

Solvent Dependency of Catalyst-Substrate Aggregation Through π - π Stacking in Photoredox Catalysis

Luke Wylie,^{*,[a]} Joshua P. Barham,^{*,[b]} and Barbara Kirchner^[a]

Assemblies of photoredox catalysts and their target substrates prior to photoexcitation is a phenomenon naïvely overlooked by the majority of synthetic chemists, but can have profound influences on reactivity and selectivity in photocatalytic reactions. In this study, we determine the aggregation states of triarylamine radical cationic photocatalysts with various target arene substrates in different solvents by specifically parameterized polarizable molecular dynamics simulations. A π -stacking interaction previously implicated by more expensive, less-representative quantum calculations is confirmed. Critically, this study presents new insights on: i) the ability of solvents

(MeCN vs DMF) to make or break a photocatalytic reaction by promoting (MeCN) or demoting (DMF) its catalyst-substrate assemblies, which is a determining factor for reactivity, ii) the average "lifetimes" of assemblies in solution from a dynamic simulation. We find that both in the ground state and the photoexcited state, the cationic radical assemblies remain intact for periods often higher than 60 ps, rendering them ideally suitable to undergo intra-assembly electron transfer reactions upon photoexcitation. Such aspects have not addressed by previous studies on synthetic photocatalytic reactions involving non-covalent assemblies.

Introduction

In the field of visible light PhotoRedox Catalysis (PRC),^[1-4] a PRCat is often (i) tailored to a target substrate group by considering the matching of specific redox potentials of catalyst and substrate, (ii) chosen based on its excited state being sufficiently "long-lived" (nano- to microseconds) to engage in diffusion-controlled single electron transfer (SET) quenching processes, and (iii) naïvely considered as a separate entity to the substrate, whose photophysical and electrochemical properties are not influenced by the substrate's presence. Despite the well-known profound effects of aggregation on the photophysical properties of organic molecules,^[5-7] such effects on the catalyst, substrate, or their combination are typically overlooked in the design of PRC reactions. However, aggregation is an especially crucial consideration in two recently-trending sub-fields of PRC, in which catalysts are more sustainable than traditional rare noble metal-based PRCats and can achieve challenging bond activations: i) radical ion photocatalysts, that are generated by an initial photoinduced SET (a so-called 'COMPET' strategy)^[8] or by an initial electrochemical SET event (so-

called electro-activated PhotoRedox Catalysis'e-PRC' strategy)^[9] ii) first-row transition metal photocatalysis, such as those employing Ni, Co or Mn photoactive complexes. In both fields (i) and (ii), the photoexcited states arise successful reactivity despite their ultrashort lifetimes (sub-nanoseconds to picoseconds) that render them too short-lived for diffusional quenching. Moreover, despite the clear prevalence of how organic molecular pre-assemblies can direct reactive outcomes in other fields such as polymer chemistry and supramolecular chemistry,^[10,11] the properties of pre-assemblies in synthetic PRC studies have rarely been studied.

The most plausible explanation for this behaviour is a preassembly of ground state photocatalyst and substrate, such that upon photoexcitation they undergo a close-proximity quenching by SET.^[12,13] This rationalization was presented by the Barham group for radical cationic and radical anionic photocatalytic examples, based upon steady-state spectroscopic, structure-reactivity observations and that photochemistry is able to occur selectively from excited states higher than the first (in an "anti-Kasha" fashion).^[14,15] This is a hallmark feature and benefit of preassembly - that can outcompete internal conversion and maximize on the photon's energy for redox. Subsequent studies on transient absorption spectroscopy have unequivocally confirmed reactivity by preassemblies via quenching of picosecond-lived excited states.^[16,17] In order to design future catalysts and reactions, it is critical to understand the driving forces for assembly formation and to resolve structural information on the interactions at play.^[18] So far, structural information on the preassemblies has so far derived from static quantum chemical (QC) calculations, which found π - π (face to face) or T- π (edge to face) stacking interactions.^[14,15] However, the costly nature of QC calculations employing high-level DFT restricts the observation of systems on a large enough scale to probe the probability of interaction between substrate and catalyst in a dynamic, multicomponent system. As

[a] Dr. L. Wylie, Prof. Dr. B. Kirchner

University of Bonn, Clausius Institute of Physical and Theoretical Chemistry, Mulliken Center for Theoretical Chemistry, Beringstr. 4, D-53115 Bonn, Germany
E-mail: wylie@thch.uni-bonn.de

[b] Dr. J. P. Barham

Institute of Organic Chemistry, University of Regensburg, Universitätsstraße 31, D93053 Regensburg, Germany
E-mail: Joshua-Philipp.Barham@chemie.uni-regensburg.de

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discussed in previous studies used to determine physical interaction and aggregation, molecular dynamics (MD) and specifically polarizable MD is a more appropriate tool for insight into the modes of interaction between such entities.^[19,20] These can be specifically helpful in the instance where the probability of π - π stacking is to be analyzed,^[21] or the presence of large aggregates are to be determined.^[22,23] For a radical ion photocatalyst to be effective, it needs initially to form an assembly with the substrate that is either favorable (exergonic) or "accessibly endergonic" in solution at room temperature. Through analysing the solvation energies of substrate-catalyst assemblies in solvent through umbrella integration, it is possible to determine the favourability of interaction.^[24] It was previously shown how tri(*p*-substituted)arylamines (TPAs) can be employed as e-PCats to transfer radical cationic character to preassembled (π -stacked) arene substrates that are otherwise highly challenging to oxidize chemically.^[15] Solvent choice profoundly impacted reactivity, with nucleophilically-trapped product yields of 80–88% in MeCN and DCM, and no reaction in DMF. Given the dielectric constants of MeCN and DMF are similar (both are common organic solvents in electrochemistry), while DCM is notably lower, such a solvent influence on reactivity is surprising and unlikely to be related to the initial electrochemical catalyst activation. We questioned the impact of solvation on the radical cation-substrate assembly. Another open, urgent question relates to the lifetime/occurrence of these assemblies in solution in the ground state, and how much this is impacted by solvent choice.

In this study, we aimed to focus on understanding the ability of substrates to form assemblies with e-PRCats and the methods by which these are formed. Different combinations of TPA e-PRCats and substrates were examined to determine the modes of assembly. The solvent used in the reaction was varied to determine the effect of the solvent on substrate-catalyst assembly formation. This was completed with polarizable MD using a specifically designed forcefield to give large-scale predictions of interactions between different fragments involved in this system.

All simulations, with the exception of umbrella integration were run on a system with 2000 solvent molecules, 50 catalyst molecules split evenly between (photochemically-active) radical cation and (inactive) neutral states, 100 hexafluorophosphate PF_6^- anions, 75 tetrabutylammonium N_{4444}^+ cations and 200 substrate, see Figure 1. Solvents tested were dichloromethane (DCM), dimethylformamide (DMF) and acetonitrile (MeCN). Tri(*p*-substituted)biarylamine (TPA) catalyst molecules included tris(4'-cyano-[1,1'-biphenyl]-4-yl)amine (TCBPA) and tri([1,1'-biphenyl]-4-yl)amine (*Tp*BPA). The pairings of e-PRCats and arene substrates studied reflected the prior experimental conditions. For umbrella integration the system contained (for each solvent tested) 500 solvent molecules with all 3 solvents tested, 1 e-PRCat cationic radical (TCBPA), 1 substrate (1,4-dichlorobenzene), 25 PF_6^- anions and 24 N_{4444}^+ cations to act as salts and neutralize the charge.

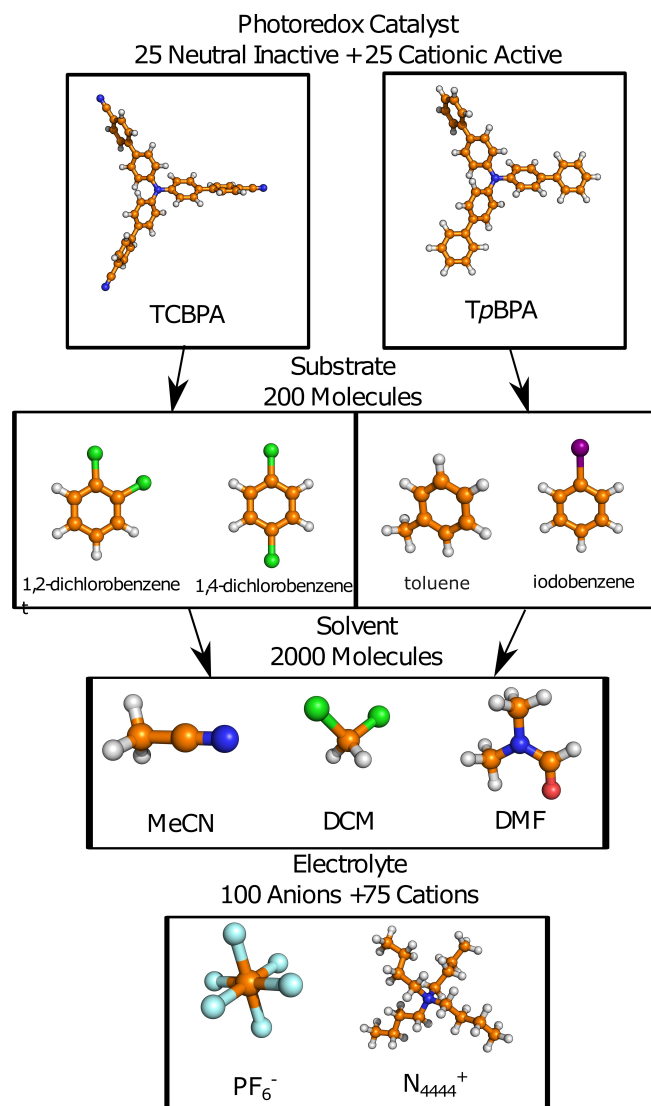


Figure 1. Ball-and-stick representation of compounds applied in this study. With systems consisting of an e-PRCat, their matching substrate to be bound, one of three possible solvents, and electrolytes to neutralize charges within the system.

Results

Initially, to determine the interaction probability between e-PRCats and substrates in a variety of different solvents, radial distribution functions (RDFs) were calculated for each system. As shown in Figure 2, the solvent applied has a large impact on the coordination number, with MeCN typically yielding the highest, while DMF gave notably lower numbers. The coordination numbers for DCM fluctuated between MeCN or DMF depending on the system studied. For example, in the case of the catalytically active TCBPA^{*+} interacting with 1,2-dichlorobenzene, MeCN gave a coordination number of 0.59 whilst DMF only gave 0.39. These results are seen to correlate to experiment, wherein DMF gives no product in the synthetic reactions, while MeCN gives high yields.

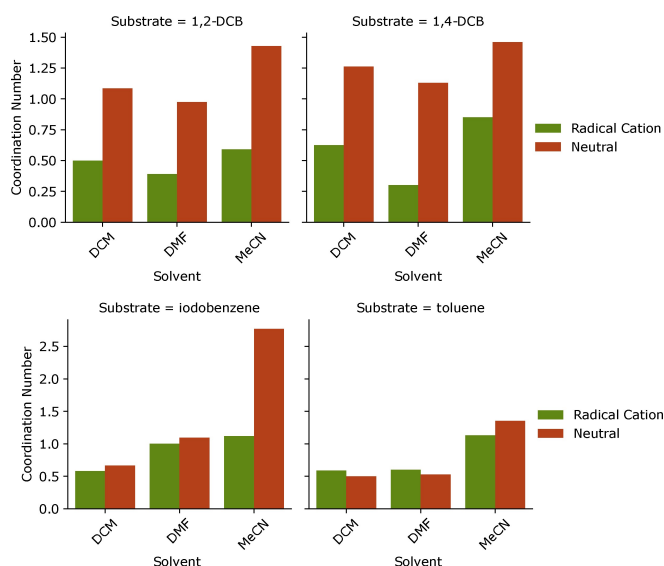


Figure 2. Coordination numbers and $g(r)$ maximum numbers of interactions between COM of inner benzene rings in the cationic radical and neutral state of TCBCPA (top) and TpBPA (bottom) with potential substrates in a range of solvents.

When comparing the (catalytically inactive) neutral e-PRCats TCBCPA and TpBPA to their radical cationic forms in different solvents, the neutral forms consistently display higher coordination numbers. For example, 1,4-dichlorobenzene and neutral TCBCPA yielded an average coordination number of 1.19 between the three solvents compared to 0.69 for the radical cation. This suggests that the oxidation of the catalyst is not necessary for the assembly formation, meaning it is probable that the assembly forms prior to oxidation at the electrode surface. This aspect was overlooked in the previous study.^[15] However, although the assembly is able to form, oxidation may alter its mode of interaction, thus meaning that the preassembly formation may not be indicative of the final assembly structure necessary for the productive SET reaction to take place.

While the differences in coordination numbers for the neutral and radical cationic e-PRCats is clear, it is important to consider differences in local solvation shell sizes. The cationic form consistently displays both a shorter max $g(r)$ peak distance, as well as a shorter first solvation shell distance given by the first minima following the maximum peak, as shown in Figure S1. This implies that SET oxidation of e-PRCats is not necessary for assembly formation with arenes; the neutral e-PRCat and arene can already assemble non-covalently.

To get a more in depth view of how the substrate interacts with the cationic catalyst, the angle of interaction was analyzed in the form of an angular distribution function (ADF) and combined with the previously discussed RDFs to give a combined distribution function (CDF). An angle of 180° or 0° represents a wholly parallel interaction with π - π stacking dominating, whilst 90° is a perpendicular interaction. Overall, we observe interactions classed as π - π but with minor interactions also where there may be 45° angles of one ring,

indicating that regardless of the solvent and substrate added, π - π stacking is preferred, see Figure 3. Notably, DCM and MeCN give an intense, directionalized signal around 180° and 0° with a noticeable reduction in intensity once the angle goes lower than 45° or higher than 135° . In comparison, DMF yields a wider range of interaction angles between TCBCPA in its radical cationic state and 1,2-dichlorobenzene. Given that catalysis of the reaction is effective in DCM, a strong π - π stacking interaction yielding a 180° or 0° degree angle is necessary to facilitate catalysis.

Following this, the lifetimes of π - π stacked assemblies analyzed in the RDFs previously discussed were investigated and compared between the various solvents tested. In this analysis, it was found that even after 60 ps, a substantial portion of these interactions remain (see Figure 4), indicating considerable longevity for the assemblies to form. Of key importance, this lifetime is substantially greater than lifetime of the excited state assembly, allowing the latter's photochemistry to occur on a < 1 ps timescale.^[16] Therefore, regardless of solvent, the assembly formation is a limiting factor determining reactivity. In addition, the long lifetimes indicate that there is a distinct possibility that assemblies may be formed prior to oxidation, then the reaction occurs on this already formed assembly following oxidation. Hence, there is ordering of solvent/arenes even in the absence of electrochemical potential that assists in reactivity once TPA is electro-oxidized within the assembly.

Aggregates of alternating substrates and cationic radical catalysts were then determined using TCBCPA and 1,2-dichlorobenzene as the catalyst-substrate combination. As detailed in Table 1, there is a strong correlation between the solvent used and the degree of aggregation. In this instance, it can be seen

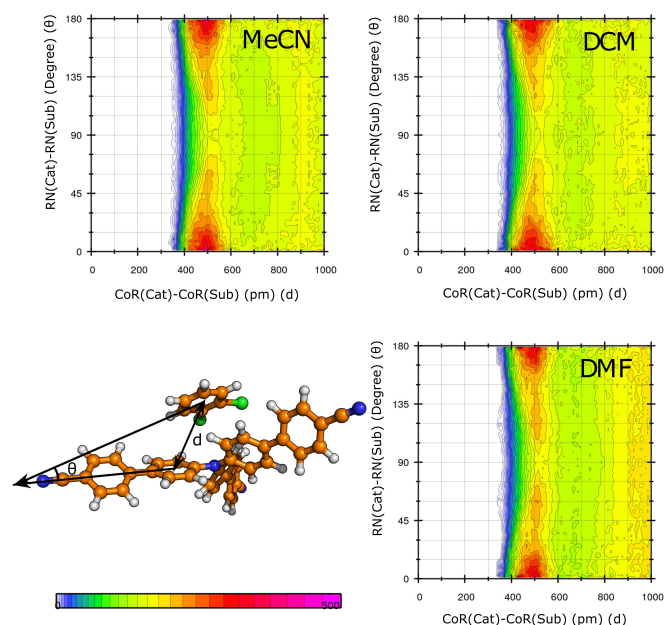


Figure 3. CDFs of systems containing TCBCPA⁺ as an e-PRCat and 1,2-dichlorobenzene as the substrate. Plotting the distance between the center of ring (CoR) of inner aromatic ring of the e-PRCat and the CoR of the binding arene ring (d) against the angle between these two points and the carbons on the substrate rings (θ).

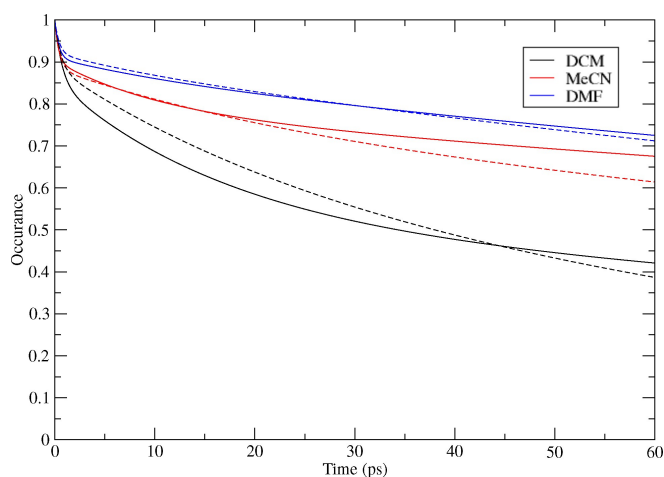


Figure 4. Autocorrelation functions determining the lifetimes of interactions between the inner ring of TCBPA*⁺ (solid lines) and TCBPA (dashed lines) with 1,2-dichlorobenzene in various solvents.

	MeCN	DCM	DMF
Monomer Probability	0.74	0.78	0.82
Dimer Probability	0.06	0.06	0.07
Trimer Probability	0.06	0.06	0.07
4+ mer Probability	0.14	0.11	0.04
% Cat. in Monomer	17%	26%	35%
% Sub in Monomer	81%	84%	88%
Average Cat. numbers	1.672	1.396	1.005

that MeCN forms the largest proportion of oligomers, whilst DMF causes the highest degree of monomers to be present. Interestingly, it can be seen that the difference in oligomers are driven by aggregates larger than trimers, with the probabilities of dimers and trimers being consistent across solvents, while the 4+ mer concentration varied greatly. This indicates that it is the long networks of assemblies in MeCN that facilitate the efficient catalysis seen experimentally. These results support those seen in umbrella sampling displayed in Figure S2, where in MeCN showed the most repulsive forces for breaking of π - π stacking between catalyst and radical, whilst DMF showed almost no unfavourable forces for separation of catalyst and substrate. This therefore indicates that the favourability of interaction between substrate and catalyst is directly related to their ability to form long, alternating oligomers. This can be used to distinguish the characteristics of the solvent which make catalysis most likely; i.e. the solvent that most readily facilitates aggregation interactions is the most favourable for catalysis.

In conclusion, by analysis of the assemblies between cationic radical e-PRCats and aromatic substrates, the solvent in use plays a vital role. In accordance with experiment, MeCN was most capable of facilitating interactions between the catalyst in its radical cationic state and the substrate, whilst DMF hindered

interactions. As shown by their higher coordination numbers, the neutral forms of the catalyst formed slightly more interactions with the substrate, supporting the idea that preassemblies form prior to oxidation. However, the coordination number of oxidized catalysts with substrates is also sufficiently high for a reaction to take place, with this interaction shown to be occurring predominantly through π - π stacking interactions. Lifetimes of dynamically formed ground state catalyst-substrate interactions, irrespective of the solvent used, was ample to enable their photochemical reactivity. This further substantiates the idea that preassemblies form prior to oxidation, which are then bound more tightly upon oxidation which then alters the UV-vis and allows a catalytic reaction to take place. Such a finding reveals the critical role that solvents play in influencing outcomes of PRC reactions even in homogeneous solutions and not only micellar dispersions^[25–27] and demands that solvent molecules are treated in experiments and calculations as an additional variable capable of tuning and not just as a spectator to the PRC reaction. Finally, our study highlights the added value of MD calculations in unravelling the mechanisms of PRC reactions that complements other theoretical approaches (QC)^[28] and experimental approaches like isolation of authentic redox states.^[29–31]

Theoretical Details

Found in the Supporting information.

Supporting Information

The authors have cited additional references within the Supporting Information.^[32–42]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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