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Electric Fields in Catalysis: From Enzymes to Molecular Catalysts

Nadia G. Léonard,[§] Rakia Dhaoui,[§] Teera Chantarojsiri, and Jenny Y. Yang*

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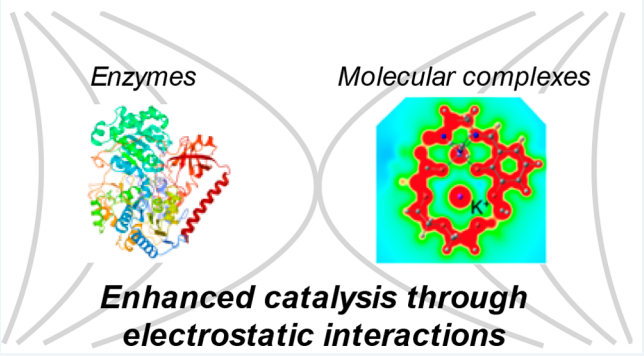
ABSTRACT: Electric fields underlie all reactions and impact reactivity by interacting with the dipoles and net charges of transition states, products, and reactants to modify the free energy landscape. However, they are rarely given deliberate consideration in synthetic design to rationally control reactivity. This Perspective discusses the commonalities of electric field effects across multiple platforms, from enzymes to molecular catalysts, and identifies practical challenges to applying them in synthetic molecular systems to mediate reactivity.



KEYWORDS: *electric fields, electrostatics, catalysis, bioinorganic, dipoles, redox reactions, transition metals*

Electric fields are believed to be key factors in the superior reactivity and selectivity of enzymatic active sites[1−8] and some zeolites.[9−11] More broadly, electrostatic interactions have been used to rationalize wide ranging reactivity—from enzymatic preorganization and ion-pairing in organocatalysis, to rate enhancement or selectivity control at transition metal complexes. Electric fields in this context stem from either positioned charges, dipoles, or induced dipoles. Modeling these types of interactions are not new. However, renewed interest in using electric fields as "smart reagents" in chemistry[12] highlights the few experimental examples where electric fields are deliberately used as a tool to control reactivity. Electrostatic catalysis places a reacting molecule in an environment that stabilizes the transition state's dipole moment or net charge.[3]

The electric field is defined as the interaction experienced at a given point in space due to the summation of charges, dipoles, and induced dipoles of all other atoms in the system. In most frameworks for modeling, the electric fields experienced by a molecule encompasses the intermolecular field created by other atoms or molecules, but the field created by its own atoms is excluded. Electrostatic interactions are defined as interactions between molecules due to their permanent charges and dipoles.[3] Intrinsic electric fields (such as those in enzymes and zeolites) or applied electric fields (such as those at surfaces, using external applied fields, or STM tips) can be described similarly, with the magnitude of the field dependent on where the field is sampled.[13]

An oriented electrostatic field of appropriate magnitude can direct chemical interactions, reactivity, and catalysis by manipulating activation energies as a function of molecular orientation. Quantum mechanical studies indicate electric fields between 1 and 10 V/nm can adjust activation barriers in the gas phase by several kcal/mol, modifying reaction rates by several orders of magnitude at room temperature.[13] The electric field alters the energy landscape by (1) stabilizing/destabilizing intermediates/transition states which can result in accelerating or prohibiting a reaction pathway and (2) tuning thermodynamic parameters (redox potential, pK_a, bond energy, ground state stabilization or destabilization, etc.). Judicious orientation of an electric field in relation to reacting partners can result in rate enhancement/inhibition,[14−17] changes in mechanism,[18−20] and improved regio- or stereoselectivity.[21,22] Figure 1 illustrates an example of rate acceleration through stabilization of a transition state by comparing the relative free energies for a reaction in the absence (black trace) and presence (blue trace) of an electric field. For a reaction with a dipolar transition state and a nonpolar reactant, application of an oriented electrostatic field lowers the free energy of the transition state and product relative to the reactants.

Computational modeling and theoretical investigations have been used to understand the principles governing electric field effects on catalysis.[13,23−25] These computational studies, as

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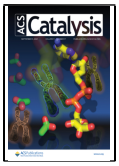

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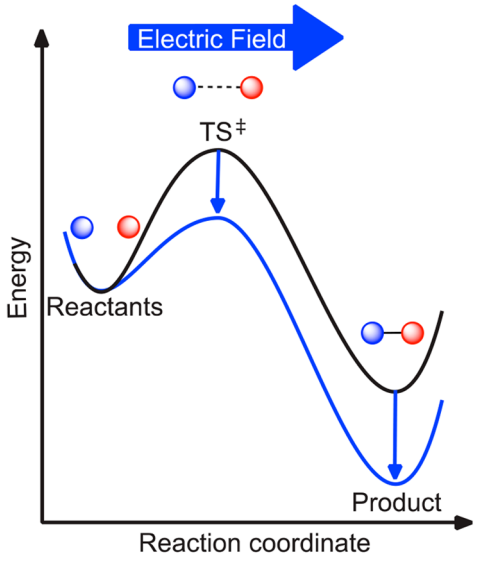

Figure 1. Potential impact of electrostatics on reaction energetics.

well as experimental examples, have been discussed in a recently published book[26] and reviews.[5,13,25,27,28] Most experimental studies of controlled electric fields on reactivity have focused on using applied biases[29] such as charged surfaces[30,31] or STM tips[32−35] to generate fields with magnitudes ranging from 3 to 50 V/nm.[13,27,28] These elegant studies quantify the impact electric fields can have on reaction energies and product selectivity. However, the scalability of these techniques is limited; the reactivity enabled through applied biases is confined to single molecules or electrode surfaces. The magnitude of the electric field also diminishes rapidly with the distance from the external source because of ion and/or solvent screening. Applied biases are also susceptible to dielectric breakdown at high magnitudes, resulting in electron transfer. Additionally, the orientation of the reacting components in relation to the direction of the electric field must be precisely controlled, even when adsorbed on a surface. Exact control of field orientation and magnitude with respect to the reactants is a general challenge with external fields. These factors complicate drawing direct parallels to enzymatic systems or use as a large-scale synthetic tool. Because of these challenges, molecular systems may provide an opportunity to control field orientation with respect to reacting partners due to binding at the reactive center prior to catalysis.

The goal of this Perspective is to highlight specific examples of electric field effects in enzymes, organic reactions, and transition-metal-catalyzed systems. By using select examples and drawing common themes between different catalytic platforms, we aim to show how these commonalities can be used to design platforms with specific electrostatic interactions to achieve reaction control.

■ ELECTRIC FIELD EFFECTS IN ENZYMES

The efficiency of enzymatic catalysis has long served as a source of inspiration for synthetic chemists. Elucidating the different factors that govern the catalytic power of enzymes is a

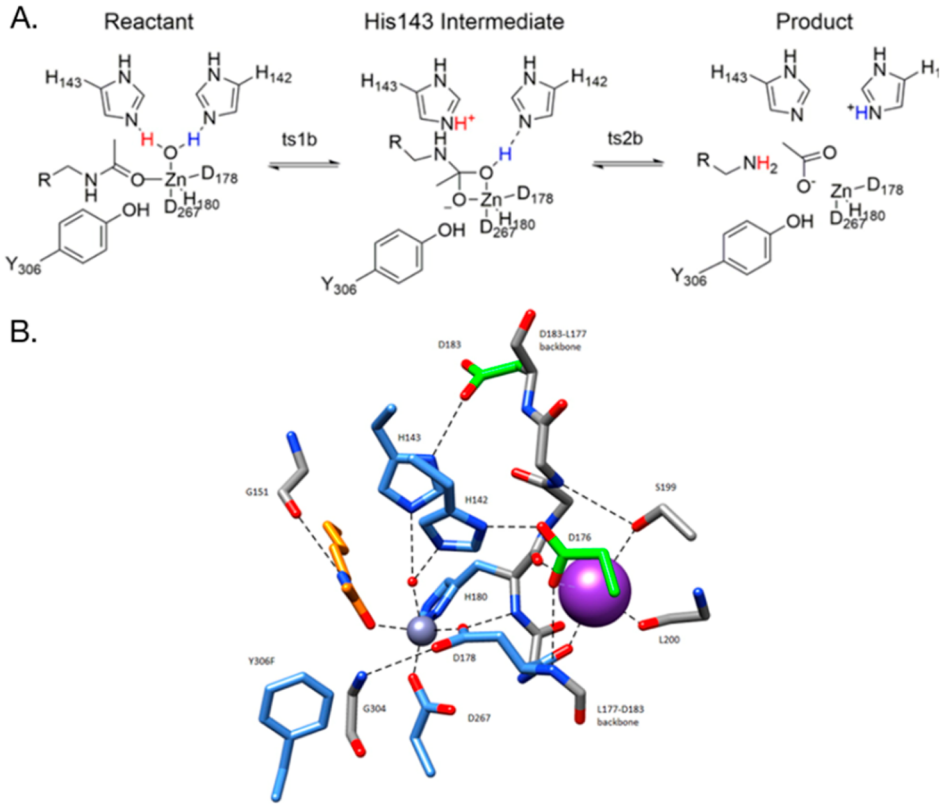

Figure 2. A. Proton shuttle mechanism for HDAC8. B. Depiction of the active site of HDAC8 from a computational study. The system consists of the central Zn^{2+} ion (gray sphere), substrate (orange), K^+ ion (purple sphere), and local residues. Reproduced with permission from ref 39. Copyright 2016 American Chemical Society.

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key step in designing synthetic catalysts that rival the activity of enzymes, from selective C−H activation[36] to energy-efficient CO_2 reduction.[37,38] The overall protein architecture forms microenvironments which exploit a variety of electrostatic interactions and preorganization to aid in catalysis.[1−8] These interactions include hydrogen-bonding networks, proximal Lewis acidic metals or charged functionalities, and the hydrophobicity or hydrophilicity of local active site residues.[39−44]

Warshel pioneered the term electrostatic preorganization as a way to describe the enzymatic environment that favors the transition state rather than the reactants, thus lowering the free energy barrier.[44] Experimental evidence for this electrostatic environment in an enzyme was confirmed by Boxer using vibrational Stark spectroscopy[45] on ketosteroid isomerase (KSI).[46] Specifically, an inhibitor containing a vibrational probe (carbonyl group) was placed in the active site. KSI strongly activates the C═O stretch, where the carbonyl stretching frequency is used as a probe for the electric field. The electric field induced by the protein scaffold on the active site was then found to linearly correlate with the activation free energy of the reaction, providing direct experimental evidence for electrostatic rate enhancement.[47]

In a computational example on the enzyme histone deacetylase 8 (HDAC8), evidence to support the underlying importance of electrostatic preorganization was investigated through the electron charge density.[48] Zinc-dependent HDAC8 catalyzes the deacetylation of a histone lysine and plays a vital role in post-translational modification during the biosynthesis of proteins.[49] Deacetylation proceeds through formation of an oxyanion intermediate bound to zinc (Figure 2A).[15,40,50] Crystallographic studies of the HDAC8 active site also revealed a K^+ ion buried into the interior of the protein (Figure 2B), approximately 7 Å from the zinc; however, the role of potassium is not understood.[51,52] Computational studies of the zinc-dependent HDAC8 suggest that K^+ plays a role in increasing substrate binding at the central zinc ion and that absence of the K^+ ion causes deactivation of the enzyme. Therefore, the distal K^+ may serve to enhance the electrostatic preorganization at the active site.

In addition to nonredox active metal cations, the electrostatic environment at active sites can also be modulated by charged residues. The active site of chorismite mutase, a metabolic enzyme that catalyzes the rearrangement of chorismite to prephenate, includes a cationic arginine. Replacement of the arginine with neutral citrulline maintains the precise substrate orientation and geometry of the wildtype enzyme but incurs a penalty in catalytic activity.[53] Another example is the formate dehydrogenase (FDH) enzyme. The active site of all known FDHs contain an arginine residue in the secondary coordination sphere.[54] This arginine has been proposed to interact with the negatively charged formate substrate to facilitate C−H bond cleavage.[55]

These three examples serve to highlight the multidimensional roles that electrostatic interactions serve in enzymes. However, there is significant difficulty in strategically pinpointing which individual effects are essential to enzymatic activity, and would thus be critical to emulate within synthetic systems.

ELECTROSTATIC VERSUS LEWIS ACIDITY EFFECTS

While charged metal ions such as alkali and alkaline earth metals leave an electrostatic footprint, they can also serve as Lewis acids. The difference is that in the former case, they are modifying the energy landscape through a noncovalent interaction, and in the latter with a through-bond orbital-overlap interaction. Cation replacement studies are useful for evaluating the relevant electrostatic versus Lewis acidic contributions. For example, the oxygen-evolving complex (OEC) of the photosystem II enzyme (PSII) features a Mn_4CaO_5 core in the active site.[56] Studies aimed at understanding the role of the Ca^{2+} ion in PSII found that displacement with all dicationic alkaline earth metals led to significantly diminished activity with the exception of Sr^{2+}, which has similar Lewis acidity to the Ca^{2+} ion.[57] These studies indicate the Ca^{2+} ion primarily functions as a Lewis acid; if it were mostly providing an electrostatic effect, replacement with any dication would result in similar activity. However, it is worth noting that in cation replacement studies, different ionic radii of alkali and alkaline earth metals may also result in electrostatic perturbations based on changes in distance or geometry to the active site.

Likewise, synthetic catalytic systems often exhibit accelerated rates with Lewis acidic metal cation additives or cocatalysts.[58−67] The Lewis acidic and electrostatic contributions can be decoupled by comparing the relative activity with other additives that are either charged or Lewis acidic, but not both. For example, additives such as noncationic borates can be used to isolate the effect of Lewis acidity. Additionally, quaternary ammonium salts (such as tetraethylammonium) can be used to introduce a local cationic charge that lacks Lewis acidity.[63,64]

SYNTHETIC SYSTEMS

Various synthetic constructs have been used to generate oriented fields of specific magnitudes across homogeneous active sites. These synthetic systems have the potential to mimic the electrostatic character found in enzymatic active sites.

For example, supramolecular hosts can mimic electrostatic aspects of enzymatic active site cavities (Figure 3A). Multiple

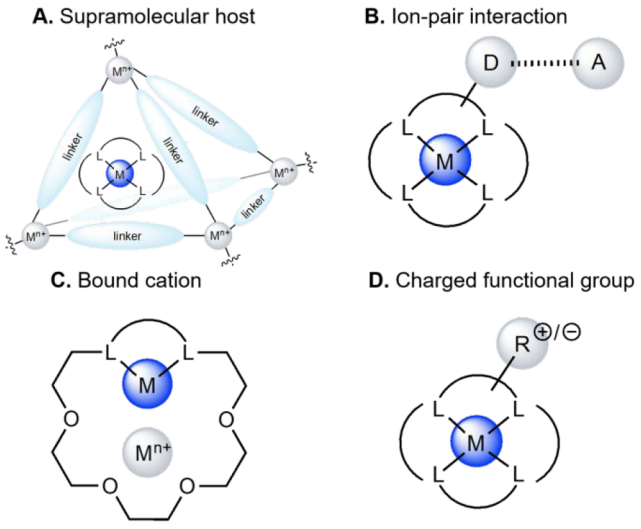

Figure 3. Types of electrostatic interactions at transition metal complexes: A. Supramolecular host, B. Ion-pair interaction, C. Bound cation, D. Charged functional group. M = transition metal; L = ligand; D = ion-pair donor; A = ion-pair acceptor; $R^{\pm} = R'_3N^+$, R'_3B^-, or M^{n+} = nonredox active metal.

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parameters, including overall charge, cavity size, and the degree of solvent exclusion can be controlled through synthetic design.[68,69] Prominent examples of charged supramolecular hosts and catalysts that invoke electrostatic effects for their reactivity include Ward and co-workers' $Co_8L_{12}^{16+}$ cube,[70] and Fujita and co-workers' $Pd_6L_4^{12+}$ octahedron.[71] Electrostatic effects in a variety of supramolecular complexes have been examined experimentally[72,73] and with computational studies.[74,75]

Electrostatic interactions have been used extensively to elicit reactivity control in organocatalysis.[76−82] For reactions with proposed transition state structures that are more dipolar than their starting materials or products, it rationally follows that use of electrostatic stabilization would enhance catalysis. Electrostatic interactions have been employed in asymmetric catalysis[83−91] and for site-selective catalysis.[92,93]

Ion pair formation (Figure 3B, the interaction of positively and negatively charged species) occurs to lower the Gibbs free energy (as opposed to ion solvation). Promoting ion-pairing interactions requires that ion−solvent interactions are minimized. In fact, use of highly polar solvents can incur a large energetic penalty to ion-pairing due to solvent reorganization. To minimize this energetic penalty, solvents of relatively low dielectric constant are often used, which can present solubility challenges when cationic/anionic charges are used to generate the electric field. In the early 1990s, Wilcox and co-workers demonstrated the electrostatic acceleration of chemical reactions in nonpolar solvents using intramolecular salt effects.[94−98] Ion-pairing in transition metal complexes[99] has been used to achieve regioselectivity either through directed substrate−ligand interactions,[100−102] steric adjustment,[103] or energetic differentiation of transition states.[104−106] Cation-π interactions have also been utilized to increase the acidity of select C−H bonds; however, this is more of an inductive effect, allowing for site-selective bond activation.[107,108]

Transition metal complexes that incorporate crown ethers to bind cations or have ammonium or sulfonate functionalities in the ligand have emerged as a powerful strategy for accessing tunable electrostatic interactions. These platforms have the potential to provide a predictable, directional, and consistent electric field at each reactive site (Figure 3C,D). However, as discussed below, the accessible magnitudes may be limited depending on solvation.

Most efforts toward ligand-based cation encapsulation in transition metal complexes have focused on applications toward phase transfer and ion sensing[109] or switchable catalysis.[110] There are fewer studies specifically investigating cation encapsulation for electrostatic effects. In order for a cation to impart an electric field at a local reaction site, the cation must be located in close proximity.[111−119] Otherwise, solvent or other ions in solution will reorient to mitigate the field. Further, solvent reorganization must be minimized in order for the electric field exerted by the cation to affect any transition state stabilization.

We and others have synthesized transition metal complexes with a macrocyclic N_2O_2 Schiff base ligand and an incorporated crown ether (Figure 4).[120−123] The electric field experienced at the redox active metal site by cation M^{n+} manifests itself through significant shifts in the redox potential of up to 600 mV, which corresponds to static electric fields greater than 1 V/nm at the transition metal.[120,124] The sizable shift in redox potential is notable because the measurements

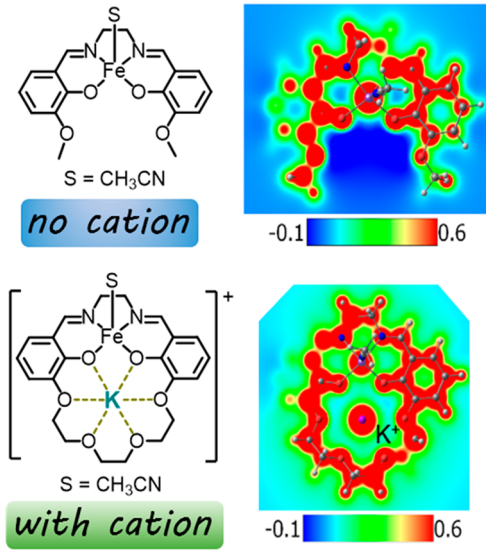

Figure 4. Electrostatic potential maps of Fe(II) in a salen framework without (top) or with (bottom) a proximal K^+ cation. S = CH_3CN. Reproduced with permission from ref 123. Copyright 2019 The Royal Society of Chemistry.

are made in solutions containing ~100 fold excess of electrolyte. The rigid positioning of the cation and molecular architecture results in an electric field that is not significantly quenched by solvation or the presence of ions in high concentrations. The Schiff base ligand also contains two imine bonds (−C═N−), which are convenient reporters of the field using vibrational spectroscopy, as evidenced by the Stark shift observed in the complexes.[120] The changes in reduction potential are largely due to the electrostatic contributions that lower the overall energy of the molecular orbitals, which contrasts with modifying reduction potentials using ligand inductive effects.[123] As a result, the addition of the cation leads to unusual reactivity—from disrupting the redox-dependent activity of an aerobic C−H oxidation reaction,[121] to an inverse free energy relationship for an N−N bond formation reaction (vide infra).[122] These changes in reactivity would not be accessible if the reduction potential were tuned using electron-withdrawing and -donating functionalities. Inductive ligand effects alter the ligand field at the metal, modifying the d-orbital splitting. In contrast, the electrostatic potential from the cations shifts the metal-based orbitals relatively uniformly, resulting in unique redox-based reactivity.[123]

Figure 5 illustrates examples of different synthetic transition metal complexes incorporating electrostatic interactions. Agapie and co-workers reported modifications in reduction potential for Mn_xO_y clusters that incorporate nonredox active Lewis acidic heterometal cations. In these systems, the changes in reduction potential correlate with both charge and heterometal Lewis acidity, indicating both electrostatic and inductive effects are involved.[125,126]

Flexible crown-encapsulated cations can influence or tune reactivity, even if they impart a smaller electrostatic effect at the metal. Gilbertson and co-workers found that an iron pyridinediimine complex with a tethered Na^+-encapsulated-crown led to accelerated reduction of nitrite to nitric oxide.[127] In this complex, the cation does not significantly shift the ligand-based reduction potential of the iron complex; instead of directly impacting the iron center, the cation preferentially

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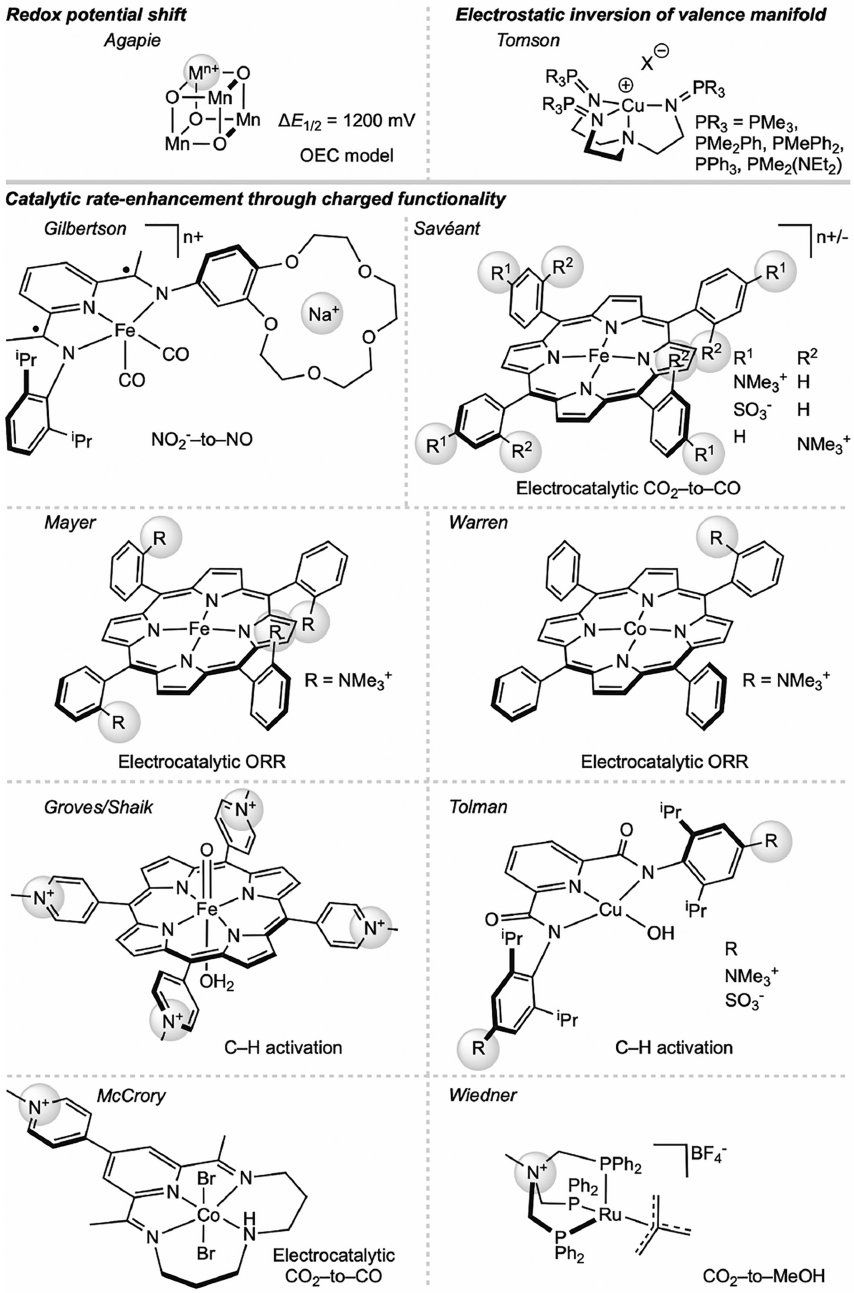

Figure 5. Reported homogeneous transition metal complexes with charged functionalities that contribute to changes in electronic structure or reactivity. Left, top-to-bottom: Agapie (refs 125 and 126), Gilbertson (ref 127), Mayer (refs 130 and 131), Groves (refs 132 and 133), Shaik (ref 134), McCrory (ref 136); Right, top-to-bottom: Tomson (ref 140), Savéant (ref 128), Warren (ref 129), Tolman (ref 135), Wiedner (ref 137).

engages in an electrostatic interaction with the substrate, NO_2^-, for reduction to NO.

Installation of charged functionalities is another synthetic modification to introduce electric fields at active sites. For example, ammonium functionalities on the periphery of iron porphyrin complexes results in accelerated electrocatalytic CO_2 reduction activity due to electrostatic stabilization of a carboxylate intermediate.[128] Proximal ammonium functionalities have also been used to accelerate electrocatalytic oxygen reduction in cobalt and iron porphyrins. For the former, computational studies indicate the cationic functionalities stabilize anionic intermediates.[129] In the latter example, the proximal cations play a complex role in pre-equilibria substrate binding due to through-space electrostatic and inductive contributions.[130,131] Additionally, Groves and co-workers reported Fe porphyrin complexes with cationic porphyrins that were exceptionally active for C−H activation.[132,133] A subsequent computational study by Shaik and co-workers indicated that the electric field generated by the cationic functionalities selectively destabilized the reactants more than the transition states, leading to the accelerated rate.[134]

Ligand-based electrostatic effects are also expected to impact thermodynamic properties related to hydrogen atom transfer reactions. Tolman and co-workers have explored the effect of cationic (ammonium) and anionic (sulfonate) ligand functionalities on copper hydroxide species. Although the charged

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functionalities impact the reduction potentials and pK_a, the bond dissociation energies remained relatively constant. However, the kinetic reactivity toward hydrogen atom transfer varies, with cation pairing to the sulfonate functionality, complicating direct attribution to electrostatic effects.[135]

McCrory and co-workers recently demonstrated the use of an *N*-methylpyridinium functionality on a cobalt pyridyldiimine complex to tune the reduction potential of CO_2 reduction catalysis.[136] Incorporation of the charged pyridinium group resulted in higher catalyst activity and a lower overpotential. In another example, Wiedner and co-workers demonstrated enhanced rates and selectivity for MeOH production from CO_2 using a Ru(triphos) hydrogenation catalyst that incorporates a cationic tetraalkylammonium in the ligand backbone.[137] In this example, it is unclear whether the cationic group imparts an inducive effect on the electronic structure of the proposed intermediate dihydrogen complex, lowering its energy, or whether there is through-space stabilization from an internal electric field. The above examples all use cationic functionalities to mediate reactivity by selectively stabilizing reactants or intermediates. However, anionic trifluoroborate groups used in Ni complexes by Anderson and co-workers have also demonstrated accelerated C−F oxidation activity.[138]

Other studies have investigated how electrostatic effects specifically impact the electronic structure of transition metal compounds.[139] Tomson and co-workers investigated a series of tetradentate tris(phosphinimine) Cu(I) complexes that incorporated cationic charges within the secondary coordination sphere.[140] The electrostatic field from the cationic charges results in a modified d-orbital manifold at the metal and significant changes to the Cu(II/I) reduction potential.

Electrostatic effects can also inhibit undesired reaction pathways, such as catalyst deactivation. Catalyst deactivation by bimolecular processes or formation of clusters is a common phenomenon in various catalytic systems.[141] To counter these unproductive pathways, catalysts often use increased steric bulk or site-isolation techniques.[141] However, electrostatic effects can be used to prevent dimerization or oligomerization without the necessity of any support material. Manganese(VI) nitrido complexes supported by Schiff base ligands can bimolecularly couple upon oxidation to generate N_2.[142] Incorporation of cationic charges into the salen framework results in anodic shifts in the Mn(VI/V) reduction potential. Despite an increase in oxidation potential, the rate of bimolecular N−N bond formation slowed with increasing charge, resulting in an inverse linear free energy relationship.[122] These results illustrate the significant effect charge can play in inhibiting bimolecular reactivity.

OUTLOOK AND CONCLUSIONS

Harnessing the catalytic power of enzymes has enormous potential in developing more robust and efficient synthetic catalysts. As reaction chemists have not yet been able to replicate enzymatic activity or specificity for most reactions, a better understanding for controlling the electric field in reaction microenvironments is necessary. We discuss various synthetic strategies for using oriented electrostatic fields at scalable, homogeneous reaction sites. Microenvironments can be emulated through the construction of supramolecular pores. Precise substrate positioning can be achieved through ion-pair interactions. Local, directional electric fields can be generated through incorporation of cationic metals or charged functional groups. Direct application of these noncovalent interactions and their impact on reactivity and molecular properties will in-turn lead to better quantitative descriptions of each approach. We hope that a more deliberate approach toward using electric fields will lead to a more comprehensive understanding of how they facilitate the formation and cleavage of chemical bonds, as well as electron transfer by manipulating activation barriers and intermediate energies.

AUTHOR INFORMATION

Corresponding Author

Jenny Y. Yang − *Department of Chemistry, University of California, Irvine, California 92697, United States;* orcid.org/0000-0002-9680-8260; Email: j.yang@uci.edu

Authors

Nadia G. Léonard − *Department of Chemistry, University of California, Irvine, California 92697, United States;* orcid.org/0000-0002-0949-5471

Rakia Dhaoui − *Department of Chemistry, University of California, Irvine, California 92697, United States*

Teera Chantarojsiri − *Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Mahidol University, Bangkok 10400, Thailand;* orcid.org/0000-0002-4951-9503

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.1c02084

Author Contributions

[§](N.G.L., R.D.) These authors contributed equally.

Notes

The authors declare no competing financial interest.

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