. A. Kabanos, S. Sproules, H. N. Miras, *Dalton Trans.* 2020, 49, 15718–15730.
- [238] M. B. Brands, J. N. H. Reek, *Inorg. Chem.* 2024, 63, 8484–8492.
- [239] H. O'Neill, E. Greenbaum, Chem. Mater. 2005, 17, 2654–2661.
- [240] A. Cherubin, L. Destefanis, M. Bovi, F. Perozeni, I. Bargigia, G. de la Cruz Valbuena, C. D'Andrea, A. Romeo, M. Ballottari, M. Perduca, ACS Sustain. Chem. Eng. 2019, 7, 10435–10444.
- [241] A. H. Teodor, L. B. Thal, S. Vijayakumar, M. Chan, G. Little, B. D. Bruce, *Mater. Today Bio* **2021**, *11*, 100122.
- [242] T. H. Bennett, M. D. Vaughn, S. Ali Davari, K. Park, D. Mukherjee, B. Khomami, *Nanoscale Adv.* 2019, 1, 94–104.
- [243] T. H. Bennett, R. Pamu, G. Yang, D. Mukherjee, B. Khomami, *Nanoscale Adv.* 2020, 2, 5171–5180.
- [244] P. Jordan, P. Fromme, H. T. Witt, O. Klukas, W. Saenger, N. Krauß, *Nature* 2001, 411, 909–917.
- [245] E. V. Puttock, P. Banerjee, M. Kaspar, L. Drennen, D. S. Yufit, E. Bill, S. Sproules, C. R. Hess, *Inorg. Chem.* 2015, 54, 5864–5873.
- [246] F. Neese, WIREs Comput. Mol. Sci. 2022, 12, e1606.
- [247] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.
- [248] D. Rappoport, F. Furche, J. Chem. Phys. 2010, 133, 134105.
- [249] M. Cossi, N. Rega, G. Scalmani, V. Barone, J. Comput. Chem. 2003, 24, 669–681.
- [250] F. Neese, F. Wennmohs, A. Hansen, U. Becker, *Chem. Phys.* **2009**, *356*, 98–109.
- [251] R. Izsák, F. Neese, J. Chem. Phys. 2011, 135, 144105.
- [252] F. Weigend, Phys. Chem. Chem. Phys. 2006, 8, 1057–1065.
- [253] A. Hellweg, C. Hättig, S. Höfener, W. Klopper, Theor. Chem. Acc. 2007, 117, 587–597.

- [254] A. Hellweg, D. Rappoport, Phys. Chem. Chem. Phys. 2015, 17, 1010–1017.
- [255] M. Byrdin, P. Jordan, N. Krauss, P. Fromme, D. Stehlik, E. Schlodder, *Biophys. J.* 2002, 83, 433–457.
- [256] A. Damjanović, I. Kosztin, U. Kleinekathöfer, K. Schulten, Phys. Rev. E 2002, 65, 031919.
- [257] B. Brüggemann, K. Sznee, V. Novoderezhkin, R. van Grondelle, V. May, J. Phys. Chem. B 2004, 108, 13536–13546.
- [258] S. Vaitekonis, G. Trinkunas, L. Valkunas, *Photosynth. Res.* 2005, 86, 185–201.
- [259] S. Yin, M. G. Dahlbom, P. J. Canfield, N. S. Hush, R. Kobayashi, J. R. Reimers, J. Phys. Chem. B 2007, 111, 9923–9930.
- [260] Y. Lee, M. Gorka, J. H. Golbeck, J. M. Anna, J. Am. Chem. Soc. 2018, 140, 11631–11638.
- [261] P. Akhtar, A. Biswas, F. Balog-Vig, I. Domonkos, L. Kovács, P. H. Lambrev, *Plant Physiol.* 2022, 189, 827–838.
- [262] C. MacGregor-Chatwin, P. J. Jackson, M. Sener, J. W. Chidgey, A. Hitchcock, P. Qian, G. E. Mayneord, M. P. Johnson, Z. Luthey-Schulten, M. J. Dickman, D. J. Scanlan, C. N. Hunter, *Nat. Plants* **2019**, *5*, 879–889.
- [263] M. K. Şener, S. Park, D. Lu, A. Damjanović, T. Ritz, P. Fromme, K. Schulten, J. Chem. Phys. 2004, 120, 11183–11195.
- [264] D. A. Semchonok, J. Mondal, C. J. Cooper, K. Schlum, M. Li, M. Amin, C. O. S. Sorzano, E. Ramírez-Aportela, P. L. Kastritis, E. J. Boekema, A. Guskov, B. D. Bruce, *Plant Commun.* 2022, *3*, 100248.
- [265] K. Kłodawska, L. Kovács, R. Vladkova, A. Rzaska, Z. Gombos, H. Laczkó-Dobos, P. Malec, *Photosynth. Res.* 2020, 143, 251–262.
- [266] S. Grimme, C. Bannwarth, P. Shushkov, J. Chem. Theory Comput. 2017, 13, 1989–2009.
- [267] J. P. Götze, H. Lokstein, ACS Omega 2023, 8, 40015–40023.
- [268] J. P. Götze, H. Lokstein, ACS Omega 2023, 8, 40005–40014.
- [269] P. Hohenberg, W. Kohn, *Phys. Rev.* 1964, 136, B864–B871.
- [270] W. Kohn, L. J. Sham, *Phys. Rev.* 1965, 140, A1133–A1138.

- [271] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, *Gaussian 16 Rev. C.01*, Wallingford, CT, **2016**.
- [272] M. J. Frisch, J. A. Pople, J. S. Binkley, J. Chem. Phys. 1984, 80, 3265–3269.
- [273] A. D. McLean, G. S. Chandler, J. Chem. Phys. 1980, 72, 5639–5648.
- [274] R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, J. Chem. Phys. 1980, 72, 650–654.
- [275] G. Scalmani, M. J. Frisch, J. Chem. Phys. 2010, 132, 114110.
- [276] W. Humphrey, A. Dalke, K. Schulten, J. Mol. Graph. 1996, 14, 33–38.
- [277] L. Goerigk, A. Hansen, C. Bauer, S. Ehrlich, A. Najibi, S. Grimme, *Phys. Chem. Chem. Phys.* 2017, 19, 32184–32215.
- [278] N. Mardirossian, M. Head-Gordon, *Mol. Phys.* 2017, 115, 2315–2372.
- [279] L. Goerigk, N. Mehta, Aust. J. Chem. 2019, 72, 563–573.
- [280] D. G. Liakos, Y. Guo, F. Neese, J. Phys. Chem. A 2020, 124, 90–100.
- [281] M. Saitow, U. Becker, C. Riplinger, E. F. Valeev, F. Neese, J. Chem. Phys. 2017, 146, 164105.
- [282] F. Neese, WIREs Comput. Mol. Sci. 2012, 2, 73–78.
- [283] F. Neese, WIREs Comput. Mol. Sci. 2018, 8, e1327.
- [284] V. Barone, M. Cossi, J. Phys. Chem. A 1998, 102, 1995–2001.
- [285] J. E. Bartmess, J. Phys. Chem. 1994, 98, 6420–6424.
- [286] L. E. Roy, E. Jakubikova, M. G. Guthrie, E. R. Batista, J. Phys. Chem. A 2009, 113, 6745–6750.
- [287] D. G. Truhlar, C. J. Cramer, A. Lewis, J. A. Bumpus, J. Chem. Educ. 2004, 81, 596.
- [288] S. J. Konezny, M. D. Doherty, O. R. Luca, R. H. Crabtree, G. L. Soloveichik, V. S. Batista, J. Phys. Chem. C 2012, 116, 6349–6356.

- [289] S. Maier, B. Thapa, K. Raghavachari, Phys. Chem. Chem. Phys. 2020, 22, 4439– 4452.
- [290] A. P. Davis, A. J. Fry, J. Phys. Chem. A 2010, 114, 12299–12304.
- [291] A. A. Isse, A. Gennaro, J. Phys. Chem. B 2010, 114, 7894–7899.
- [292] A. Francisco da Silva, A. João da Silva Filho, M. L. A. A. Vasconcellos, O. Luís de Santana, *Molecules* 2018, 23, 2129.
- [293] J. Ho, A. Klamt, M. L. Coote, J. Phys. Chem. A **2010**, 114, 13442–13444.
- [294] M. Namazian, C. Y. Lin, M. L. Coote, J. Chem. Theory Comput. 2010, 6, 2721– 2725.
- [295] M. Isegawa, F. Neese, D. A. Pantazis, J. Chem. Theory Comput. 2016, 12, 2272– 2284.
- [296] S. Grimme, M. Waletzke, J. Chem. Phys. 1999, 111, 5645–5655.
- [297] I. Lyskov, M. Kleinschmidt, C. M. Marian, J. Chem. Phys. 2016, 144, 034104.
- [298] A. Heil, C. M. Marian, J. Chem. Phys. 2017, 147, 194104.
- [299] A. Heil, M. Kleinschmidt, C. M. Marian, J. Chem. Phys. 2018, 149, 164106.
- [300] C. M. Marian, A. Heil, M. Kleinschmidt, WIREs Comput. Mol. Sci. 2018, 9, e1394.
- [301] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* 1988, 37, 785–789.
- [302] A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098–3100.
- [303] F. Weigend, M. Kattannek, R. Ahlrichs, J. Chem. Phys. 2009, 130, 164106.
- [304] S. Kossmann, F. Neese, Chem. Phys. Lett. 2009, 481, 240–243.
- [305] F. Weigend, J. Comput. Chem. 2008, 29, 167–175.
- [306] F. Neese, J. Am. Chem. Soc. 2006, 128, 10213–10222.
- [307] D. A. Kreplin, P. J. Knowles, H.-J. Werner, J. Chem. Phys. 2020, 152, 074102.
- [308] H.-J. Werner, W. Meyer, J. Chem. Phys. 1981, 74, 5794–5801.
- [309] H.-J. Werner, P. J. Knowles, J. Chem. Phys. 1985, 82, 5053–5063.
- [310] H.-J. Werner, P. J. Knowles, G. Knizia, F. R. Manby, M. Schütz, P. Celani, T. Korona, R. Lindh, A. Mitrushenkov, G. Rauhut, K. R. Shamasundar, T. B. Adler, R. D. Amos, A. Bernhardsson, A. Berning, D. L. Cooper, M. J. O. Deegan, A. J. Dobbyn, F. Eckert, E. Goll, C. Hampel, A. Hesselmann, G. Hetzer, T. Hrenar, G. Jansen, C. Köppl, Y. Liu, A. W. Lloyd, R. A. Mata, A. J. May, S. J. McNicholas, W. Meyer, M. E. Mura, A. Nicklass, D. P. O'Neill, P. Palmieri, D. Peng, K. Pflüger, R. Pitzer, M. Reiher, T. Shiozaki, H. Stoll, A. J. Stone, R. Tarroni, T. Thorsteinsson, M. Wang, *MOLPRO, Version 2012.1, a Package of Ab Initio Programs*, version 2012.1, 2012.
- [311] H.-J. Werner, P. J. Knowles, G. Knizia, F. R. Manby, M. Schütz, WIREs Comput. Mol. Sci. 2012, 2, 242–253.

- [312] H.-J. Werner, P. J. Knowles, F. R. Manby, J. A. Black, K. Doll, A. Heßelmann, D. Kats, A. Köhn, T. Korona, D. A. Kreplin, Q. Ma, T. F. Miller, A. Mitrushchenkov, K. A. Peterson, I. Polyak, G. Rauhut, M. Sibaev, J. Chem. Phys. 2020, 152, 144107.
- [313] T. H. Dunning, J. Chem. Phys. 1989, 90, 1007–1023.
- [314] R. A. Kendall, T. H. Dunning, R. J. Harrison, J. Chem. Phys. 1992, 96, 6796–6806.
- [315] W. Győrffy, T. Shiozaki, G. Knizia, H.-J. Werner, J. Chem. Phys. 2013, 138, 104104.
- [316] B. Helmich-Paris, J. Chem. Theory Comput. 2019, 15, 4170–4179.
- [317] C. A. Hunter, J. K. M. Sanders, J. Am. Chem. Soc. 1990, 112, 5525–5534.
- [318] C. R. Martinez, B. L. Iverson, *Chem. Sci.* **2012**, *3*, 2191–2201.
- [319] C. J. I. Zeman, S. Kim, F. Zhang, K. S. Schanze, J. Am. Chem. Soc. 2020, 142, 2204–2207.
- [320] F. Neese, F. Wennmohs, U. Becker, C. Riplinger, J. Chem. Phys. 2020, 152, 224108.
- [321] S. Grimme, A. Hansen, S. Ehlert, J.-M. Mewes, J. Chem. Phys. 2021, 154, 064103.
- [322] E. Caldeweyher, S. Ehlert, A. Hansen, H. Neugebauer, S. Spicher, C. Bannwarth, S. Grimme, J. Chem. Phys. 2019, 150, 154122.
- [323] H. Kruse, S. Grimme, J. Chem. Phys. 2012, 136, 154101.
- [324] S. Grimme, *Chem. Eur. J.* **2012**, *18*, 9955–9964.
- [325] Y. Guo, C. Riplinger, U. Becker, D. G. Liakos, Y. Minenkov, L. Cavallo, F. Neese, J. Chem. Phys. 2018, 148, 011101.
- [326] Y. Guo, C. Riplinger, D. G. Liakos, U. Becker, M. Saitow, F. Neese, J. Chem. Phys. 2020, 152, 024116.
- [327] E. van Lenthe, E. J. Baerends, J. G. Snijders, J. Chem. Phys. 1993, 99, 4597–4610.
- [328] C. van Wüllen, J. Chem. Phys. 1998, 109, 392–399.
- [329] J. Zheng, X. Xu, D. G. Truhlar, Theor. Chem. Acc. 2011, 128, 295–305.
- [330] F. Neese, J. Phys. Chem. Solids 2004, 65, 781–785.
- [331] H.-J. Werner, P. J. Knowles, P. Celani, W. Györffy, A. Hesselmann, D. Kats, G. Knizia, A. Köhn, T. Korona, D. Kreplin, R. Lindh, Q. Ma, F. R. Manby, A. Mitrushenkov, G. Rauhut, M. Schütz, K. R. Shamasundar, T. B. Adler, R. D. Amos, S. J. Bennie, A. Bernhardsson, A. Berning, J. A. Black, P. J. Bygrave, R. Cimiraglia, D. L. Cooper, D. Coughtrie, M. J. O. Deegan, A. J. Dobbyn, K. Doll, M. Dornbach, F. Eckert, S. Erfort, E. Goll, C. Hampel, G. Hetzer, J. G. Hill, M. Hodges, T. Hrenar, G. Jansen, C. Köppl, C. Kollmar, S. J. R. Lee, Y. Liu, A. W. Lloyd, R. A. Mata, A. J. May, B. Mussard, S. J. McNicholas, W. Meyer, T. F. Miller III, M. E. Mura, A. Nicklass, D. P. O'Neill, P. Palmieri, D. Peng, K. A. Peterson, K. Pflüger, R. Pitzer, I. Polyak, M. Reiher, J. O. Richardson, J. B. Robinson, B. Schröder, M. Schwilk, T.

Shiozaki, M. Sibaev, H. Stoll, A. J. Stone, R. Tarroni, T. Thorsteinsson, J. Toulouse, M. Wang, M. Welborn, B. Ziegler, *MOLPRO*, *Version 2023.2*, a Package of Ab Initio Programs, version 2023.2, 2023.

- [332] J. P. Perdew, *Phys. Rev. B* **1986**, *33*, 8822–8824.
- [333] J. P. Perdew, *Phys. Rev. B* 1986, 34, 7406–7406.
- [334] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, J. Chem. Phys. 2010, 132, 154104.
- [335] S. Grimme, S. Ehrlich, L. Goerigk, J. Comput. Chem. 2011, 32, 1456–1465.
- [336] C. Angeli, R. Cimiraglia, S. Evangelisti, T. Leininger, J.-P. Malrieu, J. Chem. Phys. 2001, 114, 10252–10264.
- [337] C. Angeli, R. Cimiraglia, J.-P. Malrieu, J. Chem. Phys. 2002, 117, 9138–9153.
- [338] C. Angeli, M. Pastore, R. Cimiraglia, Theor. Chem. Acc. 2007, 117, 743-754.
- [339] F. Brandl, S. Bergwinkl, C. Allacher, B. Dick, Chem. Eur. J. 2020, 26, 7946–7954.
- [340] S. Hirata, M. Head-Gordon, Chem. Phys. Lett. 1999, 314, 291–299.
- [341] F. Plasser, J. Chem. Phys. 2020, 152, 084108.
- [342] F. Plasser, M. Wormit, A. Dreuw, J. Chem. Phys. 2014, 141, 024106.
- [343] F. Plasser, H. Lischka, J. Chem. Theory Comput. 2012, 8, 2777–2789.
- [344] B. de Bruin, E. Bill, E. Bothe, T. Weyhermüller, K. Wieghardt, *Inorg. Chem.* 2000, 39, 2936–2947.
- [345] T. J. Lee, P. R. Taylor, Int. J. Quantum. Chem. 1989, 36, 199–207.
- [346] A. Yoshikawa, S. Matsika, *Chem. Phys.* **2008**, *347*, 393–404.
- [347] H. Lischka, T. Müller, P. G. Szalay, I. Shavitt, R. M. Pitzer, R. Shepard, WIREs Comput. Mol. Sci. 2011, 1, 191–199.
- [348] H. Lischka, R. Shepard, R. M. Pitzer, I. Shavitt, M. Dallos, T. Müller, P. G. Szalay, M. Seth, G. S. Kedziora, S. Yabushita, Z. Zhang, *Phys. Chem. Chem. Phys.* 2001, 3, 664–673.
- [349] H. Lischka, R. Shepard, I. Shavitt, R. M. Pitzer, M. Dallos, T. Müller, P. G. Szalay,
  F. B. Brown, R. Ahlrichs, H. J. Böhm, A. Chang, D. C. Comeau, R. Gdanitz,
  H. Dachsel, C. Ehrhardt, M. Ernzerhof, P. Höchtl, S. Irle, G. Kedziora, T. Kovar,
  V. Parasuk, M. J. M. Pepper, P. Scharf, H. Schiffer, M. Schindler, M. Schüler, M.
  Seth, E. A. Stahlberg, J.-G. Zhao, S. Yabushita, Z. Zhang, M. Barbatti, S. Matsika,
  M. Schuurmann, D. R. Yarkony, S. R. Brozell, E. V. Beck, J.-P. Blaudeau, M.
  Ruckenbauer, B. Sellner, F. Plasser, J. J. Szymczak, *COLUMBUS, an Ab Initio Electronic Structure Program, Release 7.0*, version 7.0, 2017.
- [350] U. C. Singh, P. A. Kollman, J. Comput. Chem. 1984, 5, 129–145.
- [351] A. Sali, T. L. Blundell, J. Mol. Biol. 1993, 234, 779–815.

- [352] E. F. Pettersen, T. D. Goddard, C. C. Huang, G. S. Couch, D. M. Greenblatt, E. C. Meng, T. E. Ferrin, J. Comput. Chem. 2004, 25, 1605–1612.
- [353] S. Buchoux, *Bioinformatics* **2017**, *33*, 133–134.
- [354] A. Leftin, T. R. Molugu, C. Job, K. Beyer, M. F. Brown, *Biophys. J.* 2014, 107, 2274–2286.
- [355] Å. A. Skjevik, B. D. Madej, C. J. Dickson, K. Teigen, R. C. Walker, I. R. Gould, *Chem. Commun.* 2015, 51, 4402–4405.
- [356] G. Shahane, W. Ding, M. Palaiokostas, M. Orsi, J. Mol. Model. 2019, 25, 76.
- [357] N. Kučerka, S. Tristram-Nagle, J. F. Nagle, J. Membr. Biol. 2006, 208, 193–202.
- [358] A. Damjanović, H. M. Vaswani, P. Fromme, G. R. Fleming, J. Phys. Chem. B 2002, 106, 10251–10262.
- [359] S. R. G. Balestra, R. Semino, J. Chem. Phys. 2022, 157, 184502.
- [360] S. R. G. Balestra, Codes for Computer Simulation of the Early and Late Stages of the Self-Assembly of ZIF-8, 2024.
- [361] S. Reiter, F. L. Kiss, J. Hauer, R. de Vivie-Riedle, Chem. Sci. 2023, 14, 3117–3131.
- [362] B. Hess, H. Bekker, H. J. C. Berendsen, J. G. E. M. Fraaije, J. Comput. Chem. 1997, 18, 1463–1472.
- [363] S. Páll, B. Hess, Comput. Phys. Commun. 2013, 184, 2641–2650.
- [364] T. Darden, D. York, L. Pedersen, J. Chem. Phys. 1993, 98, 10089.
- [365] U. Essmann, L. Perera, M. L. Berkowitz, T. Darden, H. Lee, L. G. Pedersen, J. Chem. Phys. 1995, 103, 8577–8593.
- [366] B. L. Eggimann, A. J. Sunnarborg, H. D. Stern, A. P. Bliss, J. I. Siepmann, Mol. Simul. 2014, 40, 101–105.
- [367] G. Bussi, D. Donadio, M. Parrinello, J. Chem. Phys. 2007, 126, 014101.
- [368] H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, A. DiNola, J. R. Haak, J. Chem. Phys. 1984, 81, 3684–3690.
- [369] M. Taravillo, F. J. Pérez, J. Núñez, M. Cáceres, V. G. Baonza, J. Chem. Eng. Data 2007, 52, 481–486.
- [370] W. Brostow, T. Grindley, M. A. Macip, *Mater. Chem. Phys.* **1985**, *12*, 37–97.
- [371] S. Cao, T. D. Bennett, D. A. Keen, A. L. Goodwin, A. K. Cheetham, *Chem. Commun.* 2012, 48, 7805–7807.
- [372] J. Wang, W. Wang, P. A. Kollman, D. A. Case, J. Mol. Graphics 2006, 25, 247–260.
- [373] J. Wang, R. M. Wolf, J. W. Caldwell, P. A. Kollman, D. A. Case, J. Comput. Chem. 2004, 25, 1157–1174.

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