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Catalysts by Design: The Power of Theory

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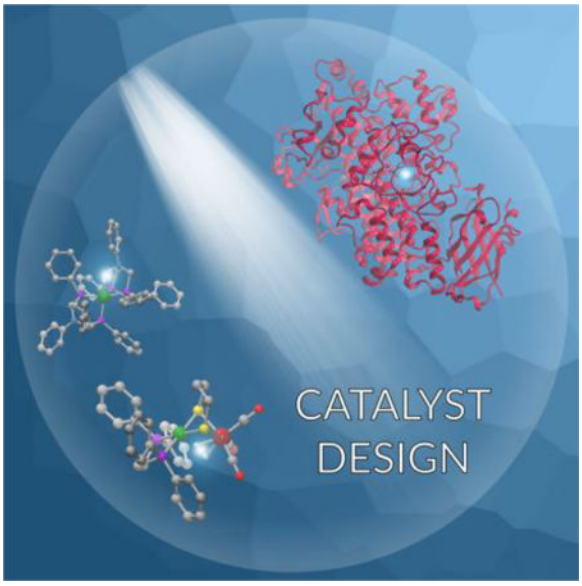
Abstract

Theoretical design of effective catalysts, in conjunction with the identification of guiding design principles and strategies, is a Holy Grail in Chemistry. Although further progress will benefit from additional computational advances, theoretical studies have already enhanced the design of molecular electrocatalysts, photocatalysts, and enzymes.

TOC graphic



Introduction

The theoretical design of effective catalysts has been a Holy Grail for decades and will most likely continue to be viewed in this capacity for future decades. Theoretically designed catalysts could potentially impact a broad spectrum of fields ranging from medicine to energy science. For example, catalysts are essential in the pharmaceutical and chemical industries in terms of the efficient synthesis of drugs, food additives, fertilizers, and plastics.[1–2] Catalyst design is also critical for developing renewable and sustainable energy sources, particularly in the form of electrocatalysts and photoelectrocatalysts for fuel cells and solar cells.[3–9] All of these fields would benefit from the guidance that theory can provide for the design of more effective catalysts.

The ultimate goal of theoretical catalyst design would be to start from first principles, without knowledge of any related catalysts, and use *ab initio* computational methods to design an efficient catalyst for a specified reaction. Achieving this goal becomes even more challenging when factors such as stability, solubility, and synthetic accessibility must also be considered. As developments in hardware and software lead to faster computations, eventually such an *ab initio* approach might be possible. Even if it were possible to design a catalyst by placing atoms and molecules into a box and simulating the *ab initio* dynamics,[10] however, this success would not represent full attainment of the Holy Grail in this field. According to my perspective, the Holy Grail in catalyst design encompasses the conceptual understanding and guiding design principles that are essential for generalizing and extending the results of specific simulations to enable the theoretical design of molecular and biological catalysts with the requisite properties.

Although the ultimate goal is to design catalysts theoretically from first principles, in practice the feedback between theory and experiment is critical for success. Often theoretical calculations assist in the interpretation of experimental data and provide mechanistic explanations. In addition, it is important for theoretical calculations to make predictions that are subsequently tested experimentally to ensure transparency and credibility within the community. While this type of theoretical prediction is challenging, several examples of successful predictions that were validated subsequently through experiments will be discussed below.

Another important aspect of catalyst design is the inspiration from biology. Bioinspired catalysts exploit basic principles and motifs present in naturally occurring biological systems. For example, hydrogenase enzymes have inspired a large number of molecular electrocatalysts for hydrogen oxidation and production,[11–12] and photosystem II has served as the inspiration for catalysts that split water into oxygen and hydrogen.[5–7] Specific examples of bioinspired molecular electrocatalysts will also be discussed below.

The guiding design principles obtained from studies of specific catalysts will enable the identification of descriptors that can be used to computationally screen large numbers of candidates for specified properties. This type of high throughput virtual screening[13] enables the consideration of a much larger number of candidates and removes a significant amount of human intervention and bias through automation. Nevertheless, the results of such screening processes depend strongly on the choice of descriptors, which will be informed by the insights gained from understanding the fundamental principles underlying molecular and enzymatic catalysis. Furthermore, many of the design principles for homogeneous catalysts will apply to heterogeneous catalysts, which also require additional considerations, such as adsorption energies and band gaps.[14–15]

Theoretical and computational tools

In general, theoretical catalyst design requires calculations of structures, thermodynamics, kinetics, and dynamics of molecules and enzymes in solution. A wide range of theoretical methods are available for such calculations. For molecular systems, quantum chemistry methods such as density functional theory are able to predict reliable structures,

thermodynamic properties such as reduction potentials and pK_a's, and free energy barriers to determine kinetic properties.[16] The solvent can be represented as a dielectric continuum or as explicit solvent molecules that are treated at a lower level of quantum mechanics or molecular mechanically. Computational studies of heterogeneous catalysts typically require the use of periodic density functional theory and associated techniques.[17–18] For enzymatic systems, mixed quantum mechanical/molecular mechanical (QM/MM) methods allow the active site to be treated quantum mechanically and the remainder of the system to be treated molecular mechanically.[19] Molecular dynamics simulations enable conformational sampling of both molecular and enzymatic systems, and free energy sampling methods facilitate the simulation of rare events such as catalytic reactions. Molecular dynamics simulations rely on accurate potential energy surfaces and sufficient conformational sampling. The choice of computational methods depends on the level of accuracy required and the complexity of the system. In some cases, nuclear quantum effects such as hydrogen tunneling must be included, while in other cases the effects of excited electronic states are significant.

In addition to these types of simulation methods, often analytical theories, such as Marcus theory for electron transfer theory or analogous theories for hydrogen transfer or proton-coupled electron transfer reactions,[20] are important for obtaining a conceptual understanding and predicting trends with respect to physical properties. Although these types of analytical theories are typically valid only in certain well-defined regimes, they provide a more direct route toward understanding and predicting fundamental chemical and physical properties. A powerful strategy for catalyst design will combine analytical theories and large-scale simulation methods.

Molecular electrocatalyst design

The main objectives of molecular electrocatalyst design are to enhance the reaction speed (i.e., increase the turnover frequency) and to lower the reaction energy input (i.e., reduce the required overpotential). Theoretical design of these catalysts utilizes a wide range of strategies to accomplish these objectives, including altering the identities of the metal centers, the ligands, and the substituents. Effective utilization of non-innocent ligands, which are able to transport protons and electrons, is another key strategy. A less widely used strategy is the incorporation of ligand flexibility to enable effective conformational sampling of configurations conducive to the chemical reaction. In addition to the objectives of high speed and low energy input, the electrocatalysts must be robust, stable, and relatively easy to synthesize, preferably from earth-abundant, inexpensive materials. The solvent and pH can also be varied to enhance performance and stability. Consideration of all of these aspects requires feedback between theoretical calculations and experimental synthesis and characterization.

The electron-withdrawing or electron-donating properties of the substituents on the ligands may be altered to impact the reduction potential and pK_a of the catalyst. This strategy has been applied to cobaloxime catalysts for H_2 production. In this case, the calculated reduction potentials and pK_a's for a series of substituted cobaloximes, as depicted in Figure 1a, were found to depend linearly on their Hammett constants.[16,21] On the basis of these linear plots, the reduction potentials and pK_a's for the cobaloxime can be estimated for any substituent

with a known Hammett constant or from the calculation or measurement of only one of these values. Knowledge of these reduction potentials and pK_a's enables the generation of the free energy diagrams for any proposed mechanism, thereby allowing the identification of the most thermodynamically favorable reaction pathway. The identity of the metal center can also be changed to impact these properties.

In addition to altering the substituents, the ligands themselves may be designed to facilitate catalysis through protonation or reduction. Such non-innocent ligands have been found to play an important role in a wide range of electrocatalysts. For the cobaloximes, the O-BF_2-O bridge has been modified to an O-H-O bridge (Figure 1a), which can be protonated in an effort to lower the required overpotential for the catalyst.[16] The hangman metalloporphyrins, as depicted in Figure 1b, serve as another example of ligand non-innocence during the catalytic cycle for hydrogen production. Initially the proton was presumed to transfer from the hanging carboxylic acid to the metal, forming a metal hydride. Calculations unexpectedly predicted that the porphyrin ligand, rather than the metal, would be reduced, leading to non-aromaticity that resulted in a phlorin intermediate (Figure 1b). The calculations indicated that proton transfer from the hanging carboxylic acid to the *meso* carbon of the porphyrin to produce a phlorin was structurally, thermodynamically, and kinetically favored for the reduced species. Despite initial skepticism about this theoretical prediction, the phlorin intermediate was subsequently isolated and characterized spectroelectrochemically using phenol as the acid, which was strong enough to form the phlorin intermediate but not strong enough to produce hydrogen.[22] These types of theoretical predictions that are later tested experimentally are an important component of theoretical catalyst design.

As mentioned above, catalyst design is often inspired by nature. A prime example is the large number of catalysts for hydrogen oxidation and production inspired by hydrogenase enzymes.[11–12] Many of these catalysts are biomimetic in that they include two metal centers corresponding to either [NiFe]- or [FeFe]-hydrogenase and, in some cases, mimic the ligands in the biological system. Computational studies have played an important role in elucidating the mechanisms of such catalysts, thereby providing guidance for enhancing the effectivity. In the [NiFe]-hydrogenase model depicted in Figure 1c, the crystal structure exhibited a tetrahedral conformation at the Ni center. However, isomerization from this tetrahedral conformation to a square planar conformation at the Ni center was revealed from theoretical calculations and was verified through ^{31}P NMR experiments.[23] The previously unobserved square planar isomer was determined to be the active species because the pK_a associated with forming the key Fe-hydride intermediate is approximately eight units higher for the square planar isomer than for the tetrahedral isomer due to electron transfer from the Ni to the Fe upon isomerization. This insight suggests that stabilizing the square planar isomer could enhance the effectiveness of this catalyst.

Another type of hydrogenase model includes only a single metal center and incorporates ligands with pendant amines that serve as proton relays, transporting protons to and from the metal center.[12] These catalysts are bioinspired in that they incorporate the concept of a proton relay positioned near the metal center from hydrogenase enzymes but do not mimic the specific structure of the active site. The popular $Ni(P_2N_2)_2$ hydrogen-evolving catalysts,

as depicted in Figure 1d, have been particularly successful in terms of high turnover frequencies at relatively modest overpotentials.[12] Theoretical calculations have provided guidance for the modification of the ligands to alter the pK_a's of the pendant amine and the metal center, as well as the reduction potentials, in ways that enhance the turnover frequency.

Additional calculations have highlighted the importance of the flexibility of the ligands in the $Ni(P_2N_2)_2$ catalysts.[24] Initially, these catalysts were designed to ensure that the pendant amine is held rigidly over the metal center to enable proton transfer between the nitrogen on the amine and the metal center during catalysis. Theoretical calculations indicated that this Ni–N distance is still too long for proton transfer in the equilibrium structure and that equilibrium thermal motions are required to decrease this distance to enable proton transfer.[24] These calculations suggested that the pendant amine ligand also needs to be flexible enough to facilitate contraction of the Ni–N distance without a prohibitive energy penalty. Thus, the design principle obtained from the theoretical calculations was that the pendant amine ligands need to be reasonably well-positioned so that the pendant amine remains in the vicinity of the metal center but also flexible enough to enable the amine to move toward the Ni center due to equilibrium conformational sampling.

Several key catalytic design strategies have arisen from these studies of molecular electrocatalysts. First, the structure must be conducive to the chemical reaction, such as positioning a protonatable hanging group near the metal center. Second, the thermodynamics must favor the catalyzed reaction, typically by tuning the reduction potentials and pK_a's by modifying the ligands, substituents, or metal center. Third, the catalyst must be rigid enough to ensure a suitable equilibrium structure but flexible enough to enable thermal fluctuations to sample configurations conducive to the chemical reaction. These three strategies correspond to structural, thermodynamic, and kinetic or dynamical properties. Successful catalyst design should consider all of these important factors.

Photocatalyst design

Given that photocatalysts are activated by light, the design of such catalysts requires simulations of excited electronic states and often transitions between these electronic states. Similar strategies to those discussed for electrocatalyst design can also be used for photocatalysts. In this case, however, the impact of modifying the metal centers, ligands, and substituents on the excited electronic states must be determined. Moreover, electrocatalysts perform under predominantly equilibrium conditions, whereas photocatalysts typically perform under nonequilibrium conditions. Because photoexcitation changes the electronic charge distribution of the molecule, the solute nuclei and the solvent nuclei are no longer at equilibrium immediately following photoexcitation. When photoexcitation results in a significant change in the molecular dipole moment, the solute, solvent, and/or protein dynamics often play a pivotal role.[25] For such photocatalysts, the nonequilibrium dynamics may significantly impact the relaxation time, as well as the pathway, from the excited state to the ground state and therefore may influence the effectivity of the catalyst. The design of photocatalysts must take these factors into account.

Enzyme design

Enzymes utilize a variety of strategies to efficiently catalyze specific chemical reactions. Hydrogen bonding and electrostatic interactions, as well as pK_a shifting, have been found to be important in a wide range of enzymes. The concepts of preorganization and reorganization are often invoked in enzyme catalysis. The active site of an enzyme is typically preorganized to ensure that the subsequent reorganization required for the chemical reaction is less than that required in solution. Preorganization may require large conformational changes, such as the opening or closing of a loop, whereas reorganization typically requires relatively small conformational changes to facilitate the chemical step. Related to these concepts, equilibrium conformational sampling caused by stochastic, thermal motions plays an important role in enzyme catalysis because such motions assist in the sampling of configurations that are conducive to the chemical reaction. Although proposals of promoting vibrational modes that are dynamically coupled to chemical reactions in enzymes have been put forth in the literature, the evidence for the catalytic significance of such dynamical effects is not convincing. Another phenomenon observed in certain enzyme reactions is hydrogen tunneling, as will be discussed further below. All of these strategies can be harnessed to design more effective enzymes.

The contributions from hydrogen bonding, electrostatics, preorganization, reorganization, and equilibrium conformational sampling have been clarified through theoretical calculations of many enzymes.[19] For example, ketosteroid isomerase is known to utilize hydrogen-bonding interactions, as well as pK_a shifting of key residues in the active site, to facilitate the catalyzed proton transfer reactions depicted in Figure 2. A series of mutants of this enzyme have been probed both theoretically and experimentally to examine the relative contributions of these factors. While the active site is preorganized, further local reorganization in the form of minor structural changes occurs during the chemical reaction to facilitate proton transfer and to accommodate changes in the hydrogen-bonding interactions.

Dihydrofolate reductase has also been studied extensively with both theoretical and experimental methods.[19,26] These studies have illustrated the importance of equilibrium conformational sampling on a wide range of time scales in the catalytic cycle of this enzyme. Such conformational sampling leads to configurations that are conducive to the catalyzed hydride transfer reaction by decreasing the hydride donor-acceptor distance, orienting the substrate and cofactor properly, and providing a suitable electrostatic environment. Moreover, distal mutations have been shown to alter this conformational sampling in ways that impact the free energy barrier and therefore the rate constant. The role of electrostatics in dihydrofolate reductase has been investigated by inserting nitrile probes at site-specific locations in the enzyme and calculating the change in the vibrational frequency of this probe for the five intermediates along the catalytic reaction pathway.[27] A combination of theoretical and experimental data on this vibrational Stark effect illustrated that the protein and ligands impose an electric field along the hydrogen donor-acceptor axis that facilitates the transfer of the negatively charged hydride, as depicted in Figure 3.

Soybean lipoxygenase is the prototypical example of an enzyme that catalyzes hydrogen tunneling, as depicted in Figure 4.[19–20] Experimental evidence of hydrogen tunneling includes the unusually high kinetic isotope effect (KIE),[28] which is the ratio of the rate constant for hydrogen and deuterium at room temperature. The KIE of wild-type soybean lipoxygenase is 80, and the KIE of a double mutant soybean lipoxygenase is as high as 700.[29] Such high KIEs are indicative of a hydrogen tunneling mechanism. This reaction has been studied with an analytical theory for proton-coupled electron transfer (PCET), which has assisted in the interpretation of the experimental data and predicted trends in terms of physical properties of this system.[20,30] A combination of this analytical theory, computer simulations, and experimental measurements of wild-type soybean lipoxygenase, as well as a series of different mutants, has provided a deep understanding of hydrogen tunneling in this enzyme. This type of understanding will be transferrable to other hydrogen tunneling enzymes.

Protein catalyst design can be framed in terms of the same three strategies discussed for molecular electrocatalysts. First, the structure must be conducive to binding the substrate and/or cofactor in a manner that enables the chemical reaction. Second, the thermodynamics and energetics should facilitate the catalyzed reaction, often through hydrogen bonding and electrostatic interactions. Third, the protein and ligands must be rigid enough to ensure a suitable equilibrium structure but flexible enough to enable thermal fluctuations to sample configurations conducive to the chemical reaction. The first and second strategies are related to preorganization, while the third strategy is related to reorganization. Successful design of enzymes should consider all of these significant factors.

Remaining challenges in theoretical catalyst design

The Holy Grail of theoretical catalyst design, in conjunction with the identification of guiding design principles and strategies for molecular and biological catalysts, has been partially attained but still remains a central challenge in theoretical and computational chemistry. Further progress requires more accurate, computationally tractable electronic structure and molecular dynamics methods, as well as more versatile approaches for describing excited electronic states, nonadiabatic processes, and nuclear quantum effects. The extension of these approaches to heterogeneous catalysis, for which surface or bulk materials actively participate in chemical reactions, is a particularly daunting task. Despite these remaining challenges, however, the design principles and strategies discovered for molecular electrocatalysts, photocatalysts, and enzymes have already aided the development of more effective catalysts in these arenas. Further progress will be achieved by combining the current understanding with new technologies.

Acknowledgments

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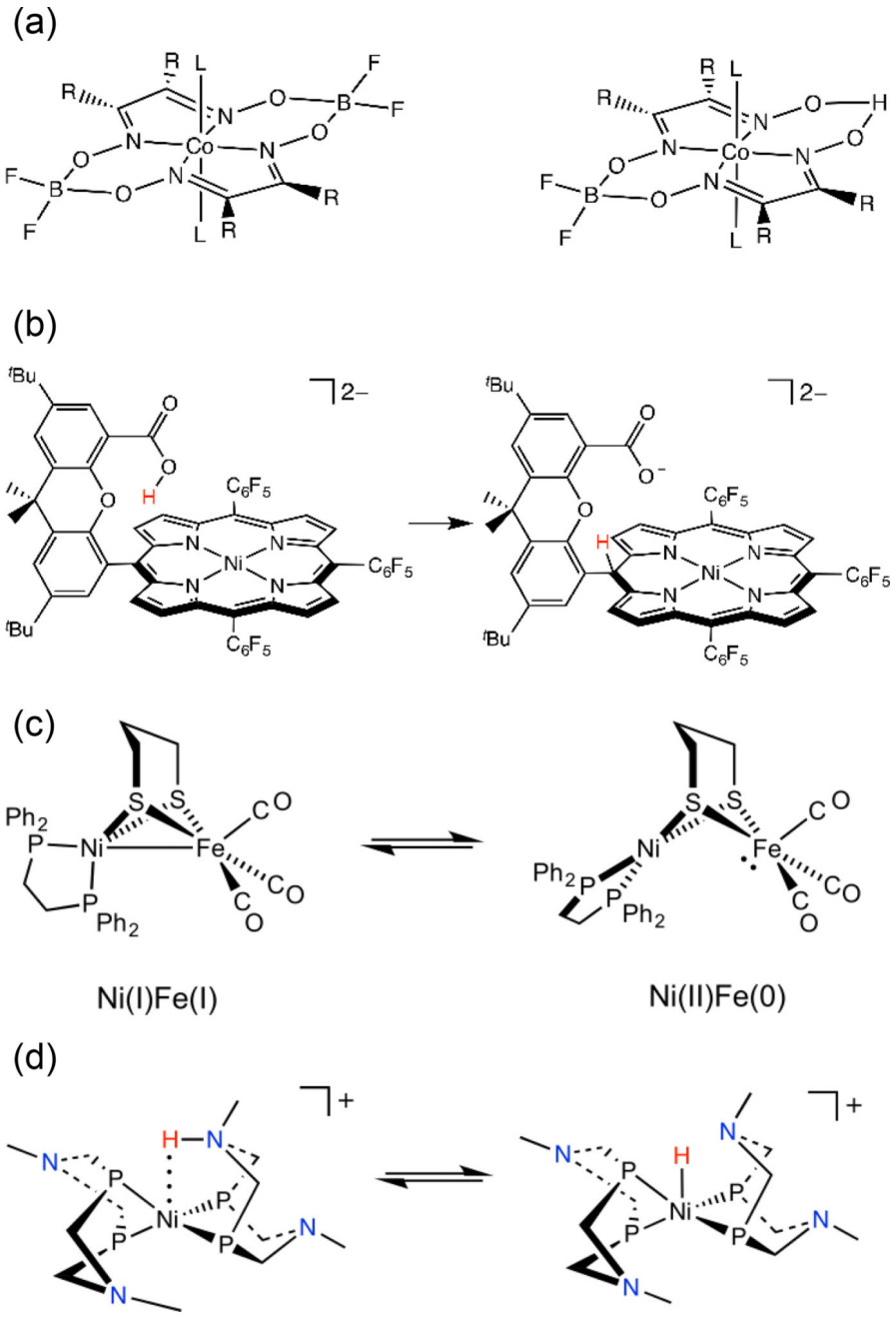

Figure 1.

Schematic depictions of molecular electrocatalysts for which theoretical calculations provided design principles. (a) Cobaloximes, for which the thermodynamic properties were determined to depend linearly on the Hammett constants of the substituents R; (b) Ni hangman porphyrin, for which the proton in red was shown to transfer to the *meso* carbon of the porphyrin to form a phlorin intermediate; (c) NiFe-hydrogenase model, for which isomerization at the Ni center revealed a previously undetected catalytically active isomer that is square planar with significantly greater basicity at the Fe center; (d) $Ni(P_2N_2)_2$ catalysts, for which the pendant amine serves as a proton relay to and from the metal center,

with the effectivity influenced by the substituents on the N and P (not shown) and by ligand flexibility to enhance thermal fluctuations of the N toward the Ni center.

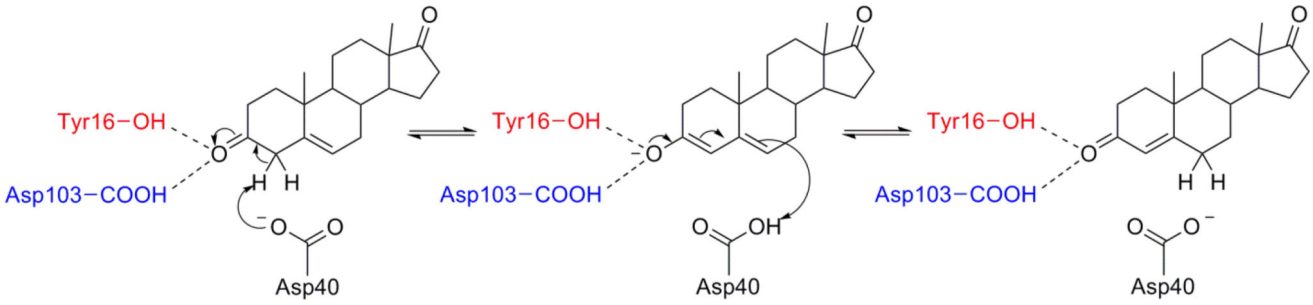

Figure 2.

Proton transfer reactions catalyzed by ketosteroid isomerase, leading to an overall isomerization reaction. The hydrogen-bonding interactions depicted in red and blue stabilize the dienolate intermediate more than the reactant and product.

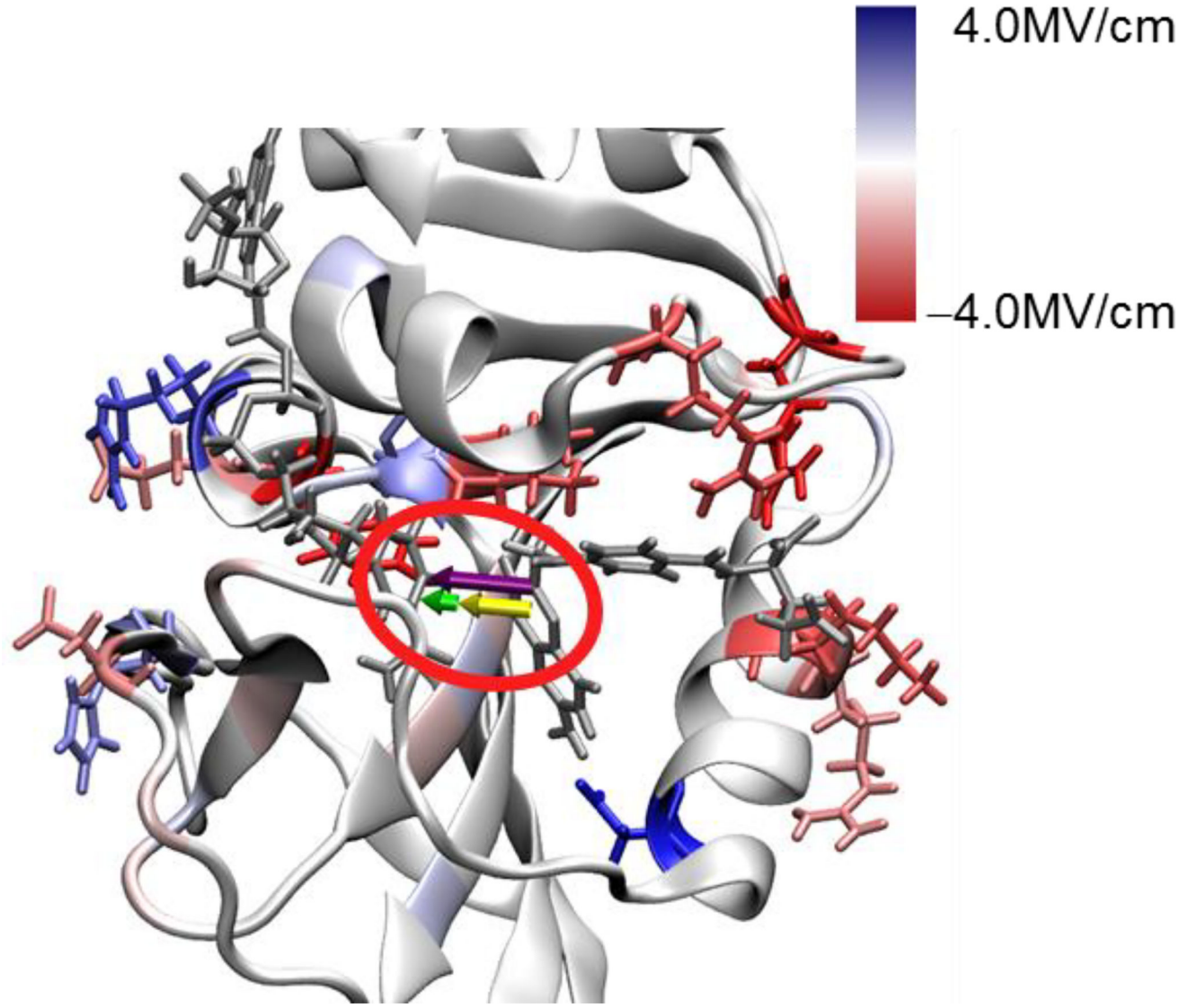

Figure 3.

Depiction of the component of the electric field along the hydride transfer donor-acceptor axis calculated from a simulation of wild-type *E. coli* dihydrofolate reductase with $NADP^+$ and folate bound. The color for each residue corresponds to the calculated field contributed by each individual residue using the color scale provided. The three arrows in the red oval represent the total electric field of −48.9 MV/cm (purple), the field of −32.4 MV/cm resulting from the ligands (yellow), and the field of −16.5 MV/cm resulting from the rest of the system (green) projected along the donor-acceptor axis. Figure reproduced with permission from Ref.[27]. Copyright 2014 American Chemical Society.

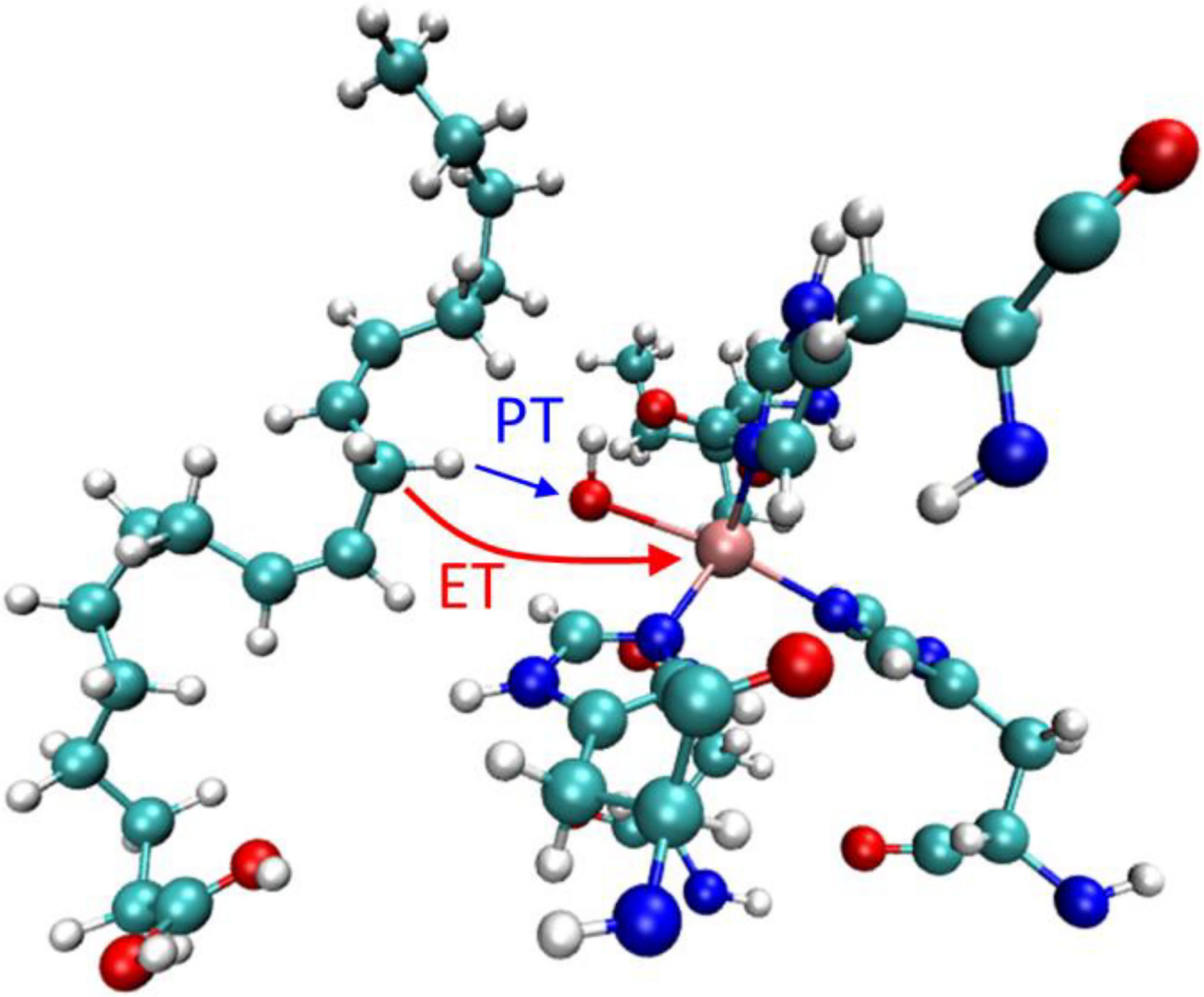

Figure 4.

Schematic representation of the PCET reaction catalyzed by soybean lipoxygenase with the linoleic acid substrate. The red arrow indicates the electron transfer from the π-backbone of the linoleic acid substrate to the iron of the cofactor, and the blue arrow indicates the proton transfer from C11 of the substrate to the iron-bound hydroxide to form water. This PCET reaction is prototypical of hydrogen tunneling in enzymes. Reproduced with permission from Ref.[20]. Copyright 2015 American Chemical Society.