FOCUS ARTICLE

Advances and challenges in modeling solvated reaction mechanisms for renewable fuels and chemicals

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We provide a critical overview of progress and challenges in computationally modeling multistep reaction mechanisms relevant for catalysis and electrocatalysis. We first discuss how the chemical and materials space of energetically efficient catalysis can be explored with computational chemistry. Since reactions for renewable energy catalysis can involve acid-base chemistry and/or ions under aqueous conditions, we then summarize how solvation can be modeled with quantum chemistry schemes using implicit, mixed implicit/explicit, and fully explicit solvation modeling. We will discuss the insights (and limitations) of these solvation models primarily through the scope of understanding CO_2 reduction reaction mechanisms, but these will also be applicable for future work elucidating other reaction mechanisms of critical importance for human sustainability such as H_2O oxidation and N_2 reduction.

KEYWORDS
Solvation modeling, cluster-continuum, mixed implicit/explicit, Pourbaix diagrams, phase diagrams, CO_2 reduction

1 | INTRODUCTION

Developing sources of renewable energy is paramount to long-term human sustainability.[1–3] For instance, CO_2 emissions correlate with severe weather patterns[4] and global climate change,[5] but more than 78% of the world's energy consumption through the year 2040 is expected to come from fossil fuels.[6] Thus, many are interested in recycling anthropogenic CO_2 into fuels and chemicals[7–11] as well as sustainably producing ammonia[12,13] and/or hydrogen.[14,15] Unfortunately, most of these are currently unfeasible on large scales due to low conversion efficiency and/or high electrochemical overpotentials. For CO_2 electroreductions into fuels and chemicals, selectivity and energy efficiency remain as major challenges for proton and electron transfers.[16] These challenges are also present in other fundamental transformations such as N_2 reduction for ammonia synthesis[17] and H_2O oxidation for H_2 generation.[18]

Computational quantum chemistry modeling can help interpret and guide experimental work in this area by providing insights into chemical reaction mechanisms. Advances in algorithms and hardware make it easier to computationally model larger scale systems with higher accuracy, but the central challenges of understanding *what* processes to model and *how* to physically model them in a reliable way still remain. Indeed, many chemical reactions have intermediate states that are stabilized by different degrees of solvating environments, and neglecting or incorrectly modeling these environments can significantly impact the quality of predictions from computational modeling. We begin this mini-review by summarizing how one can use computational modeling to explore the chemical and materials space of renewable energy catalysis through the lens of identifying energetically efficient hydrogenation pathways for CO_2 reduction catalysis. We will then summarize different approaches to model solvating environments in reaction mechanism studies while also reviewing knowns and unknowns from recent literature to offer perspective for future efforts in this and related fields.

2 | THE CHEMICAL SPACE OF (DE)HYDROGENATION REACTIONS MECHANISMS

At a fundamental level, any hydrogenation (or dehydrogenation) process for any reaction might occur as:

1. One or more covalent hydrogen atom (H·) transfers (e.g. with thermal heterogeneous catalytic processes).[19]
2. Stepwise or coupled proton and electron transfers that originate from different sites within the system (e.g. with electrochemical processes).[20]
3. Formal hydride (H^-) transfers that may also be coupled with a proton transfer (e.g. with biomimetic processes).[21]

Analogous classifications have been used by many others to distinguish different modes for hydrogenation,[22–28] and each class has been studied in different contexts of homogeneous,[29] heterogeneous,[30] or biological catalysis.[31] Clearly, the local chemical environment (especially a solvating environment) will play a role in determining the nature of the hydrogenation mechanism.

To understand how environmental conditions can influence multistep processes, we can start by defining a map of elementary electrochemical processes using a 'square-scheme' or 'schemes of squares'[32] and draw analogies to moves on a chessboard (see Figure 1). Here, a generic molecule A can undergo elementary steps to form a new reduced, hydrogenated state (AH_n). Individual proton transfer steps are normally represented as vertical steps, individual electron transfer steps are then represented as horizontal steps, and proton-coupled electron transfer steps are diagonal steps, i.e. all possible moves that a king piece is allowed to make in a chess game. Alternatively, an elementary

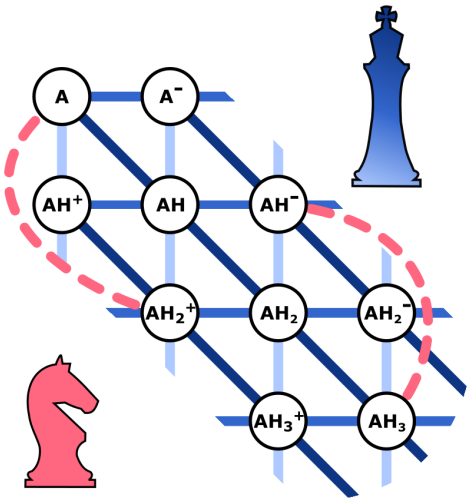

FIGURE 1 A "square-scheme" diagram of hypothetical pathways for a multistep (de)hydrogenation process.

hydride transfer would be an 'L'-shaped step that involves two electron transfers and one proton transfer, i.e. a possible move that a knight piece can make. Before going too far, some aspects warrant mention. First, it is usually rare to find a reaction intermediate having a charge with an absolute magnitude of two or more unless there is a polarizing solvent and/or counterions nearby.[33] Thus, it is usually not likely (though not impossible) to move two or more steps away from the diagonal line depicting neutral intermediate states. Second, this square-scheme shows that several different pathways may exist for any multistep process, just like there are multiple paths a chess piece might move from one corner of a board to another. To actually distinguish the different pathways requires confirmations from experiment and reliable computational modeling to assess which pathways are relevant under specific conditions. We will now describe how computational quantum chemistry can be leveraged to accelerate the discovery of energetically efficient reaction steps.

2.1 | Theoretical Phase Diagrams

If hypothetical reaction intermediates can be identified, one can then use computational quantum chemistry to calculate the absolute free energies of each species using the standard ideal gas, rigid rotor, and harmonic oscillator approximations. From these data, one can then make phase diagrams that are functions of parameters (e.g. solution pH, an electrode potential, and/or partial pressures of molecular species) that can be used to navigate chemical and/or materials space.[34] For instance, one can define a generic reaction that refers to intermediates from Figure 1 using Equation 1:

$$\mathrm{A} + \frac{n}{2}\mathrm{H_2} \rightarrow \mathrm{AH}_n \tag{1}$$

The corresponding free energy for this reaction at an arbitrary standard state (°) is simply the difference of the free

energies of the individual products and reactants:

$$\Delta G^{\circ}_{\text{rxn}} = G^{\circ}_{\text{AH}_n} - G^{\circ}_{\text{A}} - \frac{n}{2} G^{\circ}_{\text{H}_2} \tag{2}$$

Note that the free energy of H_2 is also related to the definition for the standard hydrogen electrode (SHE) potential,

$$\text{H}^+ + e^- \rightleftharpoons \frac{1}{2}\text{H}_2 \qquad E = 0\,\text{V vs. SHE} \tag{3}$$

while the free energy for protons, electrons, or other species such as A or AH_n can be expressed as linear functions of a local environmental parameters such as pH, applied potential ϕ, or the relative difference in chemical potential from its standard state $\Delta\mu_X$, respectively. Note that SHE is a commonly used reference electrode which is a hypothetical electrode immersed in a 1 M aqueous solution of proton with unit activity and no ionic interactions. Other reference electrode systems (SCE, NHE, RHE, etc.) can be computationally modeled as well, and some discussion is found the perspective paper by Marenich et al.[35] Using the SHE reference electrode model, one could define the reaction free energy from Equation 2 in an expanded form of several different species, each having a corresponding parameter (all expressed in eV units):

$$\Delta G_{\text{rxn}} = \left(G^{\circ}_{\text{AH}_n} + \Delta\mu_{\text{AH}_n}\right) - \left(G^{\circ}_{\text{A}} + \Delta\mu_{\text{A}}\right) - \left(G^{\circ}_{\text{H}^+} - 0.059\ \text{pH}\right) - \left(G^{\circ}_{e^-} - eU_{\text{SHE}}\right) \tag{4}$$

Note that values such as $G^{\circ}_{\text{AH}_n}$ and G°_{A} can be straightforwardly calculated using quantum chemistry codes. $G^{\circ}_{\text{H}^+}$ and $G^{\circ}_{e^-}$ correspond to absolute free energies of a proton and electron in some environment and can be referenced from the literature.[35] The remaining $\Delta\mu_X$ terms are treated as linear variables that describe environmental factors, e.g. partial pressure of a specific species, a solution pH, or an applied potential.

Considering large numbers of hypothetical reactions and determining the most favorable state at any given set of environmental conditions in this general framework begets "*ab initio*" atomistic thermodynamics phase diagrams that would show any ΔG for any hypothetical reaction at a specified set of conditions. For instance, if pH (x-axis) and ϕ (y-axis) were used as parameters, one would create a Pourbaix diagram, i.e. a phase diagram that depicts the thermodynamically most stable state for a system at a given pH and ϕ.[36] A representative set of Pourbaix diagrams is given in Figure 2.

While Pourbaix diagrams only provide insights into the thermodynamics of different intermediate states, they are still quite useful. First, they are a convenient representation of pK_as, pH-independent standard redox potentials, and pH-dependent proton-coupled electron transfer steps by separating the regions of the Pourbaix diagram with vertical, horizontal, and diagonal boundary lines, respectively. These properties can be useful thermodynamic descriptors for catalysis. Second, the boundaries between different regions of a Pourbaix diagram define theoretical electrochemical conditions where free energies of reaction for a (de)hydrogenation step are zero, and thus at those electrochemical conditions the process should be highly reversible and thus energetically efficient. *Pourbaix diagram boundary lines therefore show theoretical electrochemical conditions that a species would facilitate energetically efficient shuttling of protons and electrons.* One step further, if one considers a Pourbaix diagram for a reactant such as CO_2 (Figure 2a) and another Pourbaix diagram for a hypothetical catalyst (Figure 2b), one could then overlay the two on top of the other (Figure 2c). Regions where boundaries of the two Pourbaix diagrams overlap signify electrochemical conditions where one species (i.e. a hypothetical catalyst) would facilitate shuttling of protons and electrons to another species (i.e. a reactant). This can be thought as an extension to the Sabatier principle of catalysis, where optimal catalyst activity is achieved when the substrate binds strongly enough to be activated but also weakly enough that it can still be removed and not poison the catalyst. Thus, Pourbaix diagram analyses allow one to search for the *catalyst state under specific electrochemical*

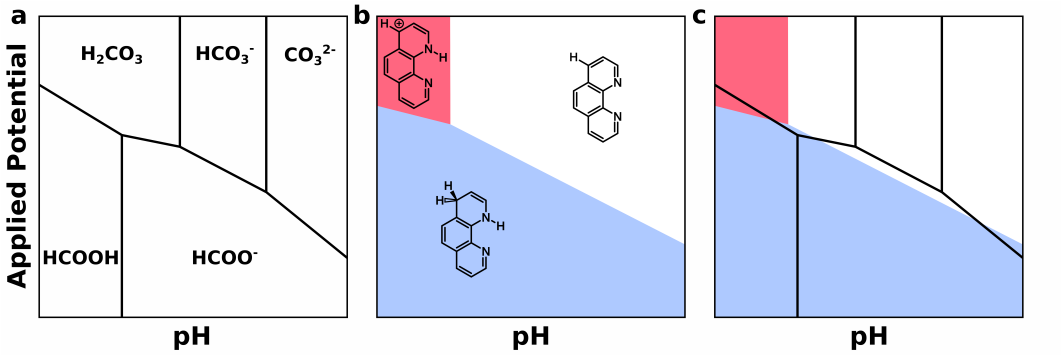

FIGURE 2 a) Pourbaix diagram showing stable states of the reactant, CO_2; b) Pourbaix diagram showing stable states of a hypothetical molecular catalyst, 1,10-phenanthroline; c) overlaid Pourbaix diagrams from a) and b) showing similar boundaries for hydrogen shuttling and CO_2 reduction. Vertical lines represent pK_as, the horizontal lines represent the pH-independent standard redox potentials and the diagonal lines represent the pH-dependent proton-coupled electron transfer steps.

environments that would provide the lowest hypothetical overpotential.

Our group has used Pourbaix diagram analyses to study a variety of homogeneous and heterogeneous catalysis systems for CO_2 reduction. Interestingly, we have predicted that reaction conditions for several CO_2 electroreduction processes ranging from homogeneous pyridinium [37,38] and homogeneous ruthenium [39]-complexes as well as heterogeneous N-doped nanocarbons [40] and partially reduced SnO_2 oxides [41] all coincidentally share a similar characteristic – all have Pourbaix boundary lines showing the formation of a new intermediate state near the conditions where CO_2 electrocatalysis has been reported. Experimentally validating these computational predictions has been difficult, in part due to difficulties reproducing experimental data that has been reported in the literature. [42,43] However, other experimental studies have implicated transiently formed hydride-containing species in CO_2 reduction that are intermediates predicted to be thermodynamically stable by Pourbaix diagram analyses. [44,45] From our perspective, we see opportunities to use computational modeling to discover new catalysts in chemical and materials space and synergistically guide experimental design with high-throughput screening. However, though numerous hurdles pertaining to modeling reaction mechanism under solvating reaction conditions must be overcome first.

2.2 | Challenges of Modeling Electrochemical Reaction Mechanisms

As stated earlier, Pourbaix analyses require that all the salient reaction intermediate states be correctly identified. When modeling catalytic reactions on surfaces, especially gas phase reactions on conducting surfaces, standard Kohn-Sham density functional theory (DFT) is normally suitable for reliably modeling charge neutral reaction intermediates. Additionally, modeling electrochemical reactions using the computational hydrogen electrode model [46] (i.e. modeling electrochemical proton and electron transfers as a 1/2 H_2 transfer coupled to a linear potential correction) can bring helpful and testable insights into electrocatalysis. However, as illustrated by Exner and Over [47] as well as Janik and Asthagiri, [48] modeling reaction mechanisms without accounting for barriers provides an incomplete picture and can result in qualitatively different outcomes that might be wrong and/or misguide future research efforts.

Carrying out thorough computational investigations is easier said than done. Calculating barrier heights requires substantial computational effort, and these efforts would all be for nothing if an unphysical model system were used.

First, simplistic models are never guaranteed to represent the actual atomistic environment, though understanding model systems can provide useful insight into which pathways are feasible and which are unlikely. Adding to this complexity, it is well known that commonly used DFT approaches have self-interaction errors that make them sometimes unphysically model charged intermediate states and/or highly correlated systems,[49–51] and so higher-level theories are required. Today, we see most development and applications in this area are using models that 1) enable enhanced sampling of reaction mechanisms to identify meaningful reaction pathways;[52–54] 2) enable physical modeling of electrochemical (i.e. potential dependent) reaction mechanisms;[55–62] and 3) improve the quality of continuum solvation energies of static systems.[63–66] There is a growing understanding that solvation is important not just in homogeneous catalysis but also heterogeneous catalysis.[67] Also, solvation modeling treatments are sometimes revealed to not be as reliable as generally believed.[68] While some computational studies are starting to explicitly account for potential-dependent reaction mechanisms in different forms, there has been little consensus of the best practices for doing so. All of these challenges are important, and the pathway to addressing them will likely be coupled. To better understand these challenges through the lens of solvation, we briefly summarize and provide our perspective on different solvation modeling techniques. Table 1 summarizes all the different solvation treatments that will be discussed in the next sections. It serves as a quick guide for the remainder of this minireview.

3 | IMPLICIT SOLVATION

Continuum solvation models have been used for many decades and there are many detailed reviews in the literature explaining the theory and the applications.[69–74] We only briefly overview how continuum solvation models work and how they are used to describe renewable energy catalysis. Figure 3 shows a cartoon model representation of implicit solvation of a methanol molecule with cluster and surface calculations.

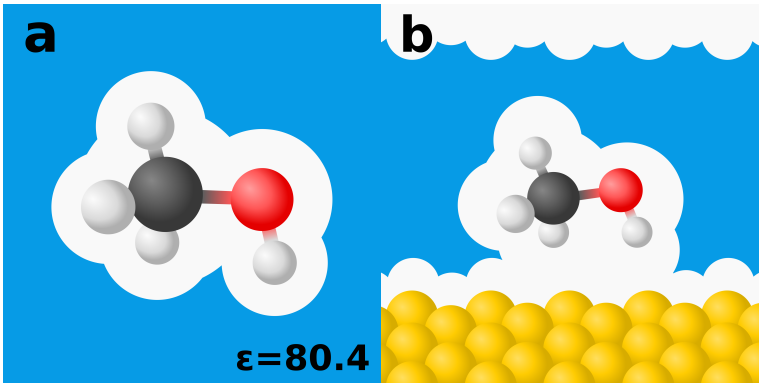

FIGURE 3 a) Illustration of a methanol molecule modeled within a cavity of a non-periodic continuum solvation model. b) Illustration of a methanol molecule modeled at a surface within a cavity of a periodic continuum solvation model.

Continuum solvation models were first developed for non-periodic systems of small and neutral molecules, and most treat the solvent as a structure-less, homogeneous medium using a polarizable dielectric described by a dielectric constant ε. In the most commonly used methods, a solute cavity is created around a solute to represent a boundary surface that allows a semiempirical calculation of a solvation energy based on the electronic structure of the system

TABLE 1 Overview of material reviewed of all solvation methods that will be discussed in the upcoming sections.

Models	Overview	Key findings
Implicit	• Are relatively computationally efficient • Are based on different mathematical formulations that may or may not yield similar results for the same modeled system • Can be used in either cluster or periodic systems • Omit explicit interactions with solvent molecules that may be important	• Calculations using periodic slabs or cluster models will result in very different solvated adsorbate binding energies, but relative energetics from the same model can be similar • Solvation energies are sensitive to cavity definitions • Implicit models can stabilize metastable zwitterion intermediates (e.g. M-$(CO_2)^-$ complexes) not observable in gas phase calculations • More developments are needed to model solvent mixtures
Mixed	• Explicit interactions are included by introducing solvent molecules into the system • There is no simple way of knowing precisely how many solvent molecules should be included and where they should go	• A complete first (or second) solvation shell should be treated whenever possible • Thermodynamic descriptors (e.g. pK_as and standard redox potentials) and reaction pathways can be calculated more accurately using mixed implicit/explicit models • Recent schemes have been found to yield similar results as fully explicit simulations
Explicit	• Computational cost is often substantially higher than for continuum solvation models • Classical molecular dynamics treatments require existing force field parameters • Born-Oppenheimer molecular dynamics (BOMD) simulations with quantum chemistry can be prohibitively expensive	• Solution phase nudged elastic band calculations can be useful as collective variables for umbrella sampling simulations • 0 K nudged elastic band and 298 K potentials of mean force calculations show interesting similarities and differences

of interest. The subtle differences in defining the cavity, the theoretical foundations, and the boundary conditions are what gives rise to the various implicit solvation models.[75–83] For instance, one of the first and most widely used continuum solvation models is the conductor-like screening model (COSMO),[84] which differs from other models by employing a scaled conductor instead of exact dielectric boundary condition, and this approximation considerably simplifies the mathematics. Also, COSMO uses a Green's function as the dielectric operator, and that enabled it to be the first continuum solvation model that was implemented with analytical gradients and used a real cavity shape.[85]

Expanding the applicability of implicit models to periodic systems requires treatment of the ionic response of charged species and interfaces.[86] Fattebert and Gygi were the first to make an isodensity continuum model adaptable to periodic systems that would be appropriate for modeling solvation on surfaces.[87] The simplest way to treat the ionic response is by using Poisson-Boltzmann (PB) theory which considers ions as point particles with mean-field interactions.[86] There are many other ways to treat a solvent implicitly on surfaces and still account for ionic responses.

For example, joint DFT was developed to combine typical electronic DFT with a classical DFT description of the liquid environment in order to reduce computational costs of large periodic systems.[88] This was first described by a modified polarizable continuum model (PCM) that has a linear dielectric response for the solvent (linearPCM).[89] The linear dielectric response approximation tends to fail with systems containing strong electric fields like ionic surfaces and electrochemical systems, so Gunceler et al. developed an improved model by using a nonlinear dielectric response (nonlinearPCM).[89] Alternatively, the self-consistent continuum solvation (SCCS) was developed to extend the utility of implicit solvation to plane–wave codes with improved robustness.[90–92] More recently, the CANDLE method was explicitly developed to handle charged species because it takes into account the charge asymmetry in the solvation structure. In this method the cavity is defined by a nonlocal functional of the solute electron density and potential that enables modeling the system's asymmetric solvent charge.[93] Additionally, separate field–aware approaches are being developed for cavity descriptions that can account for charged species without the need of continued modulation of cavity definitions to improve experimental fitting.[94]

There are several open challenges associated with applying implicit solvation models for periodic systems. In particular, it remains challenging to reliably determine electrochemical interfacial structures as well as reaction energetics. For example, some models cannot capture the local field variations from cations and in some cases default parametrization can place the ionic countercharge unphysically close to the surface.[95] Recently, there has been a number of exciting developments in implicit solvent modeling by improving numerical stability and reducing unphysical artifacts of cavities to better describe the electrochemical environments. For example, Fisicaro et al. used a continuous permittivity to model complex dielectric environments or electrolytes that should be accurate for neutral and charged systems.[96] Also, Andreussi et al. have developed an improved continuum solvation model that eliminated unphysical cavity "pockets" by smoothly varying solute cavities.[97]

Overall, one of the main purposes for an implicit solvation model is to avoid the complexity and computational cost of explicitly modeling solvent molecules. The computational expense for these systems is low and thus these methods are among the most used in applied studies of reaction mechanisms. Continuum solvation models such as COSMO, PCM, and the more recent solvation model based on density (SMD)[83] are highly cited because they are often used in diverse applications including reaction mechanism studies. We now will discuss a few applied studies in detail, but mention several others studies that have employed implicit solvation models to study aqueous CO_2 reduction.[98–107]

Note that modeling extended surfaces are more physically representative of an actual surface, but being able to model surfaces as clusters can sometimes make it easier to introduce high level theory. However, finite clusters can also have complicated spin states that need to be accounted for (e.g. Ref.[108]) while periodic analogs to these systems may not have significant spin polarization. To understand the extent that continuum solvation models can and should be used in applications of surface cluster models, Gray and co-workers computationally modeled adsorbate binding energies under the presence of continuum solvation on both periodic slab and large cluster models.[109] They modeled the Pt(111) surface with a variety of adsorbates: H*, O*, and OH* at different binding sites. It was found that sufficiently large model clusters captured similar gas phase binding energies as those obtained using periodic calculations and having relatively low surface coverages. It was found that the two fundamentally different models gave similar gas phase binding energies and thus showed promise for future work modeling heterogeneous catalyst sites using modern QM-in-QM embedding models.[110,111]

Once the gas phase energies were benchmarked for these systems, the energy contributions from continuum solvent methods could then be accounted for. Interestingly, using the COSMO model on the finite cluster resulted in a calculated solvation energies ranging from about −0.6 to −0.9 eV, and these were quite different in magnitude compared to the VASPsol energy contributions using the periodic systems that ranged from +0.1 to −0.35 eV. This should not be surprising since the surface cluster model had unphysical corners and edges that were being solvated

while the periodic slab model had no unphysical corners or edges. The net effect of this was significantly different solvated adsorbate binding energies even though the gas phase adsorbate binding energies between the two models had been found to be similar. However, we also found that the relative solvated adsorbate binding energies were similar across different sites for both the surface cluster and periodic slab models. Since the relative energetics were similar, we concluded that reaction mechanism studies using continuum solvated surface cluster models probably will give similar insights as studies using continuum solvated periodic slab models. The salient point is that if reaction mechanism studies necessitate the use of solvated surface cluster models, it will likely be the case that continuum solvation energies will be less physically relevant, but error cancellations can be leveraged to give useful insights. However, when an intermediate state is being modeled that is different from the rest, the results from a continuum solvation model should be considered with more suspicion and thus warrant additional care to ensure that the solvation model is appropriate for that case.

Another important aspect with continuum solvation models is their cavity definitions. Programs such as GAUSSIAN allow the user to select different cavities based on different empirical radii, and Yang compared some of these models on homogeneous metal complexes for CO_2 hydrogenation.[112] Yang modeled PNP-ligated metal pincer complexes for formation of formic acid from CO_2 and H_2. To model solvation effects the integral equation formalism polarizable continuum model (IEFPCM) was used with van der Waals (i.e. Bondi radii[113]) atomic radii–for geometric optimizations–and United Atom Topological Model applied on radii (UAKS)–for electronic energy corrections–to describe the cavity. UAKS is based on a model where hydrogen atoms are always enveloped within the molecular cavity while hydrogen atoms from Bondi radii cavities will appear in the cavity surface. Yang compared solvation energies of small ions and found that solvation energies using the UAKS radii were more accurate than energies using Bondi atomic radii. For the test case of $CO_2 + H_2 + OH^- \longrightarrow HCOO^- + H_2O$ it was found that UAKS cavity data were within 5 kcal/mol of experimental data while Bondi radii cavity data had an error of 16 kcal/mol. While UAKS radii have been shown to be useful in many applications, for instance when predicting pK_a values,[114] most benchmarking has been done for assessments of thermodynamic properties and reaction energies, but much less work has been done in understanding their applicability for determining kinetic barriers. In the cases of modeling (de)hydrogenation processes, it is not yet understood whether one should use a solvent model that explicitly accounts for hydrogen atoms or not. What is understood is that highly parameterized continuum solvation models are clearly very sensitive to cavity definitions, and tuning any specific radii for any specific application should be avoided.

Koper has also studied numerous mechanisms for CO_2 and N_2 reduction.[115–119] For example, his group has studied CO_2 reduction mechanisms involving cobalt porphyrins,[120] and they identified CO as being the main product from this reaction mechanism and CO_2^- as the key intermediate. Co(P) guided the formation of CO through decoupled proton and electron transfers; however, additional concerted proton–coupled electron transfers involving CO resulted in minor CH_4 formation. This work was made possible using the COSMO implicit solvation model to account for solvation effects. One complex modeled to form during the reaction, $[Co(P)—(CO_2)]^-$, was only stable when solvation treatments were included; however, another complex was still not stable when implicit solvation was included in the calculations ($[Co(P)—(CO_2)]^0$). An analogous observation was also seen in work by Carter,[33] who modeled an anionic complex, $[Re(bpy)(CO)_3\text{-}(CO_2)]^-$, and found it was only stable with an explicit counter ion or under the presence of a continuum solvent method. Thus, continuum solvation models have been and will likely continue to be used to assess metastable (and potentially zwitterionic) reaction intermediates in homogeneous reaction mechanisms.

With the success of implicit models in previous studies, many researchers are attempting to apply these techniques to reactions involving solvent mixtures. Garza et al. studied a tetraaz $[Co^{II}N_4H]^{2+}$ catalyst to understand the selective reduction of CO_2 to CO.[121] Those authors used PCM to include the solvent effects. They used pure acetonitrile in their calculations although the experimental contributions used a wet (10 M water) acetonitrile environment. Mixed solvents present a challenge for computational modeling since only a few models such as COSMO-RS can be used to model

mixed solvents, and this model has not yet been as extensively used for mechanistic investigations as the conventional COSMO approach. [122] Garza et al. modeled both pure H_2O and acetonitrile systems and noted that their calculated reaction energies do not differ significantly between these two solvents, and we have observed similar results as well. Those authors then inferred that mixed solvents would also not be significantly different even though experimental data has shown that mixed solvents can bring peculiar and non-intuitive solvation energies depending on the solute and the mixed solvent composition. [123,124] From our perspective, since continuum solvation models generally cannot be trusted to recognize the significance of an explicitly bonded solvent molecule, they should not be assumed to be a physical model for any mixed solvent in an arbitrary solvent composition. It is true, however that any errors arising from an insufficient solvation treatment of any one intermediate might cancel out with errors from a different intermediate, and thus the relative energy difference between the two would be reasonably accurate due to fortuitous error cancellation.

Another study by Cao et al. considered Ir(III) pincer dihydrides as electrocatalysts for CO_2 reduction to formate (or formic acid) in acetonitrile/H_2O mixtures. [125] They used IEFPCM with UAKS radii and cavity-dispersion-solvent-structure terms from the SMD solvation model to describe the solvation effects using the GAUSSIAN code. Experiments show that the reaction does not happen in anhydrous acetonitrile and that a water concentration of 5% or more is needed. As with the study by Garza et al, these authors used continuum solvation models to gain insights into chemical reactivity in pure H_2O and acetonitrile solvents. They mainly discuss reaction pathways under acetonitrile because the experimental conditions had a higher percentage of acetonitrile; however, almost all of the calculated barriers are very similar in magnitude compared to calculated barriers in pure H_2O. The barrier for formation of the formate anion appears to have lower energy when it is modeled in water, which indicates that water explicitly plays an important effect in this reaction mechanism by forming hydrogen bonds with the formate.

To summarize this section, we note that continuum solvation models are very useful, but they are sometimes unreliable and thus should be used cautiously when making predictions. Users should be aware that modeling and comparing different solvents, such as water and acetonitrile, generally only involve a slightly different cavity definition and dielectric constant that may result in a relatively small solvation energy difference. As a result, it should not be surprising when a continuum solvation model gives similar solvation energies for different solvent systems. However, mixed solvent systems are known to exhibit non-linear effects as a function of solvent composition, and standard continuum solvation models have not yet reproduced this behavior. [123,124]

4 | MIXED IMPLICIT/EXPLICIT SOLVATION

One technique to improve the performance of continuum solvation models is with so-called mixed implicit/explicit or cluster–continuum solvation modeling, which has been used in practice in an ad hoc manner for decades. [126] Instead of a lone solute being considered, some number of explicit solvent molecules are added to the system, and the resulting cluster of molecules is placed into the dielectric medium. In periodic systems of face-centered cubic metals, explicit solvent molecules are generally added as one or more layers of solvent molecules and then an implicit solvation model can be used on top of that. On other surfaces one or more solvent molecules need to be added to the system in an ad hoc manner to build up an interfacial solvation structure. Mixed implicit/explicit solvation approaches usually used calculations using an implicit solvation model is not sufficient to model a system of interest. For instance, mixed implicit/explicit solvation is used to predict energy calculations of ions and/or small molecules, [127,128] though it is also used for studying reaction mechanisms that involve the participation of the solvent molecule. A model cluster is shown in Figure 4 with three explicit solvent molecules and implicit solvent.

The main challenge of mixed implicit/explicit solvation modeling is to know how many solvent molecules are

required to capture the crucial solvation effects and where to place those solvent molecules in a meaningful way. The most commonly used way to overcome this challenge is to place solvent molecules according to chemical intuition and/or with trial and error attempts. This requires *a priori* knowledge of the reaction mechanism and the active sites that need to be stabilized. Even if one can place the solvent molecules with chemical intuition, there is still the open question of how many solvent molecules are needed. Furthermore, one should keep in mind that an entropic penalty would be expected to form solvent clusters, and that might play an important role in interpreting calculated energies.

Different research groups show different preferences about determining how many solvent molecules are needed for an accurate calculation. Some will only add a single solvent molecule at the site of interest while others may add more solvent molecules until a desired result is achieved. Ahlquist studied CO_2 hydrogenation with a homogeneous iridium catalyst using two explicit water molecules together with Poisson-Boltzmann self-consistent reaction field as defined in the Jaguar simulation package.[129] Ahlquist reported agreement with the experimental values only when both implicit solvation and two water molecules are present in the system. Groenenboom et al. modeled thermodynamic descriptors for a large set of aromatic N-heterocycle molecular catalysts for electrochemical CO_2 reduction.[38] Across 27 different molecular catalysts, using one explicit water molecule located at the relevant hydrogen bonding site for each molecule improved direct pK_a calculations to reasonably low errors of about 1 pK_a unit.

For reaction mechanisms, including explicit solvent molecules plays an important role as well. Lim et al. studied hydride transfer pathways from dihydropyridine to CO_2 by including one or two explicit water molecules together with CPCM model in their system.[130] Those authors found that this was an adequate treatment of the solvent because the resulting polar transition state structure was substantially stabilized by explicit solvent molecules that also facilitated a proton shuttle mechanism. Those authors also looked at a similar system where they used pyridine to catalyze CO_2 reduction by using different degrees of solvation. In this study they considered up to three solvent molecules as participating in their reaction mechanism as well as up to ten more solvent molecules to further solvate the reaction-relevant molecules, and then the entire cluster was then embedded in CPCM implicit solvation model. The authors reported good agreement with experimental values when they used three solvent molecules in the active reaction mechanism and ten solvent molecules to solvate the core structure (calculated: 13.6 kcal/mol; experimental: 16.5 kcal/mol), and thus it is not clear if the experimental barrier relates to what was modeled or to a different process such as hydrogen evolution.[42,43] While the computational results may or may not reflect the actual mechanism, they do highlight the important role of proton shuttling networks that standard continuum solvent models (as well as explicit solvent molecule using classical force fields) would not be able to physically model.[131]

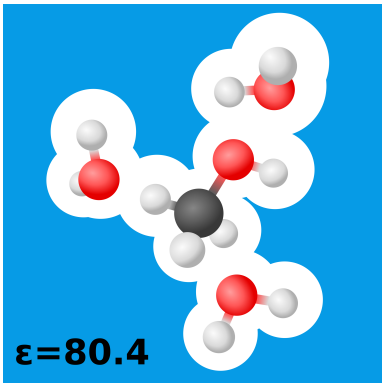

FIGURE 4 A model cluster with three explicit solvent molecules and implicit solvation.

Lim et al. also revisited the pteridine molecule [132] that had been proposed as a potential CO_2 reduction catalyst with some controversy. [42,133] The authors' model system included seven water molecules and the entire cluster embedded in the CPCM model. They then benchmarked results from this implicit/explicit solvation modeling treatment to QM/MM simulations (*vida infra*) where the seven water molecules were kept in a QM region and the rest of this cluster was explicitly solvated with 200 water molecules treated using a classical force field. The authors found that the two solvation treatments resulted in very similar energies, and they also found that the reaction barrier was consistently too high to be valid for a reaction that would be expected to occur at room temperature (QM/MM: 29.7 kcal/mol, QM: 30.9 kcal/mol). Savéant has commented that QM calculations were not necessary to rule out some pathways, [42] but Lim et al.'s work is is nevertheless useful because it demonstrates that simpler cluster continuum models can provide similar results as far more computationally intensive QM/MM simulations and thus suggesting other means forward for modeling these systems besides computationally costly QM/MM simulations. The important role of solvent molecules in reaction mechanisms is not only limited to just H_2O. Rohmann et al. studied CO_2 reduction to formate with a homogeneous ruthenium complex. They modeled their system in DMSO solvent using 10 explicit solvent molecules together with SMD solvation model. They show DMSO solvent molecules are vital for the mechanistic study because the hydrogen bonding between the formate (the end product) and the solvent results with a thermodynamic driving factor for desirable concentrations of the products. [134]

There are far fewer studies on mixed implicit/explicit solvation on periodic surfaces. Carter has studied CO_2 reduction on GaP (110) surface by modeling it as a cluster that can be straightforwardly solvated with a non-periodic solvation model, [135] similar to the work by Gray et al. mentioned previously. Their treatment used structures arising from a full monolayer of half-dissociated water molecules together with the SMD solvation model. They identified 2-pyridinide as an active intermediate in Py-cocatalyzed CO_2 reduction at p-GaP photoelectrodes.

As stated before, there is no easy way to determine how many solvent molecules are needed for an accurate and reliable treatment of mixed implicit/explicit solvation. As a test to deconvolute the relative energy contributions of electronic correlation, explicit solvation, as well as the presence of a counter ion in a reaction mechanism, Groenenboom and Keith followed work by Johnson [136] who studied borohydride hydrolysis using a procedure involving high temperature Born–Oppenheimer molecular dynamics (BOMD) simulations to observe an elementary hydrogenation process and then characterized that pathway using nudged elastic band methods. [137] Groenenboom and Keith used a similar procedure to model CO_2 reduction by $NaBH_4$ and $NaBH_3OH$. Molecular clusters from the NEB calculations were then used with different analyses using high-level single point energy calculations and implicit solvation. In general, it was found that the full first solvation shell along with COSMO solvation resulted in an energy profile almost identical to the fully explicit solvated case. Somewhat surprisingly, a range of different levels of theories found calculated barriers differing by only 0.1 eV while using a continuum solvation model without the first solvation shell resulted in differences as large as 1 eV. This study points out the importance of the solvation treatment however using BOMD simulations together with NEB calculations can become very computationally expensive. It would be especially interesting if there were a means to sufficiently solvate reaction intermediates without the need for dynamics or even fully explicit solvation models. Recently Basdogan and Keith have demonstrated a generalizable modeling scheme that facilitates mixed implicit/explicit solvation treatments for reaction mechanisms, i.e. systems where where implicit models are known to sometimes fail. The calculation scheme involves generating microsolvated clusters using a global optimization code called ABCluster, [138] and after identifying globally optimized clusters they used single-ended GSM calculations [139–141] to explore reaction pathways systematically.

5 | EXPLICIT SOLVATION

Many research groups explicitly solvate their systems to gain detailed information not available from implicit methods. Studies typically use Monte Carlo (MC) or molecular dynamics (MD) to treat the entire solvent box as shown in Figure 5. Still, complications could arise when studying polarizing systems or significant electron density changes. Born-Oppenheimer molecular dynamics (BOMD) and its variant Car-Parrinello Molecular Dynamics (CPMD) [142] have been critical in broadening the scope of systems we could study explicitly. Both use real-time electronic structure calculations to describe the system's behavior instead of parameterized force fields or potentials; however, they are only meaningful if the run time is long enough for the system to visit all energetically relevant configurations. For complicated systems, large energy barriers could separate chemically relevant configurations and severely limit sampling.

Currently there are a couple of ways to avoid the high computational costs of BOMD. First, is to use simulation schemes that are computationally faster. These methods often depend on reducing the frequency of full electronic structure calculations or simply reducing the region being treated quantum mechanically and employing a classical treatment for the remaining system. The latter solution is referred to as quantum mechanics/molecular mechanics (QM/MM) which is a hybrid method that combines QM and MM frameworks to make simulations faster than BOMD and more accurate than MM. In QM/MM simulations, the system is divided into primary and secondary subsystems. [143] The primary system is the QM region which contains the reaction-relevant molecules under investigation. The secondary subsystem is the environmental zone where the other solvent molecules are modeled with forcefields to capture the bulk solvation effects.

It is common practice to include solvent molecules from the first solvation shell in the QM region to capture the crucial solvation effects using a higher level of theory. Although difficulties can arise when trying to keep the simulation as physically realistic as possible. Solvent molecules, in real solutions, will migrate towards and away from solute regions. This poses a problem in garnering expensive and highly accurate data on short-ranged solvation effects when a solvent molecule drifts away. Researchers sometimes employ constrained QM/MM; in which a bias is applied to keep solvent molecules from leaving the predefined QM region. [144–146] While this provides reasonable accuracy, the fundamental issue with this type of modeling is its unphysical treatment of an essentially frozen solvent shell. Alternatively, a method of switching the subsystem designation (QM or MM) of solvent molecules based on the proximity to the solute in real time can be used and is common practice today. [143,147,148] This adaptive QM/MM scheme is very useful, but it could still benefit from a reduction of spatial artifacts that affect multiscale modeling. [149] We expect to see substantially more

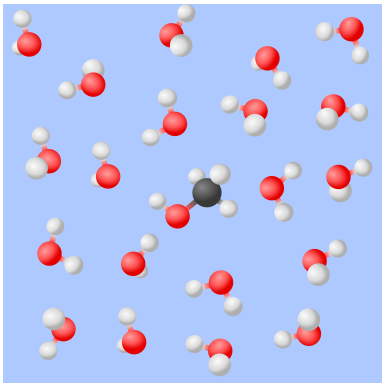

FIGURE 5 A methanol molecule being explicitly solvated by water.

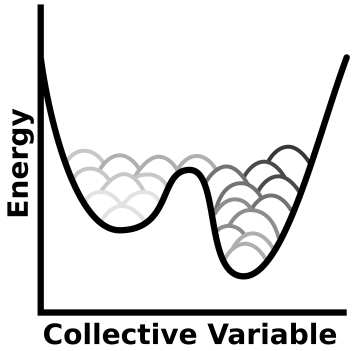

FIGURE 6 A model metadynamics simulation profile. Gaussian functions are placed on the free energy surface to flatten the energy wells over time during the simulation (lighter to darker curves). This is used to reduce oversampling of the local minima and pushes the system away from it.

applications of these methods in the coming years as they can allow higher levels of QM theory for improved insights into catalytic reactions. [150,151]

5.1 | Sampling Techniques

QM/MM free energy simulations are commonly used to sample free energy surfaces. In renewable energy catalysis a reaction often needs to be modeled by bond breaking or forming. In order to model such catalysis one needs to treat the system with quantum chemistry. However, the calculations will become very expensive if the entire system is treated with quantum chemistry, i.e. using some variant of BOMD. To overcome this challenge, algorithms are applied to enhance the sampling of reaction-relevant areas of free energy surfaces. These algorithms can vaguely be distinguished into two categories as methods that either introduce additional degrees of freedom along which the free energy is calculated (metadynamics) or methods that sample the system in equilibrium (umbrella sampling). In the following sections we will broadly introduce one technique from each category.

5.1.1 | Metadynamics

Metadynamics is a sampling technique that is based on adding an additional bias potential that acts on a selected number of collective variables (CV). For reactive systems, bond breaking or bond forming are two examples of widely used collective variables. [152–156] To accomplish this, Gaussian potentials are placed on the free energy surface in order to flatten the energy wells and reduce oversampling of local minima. A very simplified representation is shown in Figure 6. It is an accelerated sampling technique of rare events that is based on pushing the system away from the local minima. Metadynamics is generally used to explore new reaction pathways without *a priori* knowledge of the free energy surface. However, one must be careful to identify a set of CVs appropriate for describing complex processes. [157] CVs should be a function of the microscopic coordinates of the system and should distinguish between the initial and final states while also describing relevant intermediates. If one can come up with CVs that meet all the requirements then metadynamics should work effectively to model free energy surfaces. [153]

There are handful of examples where *ab initio* metadynamics is used to study CO_2 reduction or any reaction

mechanism. Urakawa et al. was exploring a ruthenium dihydride catalyst and its ability to hydrogenate CO_2.[158] Their work demonstrated that a *trans* isomer route was more energetically favorable (higher stability intermediates) while the rate-limiting step was the insertion of H_2 into formate, but there were no explicit solvent molecules included in this study that would account for their role in the reaction mechanism. Ghoussoub et al. studied the effect of temperature on frustrated Lewis pairs on nanoparticles for heterogeneous catalytic reduction of CO_2.[159] They concluded that at higher temperatures, CO_2 adsorbed more easily on the surface which suggests an adsorptive reaction mechanism may be relevant. This study also did not consider how solvation can affect the reaction mechanism, but they investigated H_2O adsorption on the surface at different temperatures. Gallet et al. used metadynamics to simulate the reaction of CO_2 with one, two, or three explicit solvent molecules in the gas phase.[160] This work provides a useful and thorough protocol to study relatively small systems. Future advances of computation resources will continue to allow more extensive studies to be carried out.

There are few studies on CO_2 chemistry that used metadynamics with fully explicit solvation models. Stirling studied the free energy barriers of reversible bicarbonate formation in water at high pH.[161] It was determined that the free energy barrier of $CO_2 + OH^- \longrightarrow HCO_3^-$ was 13.8 kcal/mol, which coincides with the 11.5 kcal/mol experimental value. Interestingly, the forward reaction free energy barrier was mostly entropic while the reverse barrier was mostly enthalpic. This conclusion was only possible because extensive metadynamics simulations had been performed with explicit solvent. This study outlines an accurate way to calculate free energy barriers of other processes in solvated systems as well; however, the number of reacting atoms that need to be considered will be a limiting factor. Galib et al. also examined the mechanistic and energetic effects of solvent cluster size on the decomposition of H_2CO_3.[162] They selected atoms to form two small (6 and 9) and large (20 and 45) water clusters around a H_2CO_3 molecule in a Car–Parrinello molecular dynamics simulation. Metadynamics then allowed sufficient sampling to demonstrate that the small and large clusters led to a concerted and stepwise mechanism, respectively. Thus, H_2CO_3 decomposition likely follows a stepwise mechanism in bulk-like water, but it might be different in other environments like an air/water interface. Goddard and co-workers have investigated multiple aspects of CO reduction on copper surfaces and copper nanoparticles with explicit water layers at different pH levels.[57,163–166] Their studies of solvated systems were carried out using reactive force fields which significantly decrease the computational time required. However, even well-parameterized reactive potentials should be assumed to be less accurate than the QM calculation, and thus interpretations based on predictions from these model warrant more caution than all-QM methodologies.

5.1.2 | Umbrella Sampling

Umbrella sampling is another technique to calculate the free energy profile of reaction mechanisms.[167] The main idea behind umbrella sampling relies heavily on splitting the reaction pathway into windows and sampling each window individually. However sampling a full momentum space is difficult, and that is why a bias potential is introduced as an additional term to the energy expression as shown in Equation 5.

$$E^b(r) = E^u(r) + \omega_i(\xi) \tag{5}$$

This additional term ensures efficient sampling along the reaction pathway by allowing the reaction variable to vary along a biased potential (restrain) and not limiting the variable to a constant value (constrain). The most commonly used biased potential is the harmonic potential as shown in Equation 6.

$$\omega_i(\xi) = K/2 * (\xi - \xi_i^{ref})^2 \tag{6}$$

Harmonic potentials are appealing because they contain only few parameters: K (spring constant), the number of images (i), and a reference point of the respective window i (ξ_i^{ref}). One needs to decide on the K value before starting the simulations, and make sure it is large enough to drive the system over the energy barrier.[168,169] This is important because if K is too large there will be too narrow sampling and thus sufficient overlap between the windows will not be achieved. A good example of overlapping windows is shown in Figure 7. Having adequate overlap is required to analyze umbrella sampling with weighted histogram analysis (WHAM) or umbrella integration which depends less on overlap but is still advantageous.[170–172]

Umbrella sampling is widely used for physical transformations from ion solvation to protein folding with force fields;[173] however, modeling chemical reactions is more computationally extensive since it generally requires BOMD simulations. Leung et al. computationally examined a cobalt porphyrin catalyst for CO_2 reduction to CO in water.[174] First they used DFT calculations with implicit solvation and then validated their results with BOMD simulations with an explicit aqueous environment. These simulations demonstrated that the water molecules stabilized the reaction intermediates from the CO_2–cobalt complex. With the use of potential of mean force (PMF) calculations they were able to identify the rate limiting step as the transfer of electrons between the polymerized catalyst and gas diffusion electrode. This study is a good example of how to use umbrella sampling to calculate free energy barriers and identify transition state structures, however one must keep in mind that it is very computationally expensive and limits the number of reactions that can be studied.

Several studies have been dedicated to understanding the hydrophobicity of aqueous CO_2; however, many employ classical force field methods which demonstrate sensitivity to Lennard-Jones parameters.[175] To reduce parameter dependence, Leung et al. performed BOMD simulations to investigate the solvation shell of CO_2 and other dissolution species in water.[176] Ultimately their computations supported the previously observed hydrophobic nature of CO_2 in water. Furthermore, they calculated the free energy change of bicarbonate formation from CO_2 and H_2O to be -9.8 kcal/mol which agrees with the -9.4 kcal/mol experimental value.

In work related to the previously mentioned CO_2 reduction with sodium borohydride, Groenenboom and Keith used calculated reaction energy barriers from NEB calculations at 0 K and compared them to free energy barriers obtained at 300 K using PMF calculations from umbrella sampling. They show two different free energy barriers with NEB and PMF calculations which suggests both temperature effects and solvent molecules would play an important role in this reaction mechanism. The NEB pathway obtained at 0 K only slightly differed from the pathway used for the PMF calculation, but energies along the two pathways were found to vary by as much as 0.25 eV. The overall barrier

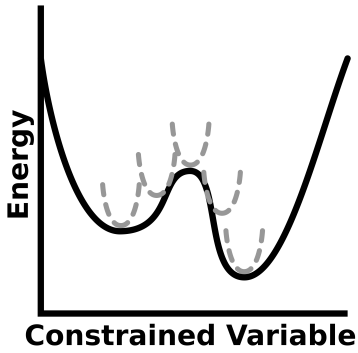

FIGURE 7 Simplistic view of umbrella sampling along a hypothetical constrained variable.

heights from the 0 K NEB calculations and the 298 K PMF calculations for three different elementary steps were quite similar as well. However, the overall reaction energies from the NEB and PMF calculations differed by as much as 0.6 eV when the NEB pathway was based on local minima and the PMF calculations sampled lower energy states. [177] Thus, PMF calculations based on umbrella sampling appear to be more reliable for insights than NEB calculations alone, but PMF calculations are also far more costly.

6 | CONCLUSION

We have given a review of recent and legacy approaches that are used to model reaction mechanisms under solvating environments. We introduced our perspective of where computational catalysis is heading. It will be critical to integrate solvation energy contributions and other environmental parameters into future high-throughput screening approaches, and so we give an overview of implicit, mixed implicit/explicit, and explicit solvation modeling that would be needed to do so. Though already widely used, continuum solvation models still have room for improvement. Notably, few if any can reliably treat explicit solute-solvent bonding or solvation effects that can arise, and they should not be used to glean insights into systems involving solvent mixtures. There is are still paths forward for computational modeling using more robust (though computationally cumbersome) techniques that incorporate explicit solvation at least in part. In the absence of accurate forcefield parameters and/or computational resources to run lengthy BOMD simulations, mixed implicit/explicit procedures are a promising route for studying reaction mechanisms in complex environments. Future directions continue to point toward more mixed implicit/explicit modeling as well as the development more accurate and physical continuum solvation models and explicit solvation models. These advances will help improve the quality of computational predictions that would guide the development of technologies for renewable fuels and chemicals.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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GRAPHICAL ABSTRACT