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Computational Optimization of Electric Fields for Better Catalysis Design

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ABSTRACT

Although the ubiquitous role that long-ranged electric fields play in catalysis has been recognized, it is seldom used as a primary design parameter in the discovery of new catalytic materials. Here we illustrate how electric fields have been used to computationally optimize biocatalytic performance of a synthetic enzyme, and how they could be used as a unifying descriptor for catalytic design across a range of homogeneous and heterogeneous catalysts. While focusing on electrostatic environmental effects may open new routes toward the rational optimization of efficient catalysts, much more predictive capacity is required of theoretical methods to have a transformative impact in their computational design – and thus experimental relevance – when using electric field alignments in the reactive centres of complex catalytic systems.

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INTRODUCTION

The ability to control and accelerate chemical reactions is a challenge that is ubiquitous in applications ranging from the creation of new enzymes for biofuels[1] and medicines[2], enhancement of the Haber-Bosch process for ammonia production[3], and the development of the next generation of fuel cells, photovoltaics, and light emitting devices[4]. Because of the great technological importance of natural and synthetic catalysts in these translational endeavours, basic science efforts in theory and experiment are driven toward improving their efficiency through a strong primary focus on reactive centre energetics.

The design goal of any type of catalyst is to optimize the reaction pathway such that it lowers the activation free energy of the chemical transformation, thereby increasing the reaction rate toward products with rapid turnover. This statement is agnostic as to the origin or means for achieving the best reaction pathway and optimality of the transition state stabilization. To this end, natural biocatalysts are highly instructive since enzymes have evolved to yield functional catalytic rates that are remarkable – and whose magnitude is often calibrated by the catalytic perfection of being as fast as reactant substrates can reach the enzyme active site pocket in the diffusion-controlled limit. Warshel and colleagues were the first to show that an enzyme is more than just an optimized active site – it also has developed a pre-organized electrostatic environment that stabilizes the charge distribution of the substrate in the transition state.[5] This contrasts with the uncatalyzed reaction in water where the solvent molecules have to rearrange to accommodate the change from reactant to transition state.[6] In other words, there is no reorganization cost associated with the charge redistribution occurring during the enzymatic reaction, since this cost is paid up front through an enzyme's folded structure. This means that short-ranged interactions involving steric, dispersion, and hydrogen-bonding interactions of amino acid constituents in the active site help chemically position the substrate, while at the same time the remaining folded scaffold provides an environment in which long ranged electric fields align favourably to further lower the barrier of the catalytic step.

Controlling chemical reactions locally through greater environmental organization of electric fields need not be specific to enzymes. Chemical bonds and therefore reaction mechanism, rates and selectivity are affected by an electric field through field-bond-dipole interactions that transcend the specifics of any type of catalyst[7], although this general principle is not always exploited in better catalysts design. At the outset we reassert the great importance of what most

catalysis research is focused on, which is the optimization of the active site chemistry for enhancing catalytic performance. But in this Perspective, we also look beyond the active site by analysing how the non-local environment of a catalytic centre can play a highly non-trivial role in achieving gains in catalytic activity. We outline recent progress toward the computational optimization of synthetic enzymes that could spark innovation in biocatalysis and expand on how better designed electric fields could impact our ability to create improved heterogeneous catalysis as exemplified by zeolites and electrochemical interfaces, as well as homogeneous catalysts using nanoconfined molecular liquids and supramolecular capsules.

NATURAL AND SYNTHETIC BIOCATALYSIS

The interplay of local chemical positioning at an enzyme active site and long-ranged electrostatics from the folded scaffold and solvent ultimately stabilizes the reaction transition state relative to the reactant state. Given an electronic model of either classical bond dipoles[8] or derived from the Stark tuning rate along the vibrational mode of the relevant chemical bond[9], estimates of the electrostatic transition state stabilization free energy can be determined from a physical interpretation of the Stark effect[10] using Eq. (1)

$$\Delta G^{\ddagger}_{elec} = -(\bar{\mu}_{EL^{\dagger}} \cdot \bar{E}_{EL^{\dagger}} - \bar{\mu}_{EL} \cdot \bar{E}_{EL}) \quad (1)$$

where $\bar{\mu}$ is the bond dipole and $\bar{E}$ is the electric field evaluated in the ground (EL) and transition ($EL^{\dagger}$) states. The electric fields can be decomposed further into contributions from each residue of the enzyme, as well as from the surrounding solvent.[8,9] This helps quantify the free energy stabilization from the local effects in the catalytic centre (active site) and to separate them from the longer-ranged electrostatic environment from the protein (scaffold) and from water, which includes the hydration layer and bulk water contributions, to understand how each contributes to the catalytic activity of the enzyme.[8,9] We note that Eq. (1) assumes a sign convention that the positive direction for both the dipole and the electric field are chosen as to promote the flow of electrons in the transition state that contribute to free energy stabilization.

The natural enzyme Ketosteroid Isomerase (KSI) catalyses the isomerization of a wide variety of steroids to their conjugated isomers, and exhibits a Michealis-Menten catalytic efficiency as measured by k_{cat}/K_M that is close to diffusion controlled.[11] This makes KSI an ideal system to demonstrate how electrostatic preorganization concepts can explain and quantify KSI catalytic activity.[12] In particular, Warshel and co-workers analysed experimental binding energies

of transition state and transition state analogues in KSI and extracted the contribution from electrostatic interactions. It was found that the transition state binding energy was 8 kcal/mol larger than that of the transition state analogue, and that 70% of this difference was electrostatic in nature.[12]

More recently, vibrational Stark spectroscopy measurements by Fried and Boxer were used to quantify the relative importance of chemical positioning of the substrate in the active site of KSI with respect to electrostatic preorganization contributed by the protein.[13] They showed that the KSI environment created very strong electric fields of +144 MV/cm in the active site of the enzyme. Using the assumption that the electric field in the active site of KSI was the same in the reactant and transition state (an assumption that differs from Eq. (1) and is considered in more detail below), they used the reaction difference dipole to estimate that electrostatic interactions contributed ~7 kcal/mol to the reduction of KSI's activation energy. This accounts for about 5 orders of magnitude of the catalytic power of the enzyme, as traditionally measured by the k_{cat} speed up compared to the uncatalyzed reaction in water. Given the known catalytic rate that has been measured for KSI, this suggests that the tuned position of the substrate in the active site contributes ~2-3 orders of magnitude less to the catalytic activity of KSI. Although some have contested their analysis in regard to these relative local vs long-ranged magnitudes[14,15], there is no disagreement on the fact that electrostatic forces play a constructive role in the catalytic performance of KSI. More specifically, the folded structure of the KSI scaffold is commensurate with the natural enzyme's active site, resulting in electric fields that are optimally aligned to stabilize the transition state chemistry at the catalytic centre.

We have recently calculated electric field values for KSI using atomistic simulations with a polarizable force field model in which the classical electrostatic model is very robust.[8] We found that the scaffold plays a stabilizing role for the KSI catalytic activity, contributing +16 MV/cm (~28%) to the total electric field, although an additional +41 MV/cm emanated from the local active site environment, thereby contributing a majority share.[8] Markland and co-workers confirmed that the scaffold exerts an overall stabilizing electric field from *ab initio* molecular dynamics (AIMD) simulations that include Nuclear Quantum Effects (NQE)[16], however, they report that 98% of the overall electric field value of ~150 MV/cm they calculated for KSI emanates from the active site hydrogen bond network involving residues Tyr-16 and Asp-103. This is an important point that precise chemical positioning is required to fully exploit the short- and long-

ranged electrostatics for optimal electric field alignments along the transforming bonds at the transition state.

However, this basic pre-organization principle is found to be fully lacking in the design of so-called *de novo* enzymes, in which an active site model for a desired reaction not found in nature is engineered into an accommodating folded protein. This is because the current design of new synthetic biocatalysts often relies almost exclusively on optimizing the position of the substrate with respect to the main catalytic residue, largely regarding the rest of the protein as a physical support system for the reaction centre but not as a chemical support system to aid catalysis.[8] To illustrate this issue, much of *de novo* enzyme design methodology is currently focused on the Kemp eliminase family of synthetic enzymes that serve as a prototype for catalysed proton abstraction from carbon.[17] There are now many examples of related catalytic reaction centre motifs for the Kemp eliminase reaction that have been incorporated into a range of TIM barrel scaffolds such as KE07, KE70, KE59, HG3, and HG3.17.[18] We have shown that the TIM barrel scaffold contributes –25 MV/cm and –12 MV/cm to the electric field in the active site of the Kemp eliminases KE07 and KE70, respectively. Thus, unlike the natural enzyme KSI, the *de novo* scaffold actually disfavours the catalytic reaction in both cases.[8] Furthermore, 90% (75%) of the active site contribution to the electric field in KE07 (KE70) comes from the catalytic base Glu-101 (His-17 Asp-45 dyad). This means that neither the scaffold nor the active site is truly optimized to support the reaction.

An additional salutatory lesson can be drawn from laboratory directed evolution (LDE) of Kemp eliminases. The best known LDE improved variant for Kemp Eliminases is HG3.17, which yields a k_{cat} of 700 s^{-1} after 17 rounds relative to 0.68 s^{-1} for the design; LDE applied to KE07 and KE70 saturates at an order of magnitude improvement in k_{cat} after only 6 to 7 rounds. In fact, we showed that the catalytic base in KE07 R7.2 (the best LDE optimized KE07 variant) contributes 40 MV/cm more to the total electric field than the original design, while the rest of the active site and the scaffold contribute equally in both the original design and LDE optimized enzymes. This led us to make the simple empirical estimate that LDE would ultimately reach a speed limit of around 3 orders of magnitude improvement over the uncatalyzed reaction in water, because most sequence optimization will come through local electric field improvements in the active site.[8] This can be rationalized by the fact that each individual mutation of the protein scaffold will only contribute small effects due to the decay of electrostatic interactions at long-range. As a result, it

would likely require vast reengineering of the *de novo* designed sequence, and thus the wholesale refolding of the synthetic enzyme to a new structure commensurate with the new active site chemistry, to gain the qualitative changes of a chemically supportive scaffold of a natural enzyme like KSI using LDE. A corollary to this is that even though electric field effects are much larger in the active site due to close-ranged interactions, there is a corresponding sizeable reduction in the sequence space to explore in the active site, which ultimately limits the capability of reaching native enzyme performance using design and LDE.

This line of reasoning is consistent with the work of Warshel and co-workers, who also have extensively reported on the limitations of LDE for Kemp eliminases. Using Empirical Valence Bond (EVB) methods combined with umbrella sampling, they computed activation free energies of a series of Kemp eliminases and extracted the electrostatic contribution from the protein residues.[19,20] They concluded that the polarity of the active site in the KE07 does not easily accommodate the charge distribution in the transition state, such that the LDE process only lowered the transition state in KE07 R7.2 by 2.5 kcal/mol compared to the design.[19] In contrast, the reactant state is raised by 17.3 kcal/mol, meaning that in this case LDE improvement are due to ground state destabilization rather than transition state stabilization. Furthermore, Fuxreiter and co-workers demonstrated that some of the mutations selected by LDE had little impact on the energy barrier of the reaction but rather decrease the reorganization energy in KE07.[21] This reinforces the idea that the local electrostatic environment in synthetic enzyme is so poorly adapted to the chemistry of the reaction that even LDE cannot overcome this limitation.

This suggested to us that computational optimization of the electric fields and catalytically competent conformations in the active site could be used in earlier stages of the *de novo* design as a replacement for the current mandatory LDE step. With these principles in mind, we identified mutations that enhance better catalytic base alignment with the 5-nitrobenzisoxazole substrate as well as electric field alignments of the transforming chemical bonds that contribute to free energy stabilization of the transition state using Eq. (1), for the Kemp Eliminase enzyme KE15 for which no LDE was applied.[22] Note that Eq. (1) is a more general expression of the electrostatic stabilization free energy of the transition state than what was employed by Fried and co-workers[13,16]; this is because the electric field calculated in the reactant and transition states are different and cannot be factorized in front of the reaction dipole difference.[8,22]

Starting from the original design with a k_{cat}/K_M of 27 $M^{-1}s^{-1}$, we created a computationally improved variant through introduction of 4 targeted mutations to yield a k_{cat}/K_M of 403 $M^{-1}s^{-1}$. While we determined that some of this improvement came from a modest reactant state destabilization of ~ 0.7 kcal/mol, almost all of the enzyme improvement was realized through a 2.25 kcal/mol stabilization of the transition state that led to the 43-fold improvement in k_{cat} (Figure 1). This is equivalent to roughly 5 rounds of LDE applied to other Kemp eliminase designs, thereby demonstrating that computational optimization using electric fields can augment the LDE process through the creation of much better starting sequences.[22]

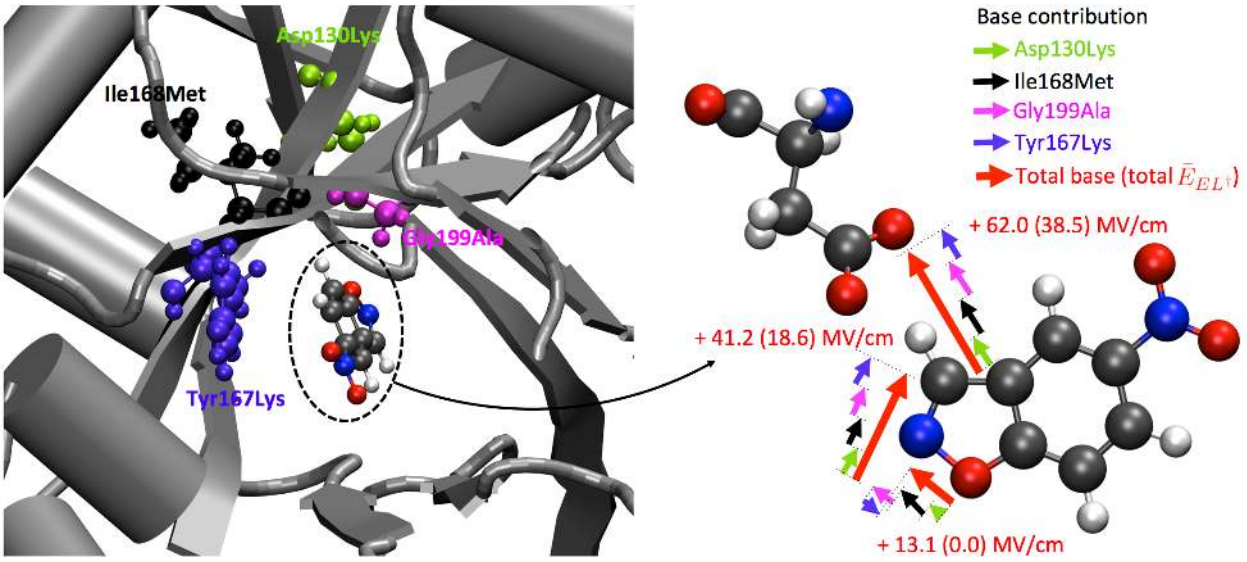

Figure 1. *Optimization of electric fields in the KE15 Kemp Eliminase synthetic enzyme*. Shown is the location of the 4 mutations of KE15 best variant (left) and the total electric field contributions to the transition state relative to the original design (right).[22] The positive direction for the bond dipole is the same as for the electric field (from C to H, from N to C and from O to N for the CH, CN and ON bond respectively with magnitude +1 , +0.4 and +2.3 Debye). The efficiency of these computationally designed variants was measured and confirmed experimentally. The quadruple mutant yields a k_{cat}/K_M of 403 $M^{-1}s^{-1}$ relative to a k_{cat}/K_M of 27 $M^{-1}s^{-1}$ for the design.

POROUS SUPERMOLECULAR CAPSULES AND ZEOLITE CATALYSTS

The enclosing microstructure of the reactive site within a porous structure is capable of altering the reactivity of guest molecules; by encapsulating specific reactants, these structures mimic the active site of enzymes and protect the guest substrate from undesired reactions in solution.[23] Although structurally they are very different than enzymes, the same interplay between electric fields and nanopore structure is also applicable to zeolite catalysts.[24] Zeolites are microporous aluminosilicate minerals widely used in industry due to the uniformity of its pores as well as the

adjustability of its structure and acidity.[25] Diffusion is highly constrained within the zeolite framework, protecting reactive species from undesired bulk reactions[26], similar to the design principles of supramolecular capsules. Zeolites cages and channels are therefore highly favourable to promote specific chemical reactions with the catalytic process dependent upon the pore shape and size; this is manifested by the development of numerous manufacturing techniques aiming to carefully engineer pore structures in zeolites.[27]

However, zeolites are also characterized by modest to large electric fields (10-100 MV/cm) that would have impact on the reactive chemistry within the poorly-shielded pores.[28] For example, the GaH_2^+ site in the H-MFI zeolite that was previously considered inactive for ethane dehydrogenation, may in fact be active when the impact of long-range interactions on the predicted activation energy is taken into account.[24] This in turn would suggest that better catalysis in zeolites can also be designed via electric field optimization of relevant transition states. The primary and open research question is how to control the electric field magnitude and direction (in proportion to the reaction dipole as shown in Eq. (1)) for stabilizing the transition state with respect to the reactant state of the rate determining step; for zeolites, the primary synthetic variables are limited to the pore size and shape and the Al/Si ratio, since the chemical structure is fixed and functionalization of the zeolite are more limited than other catalysts.

By contrast, pore reactive centres can in principle be designed within a controlled environment in a supramolecular capsule, whose catalytic function can be easily tailored through synthesis. The first capsule to exhibit catalytic efficiency comparable to natural enzymes was reported by Raymond and Bergman using a tetrahedral assembly $K_{12}Ga_4L'_6$ (L'=1,5,bis catecholamidenaphtalene), which accelerates the Nazarov cyclization of 1,3-pentadienols by six orders of magnitude.[29] The conceptually similar assembly $K_{12}Ga_4L_6$ (L=N,N'-bis(2,3-dihydroxybenzoyl)) was also shown to exhibit remarkable catalytic activity for accelerating the hydrolysis of orthoformates or the alkyl-alkyl reductive elimination from gold complexes.[30] Fruschicheva et al. demonstrated that the catalytic effect of $K_{12}Ga_4L_6$ (L=N,N'-bis(2,3-dihydroxybenzoyl)) was electrostatic in nature.[31] Here, we focus on the alkyl-alkyl reductive elimination from gold (III) complexes, a fundamental, rate-limiting step in transition metal chemistry. Experimental evidence suggests that the reaction begins with dissociation of the halide from the $P(CH_3)_3AuMe_2I$ complex to form the $P(CH_3)_3Au^+Me_2$ intermediate, as shown in Figure

2. The subsequent encapsulation of $P(CH_3)_3Au^+Me_2$ in the $K_{12}Ga_4L_6$ cage gives rise to the reductive elimination step that follows a Michaelis-Menten-like mechanism.[30]

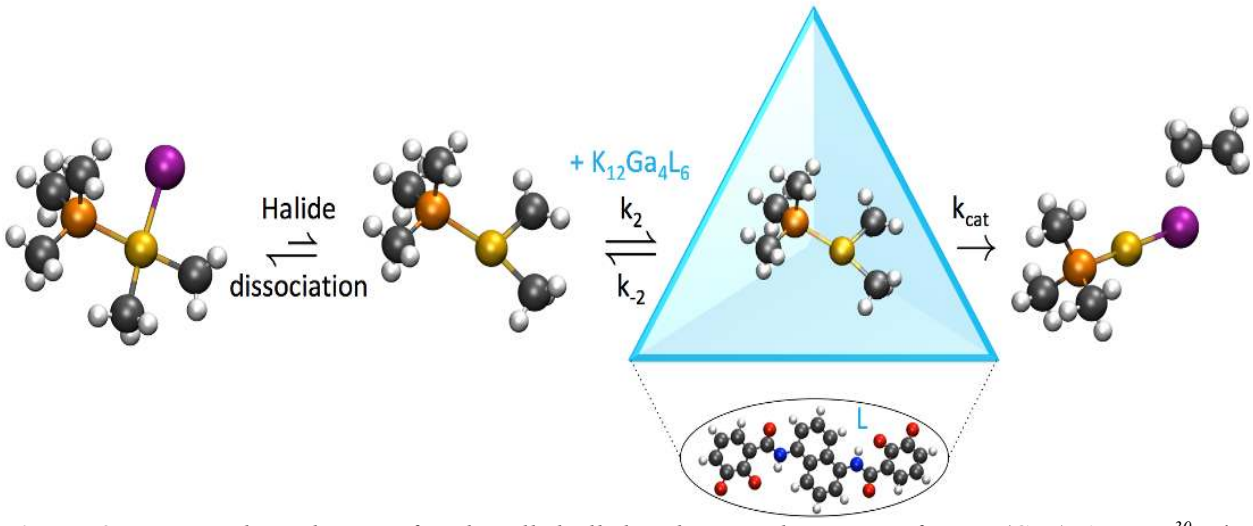

Figure 2. *Proposed mechanism for the alkyl-alkyl reductive elimination from $P(CH_3)_3AuMe_2I$.*[30] The tetrahedral assembly (in blue) mimics the role of an enzyme in the Michaelis-Menten-like process that follows the halide dissociation. Colour key: grey=carbon, white=hydrogen, gold=gold, orange=phosphorous, purple=iodine.

We can extend the physical principles of electric fields, that we found to be predictive for biocatalysis, to this non-biological system. For this purpose, we aim to calculate the electric fields projected along the reactive metal - alkyl ligand bonds of the $P(CH_3)_3Au^+Me_2$ complex. Note that the presence of transition metal gold atom requires us to go beyond classical MD to describe the interactions of the system at sufficient chemical accuracy using quantum chemistry methods. Using Density Functional Theory (DFT) at the meta-GGA level with Van der Waals correction we calculate the internal electric field of the molecule in the gas phase (e.g. the field created by the molecule itself) and the field when the molecule is encapsulated within the nanocage pore (Figure 3). We find that the supramolecular microenvironment with its medium range electrostatics arising from the capsule increases the magnitude of the electric field by ~50 MV/cm along the two gold-alkyl ligand bonds, relative to the internal (gas phase) electric field.

With an appropriate theoretical model for the bond dipoles in the reactant and transition state structures, our future work will be able to utilize Eq. (1) to predict how much of the catalytic activity of the current supramolecular capsule arises from electronic rearrangements at the catalytic metal centre vs. contributions from the electric field environment – the latter of which we suspect will be significant due to the larger electric fields created by the nanocage structure. Even if the

electronic rearrangements induced by the transition metal are the larger effect – we can also propose synthetic modifications that will specifically alter the electrostatic environment to further enhance the catalytic activity.

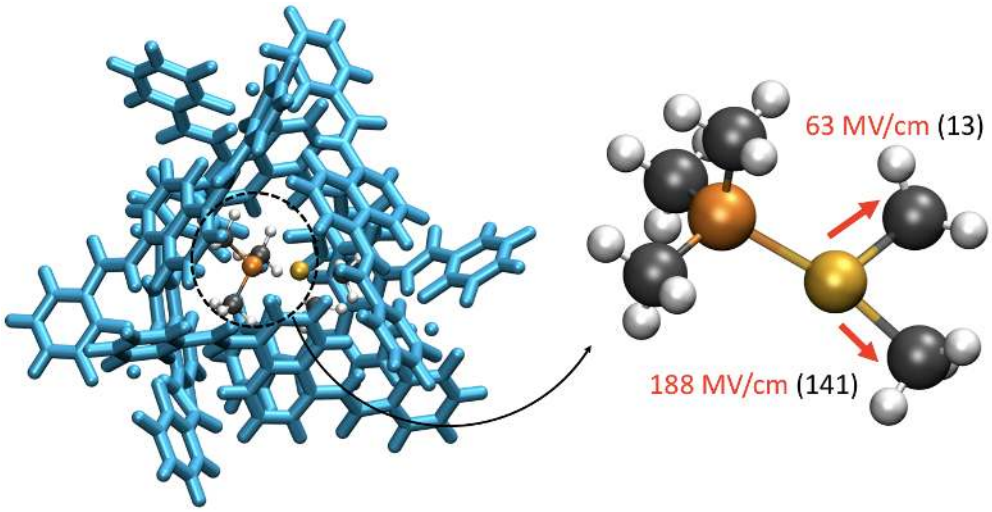

Figure 3. *Electric field enhancements on alkyl-alkyl reduction in a supramolecular capsule*. The unhalogenated gold complex encapsulated in the tetrahedral assembly $K_{12}Ga_4L_6$ (left) and corresponding electric field projection onto the gold–alkyl ligand bonds (right, in red). For reference, the intramolecular electric fields from the $P(CH_3)_3Au^+Me_2$ complex projected onto the same bonds in gas phase are given in parentheses in black. The electric fields emanating from the supramolecular capsule were calculated using DFT with the B97M-V functional[32,33] and a DZVP basis set as implemented in the CP2K software package.

ELECTRIC FIELDS FOR HETEROGENEOUS AND HOMOGENEOUS CATALYSIS

Electric fields have been known to influence the activity of many heterogeneous catalysts for a while now.[34-36] We start by considering design principles based on electrostatic effects for catalysts that promote chemical reactions occurring on an electrode-electrolyte interface, since in this case electric fields are readily exploitable. One of the most studied example is the electrocatalytic reduction of CO_2 on metal surfaces for the production of renewable energy, chemical feedstocks and energy storage.[37] From a macroscopic point of view, the ions in solution organize in a double layer such that the reaction can be somewhat controlled by the nature and concentration of these solvated ions. Alkali metal cations for example are known to increase the local concentration of CO_2 near the interface, thereby facilitating the reaction.[38] This effect can be rationalized at the atomistic level by considering the image charges of the ions in the electrode[37], in which the field generated by the ion-image-charge pair affects the local properties of the interface and changes the strength of the bond of reactants and products. In particular, these non-uniform fields interact with polar adsorbates at a longer range than covalent adsorbates for which the double layer has mainly

a direct chemical effect. This suggests that surface functionalization with ions chosen to induce long-range electrostatic changes in key reaction intermediates is an effective means to control the kinetics of electrochemical reactions. Furthermore, the magnitude of these electric fields was shown to be ten-fold higher in a nanostructured electrode compared with its planar counterpart, with remarkable increase in reaction yields.[38]

Recently, Dawlaty's group has used vibrational sum frequency generation techniques to measure interfacial electric fields at the junction of a conductor and a dielectric.[39,40] They rationalized their measurement with a modified Onsager model that accounts for the asymmetry of the system. They showed not only that the metal plays an important role in the molecular polarization of tethered molecules, but also that these interfacial electric fields can be modulated by the ionic concentration in the electrolyte. Providing a positive potential, these effects results in an increase of the thermodynamic drive for electrochemical reactions, thereby demonstrating the fundamental role of electric fields in these systems.

By contrast, exploiting electric fields in the optimization of catalytic reactions in homogeneous solution is notoriously difficult, and for water in particular, because solvent molecules are dynamical and undergo rapid reorientation, thereby averaging out favourable electrostatic effects that are quenched in the polar media.[41,42] Therefore, ground-breaking progress in homogeneous catalysis must encompass the design and synthesis of new hybrid catalytic materials that preserve the activity and selectivity of molecular catalysts, but in a heterogeneous and robust interfacial support system[43,44], creating an opportunity for using electric fields as a design principle for controlling the molecular catalyst.

We illustrate this possibility with the well-known Diels-Alder reaction in water. The Diels-Alder reaction is known to be accelerated in bulk water compared to organic solvents[45], and yields are higher and reactions even faster when the reaction is performed at a different state point such as in supercritical water[46] or in an alternative solvent such as an ionic liquid[47]. Recently, it was shown that the rate of the Diels-Alder reaction was increased 5-fold when electric fields aligned as to favour the reaction were applied using Scanning Tunnelling Microscopy (STM) using single molecule techniques.[41] A variety of molecular explanations have been put forward to explain these rate enhancements, for example showing that the hydrophobic (entropic) effect drives the cycloaddition by reducing hydrophobic surface area of the diene and the dienophile construct[48], or the enhancement of stabilizing electrostatic effects on the transition state[41], and better solubility of

the reactants[47]. The primary point is that there are a variety of molecular features that are important for a catalytic reaction that therefore can be tuned through interfacial supports that optimize a range of homogeneous solvent properties - dipolar response, density fluctuations and compressibility, increased or decreased solubility of reactants and products, dynamics, and electrostatic fields –to enhance desired reaction outcomes in the confined liquid.

Numerous studies have shown that the dielectric properties of water, and hence the electric fields relevant to aqueous chemical reactions, are greatly affected by nanoconfinement.[49,50] It has been shown that the ferroelectric properties of nanoconfined water could be effectively tuned by an external electric field.[51] A recent study has gone a step further by providing direct quantitative evidence of the relation between the anomalous dielectric properties of nanoconfined water and chemical reactivity, interpreted as an enhanced dielectric constant of water in the direction parallel to the confining surfaces favours water self-dissociation.[52]

The high sensitivity of liquid properties to confinement conditions would suggest that confinement induced electric fields can be used as an effective tuning tool for accelerating reaction chemistry in homogeneous phases. For example, under planar confinement conditions, we suggest an isomorphism that both the separation distance, *d*, of the extended confining surfaces, or the variation of the surfaces' chemistry and roughness (Figure 4), can be thought of as a thermodynamic gauge that can be used to dial-in particular solvation features in nanoscale systems. To illustrate, a difference of less than one Angstrom in the nanoconfinement distance can mean the difference between liquid and ice phase and their coexistence[53], where the large difference in the dielectric constant could be used as an electric field enhancer for chemical reactions under confinement.

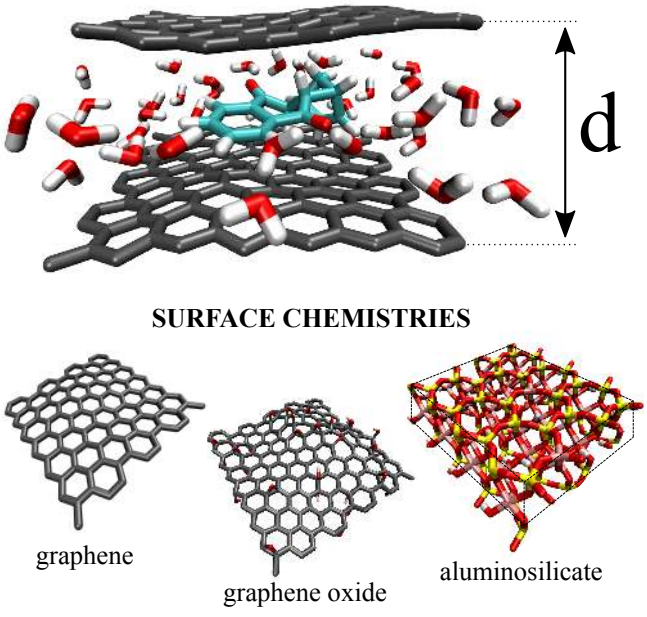

Figure 4. *Atomistic representation of a Diels-Alder reaction under nanoconfinement*. The reaction occurs between cyclopentadiene and 1,4-naphthoquinone in water. Some possibilities for the surface chemistry of the confining surfaces are shown that span from hydrophobic (graphene) to hydrophilic (graphene oxide and aluminosilicates).

By systematically calculating the free energy barriers of the reactions as a function of the confinement conditions, we can gain insight and derive guidelines of how to better control electric field alignments (and other liquid state properties) for accelerating chemical reactions in a homogeneous solution phase.

SUMMARY AND FUTURE DIRECTIONS

In many respects, electric fields are appreciated as being fundamentally important for catalytic acceleration in a range of catalyst types, but at the same time electric fields are seldom fully exploited in the design or creation of new catalysts. We have shown that we can utilize theoretical models to help guide the improvement in synthetic enzymes and have considered how these ideas might be extended to a range of catalytic systems. This has been illustrated in the Perspective across synthetic enzymes, nanoconfined liquids, supramolecular capsules, zeolites and surface (electro)catalysts, in which electric fields can be seen as a unifying descriptor to understand and ultimately optimize catalytic performance. The theoretical challenge for all catalytic applications—whether a nanocage or an electrolyte-electrode interface—is how to utilize the electrostatic environment in order to understand and/or improve the targeted catalytic reaction given the multiphysics nature of the problem. Hence we foresee a need for more advanced theoretical treatments of electric fields which should combine the theoretical frameworks of dielectric continuum models, electronic structure theory, statistical mechanics, and nuclear quantum effects (NQEs).

To illustrate, recent work has shown that continuum treatments of the electric field emanating from the aqueous electrolyte near the electrode interface are failing in the description of the interfacial properties like the potential of zero charge[54] and for simulating the microkinetics of oxygen reduction on metal surfaces[55]. Raising the resolution of the model to account for electrolyte density structure has further revealed the inaccuracy of the continuum description[56]. Even so, Cox and Geissler have shown that dielectric continuum descriptions can provide highly accurate finite size corrections for ion solvation at planar interfaces.[57] Together these results make clear that the key is to unravel the local and non-linear electrostatic effects through explicit atomistic or variable density representations, that is then embedded in or corrected by a continuum model for the long-range electrostatic effects. This is likely why modified Poisson Boltzmann

treatments/DFT[58] and classical/quantum DFT approaches[56] have been quite effective for describing the energetics of solid-liquid interfaces for electrocatalysis.

Because electric field magnitudes and their alignments are very sensitive to molecular interactions within the reactive center[59], sufficient chemical accuracy will be needed to describe covalent interactions, organometallic bonding, many-bodied non-bonded forces, and barriers to conformational and electronic rearrangements in the active site. For tractability, often quantum mechanical-molecular mechanics (QM-MM) hybrid approaches are used in enzyme, nanocages, and zeolite models where active sites or periodic structures are well defined. As such, improvements in QM/MM reaction free energies must adequately address the long-standing issue of properly accounting for the QM and MM interface, and the dependence of results on the size of the QM region and the quality of the QM theory. Very recent studies are showing that replacement of the generalized gradient approximation (GGA) of DFT with new semi-empirical meta-GGAs[60] and recent hybrid and double hybrid functionals which incorporate some percentage of exact exchange, are addressing better QM accuracy[61], and new approaches have been introduced that incorporate true many-body polarization effects across the QM/MM boundary.[62,63] This line of research has allowed for accurate rate constant prediction for molecule-surface reactions[64], while Piccini et al. showed how energy barriers for large systems like zeolites (over 1000 atoms) could be calculated within chemical accuracy (within 4 kJ/mol) using Density Functional Theory (DFT) methods.[65] But there are still significant difficulties for metal catalysts, for example metalloenzymes, where there may be multiple reactive sites requiring a QM description[66], and for which errors in relative free energies do not generally fall below 20 kJ/mol due to poor accounting of strong correlation using DFT[67].

Given the ubiquitous nature of hydrogen bonding, isotope effects, proton transfer, and tunnelling in catalysis, nuclear quantum effects (NQEs) are an important missing factor in the theoretical model for catalytic processes ranging from enzymes to metal nanoparticle catalysts.[68] Although earlier approximations have been used by Warshel and co-workers that take into account NQEs in enzyme catalysis[69], recent theoretical work have successfully focused on significant cost reduction of NQEs[70] or increasing their accuracy through electronic-nuclear coupling[71]. While the quantum nature of the nuclei have been shown to be important in water and enzyme active sites[16], they are still typically ignored in the calculation of the electric field and their effects on the ground state and transition states of the chemical step. This may change in the future as algorithmic

improvements for calculating NQEs become more tractable[70], and their importance for enzymes[16] and nanocatalysts[16,68] continues to be established.

Superimposed on the energetics are the statistical fluctuations of thermal motion, and for systems undergoing driven dynamics, changing fluxes through reaction kinetic barriers that might be gated by the active site coupling to the long-ranged electric fields.[72] This is evident from atomistic molecular dynamics treatments at constant electrode potential which have shown that the electrolyte is spatially heterogeneous in the plane parallel to an electrode on timescales of nanoseconds[73]. The most desirable solution is a full *ab initio* molecular dynamics (AIMD) treatment of large catalytic environments for thousands of atoms and hundreds of nanoseconds (or longer), but this is well beyond current capabilities of AIMD. Bridging this length and time scale gap will be realized through algorithmic developments that would decrease the number of cycles in the self-consistent cycle of AIMD[74], substantially increase the time step in a stable manner[75], achieving linear scaling in an accurate and reliable way[76], as well as coupling AIMD to the Grand Canonical ensemble[77], and use of advanced sampling methods[78] such as the low energy alternative side chain arrangements of an enzyme using Monte Carlo (MC) to create QM/MC approaches to determine fluctuating electric fields[22,79]. The emergence of more detailed molecular *in situ* and *operando* catalytic experiments[80] are observing the formation of transient intermediates under non-equilibrium conditions that ultimately modulate the flux through kinetic barriers of the catalytic step. In this case the classical thermodynamic framework breaks down, and the most probable conformations or reaction pathways cannot be inferred by mapping the free energy of the system. Alternative computational and theoretical methods that can sample and interpret these non-equilibrium steady states and their coupling to electric field effects are a formidable but highly interesting problem.

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