Computer Simulation of Proton Solvation and Transport in Aqueous and Biomolecular Systems

GREGORY A. VOTH*

Center for Biophysical Modeling and Simulation and Department of Chemistry, University of Utah, Room 2020, 315 South 1400 East, Salt Lake City, Utah 84112-0850

Received September 30, 2005

ABSTRACT

The excess proton in aqueous media is critical to many aspects of chemistry, biology, and materials science. This species is at the heart of the most elementary of chemical (e.g., acid−base) and biological (e.g., bioenergetics) concepts, yet to this day, it remains mysterious, surprising, and often misunderstood. In this Account, our efforts to describe excess proton solvation and transport through computer modeling and simulation will be described. Results will be summarized for several important systems, as obtained from the multistate empirical valence bond (MS-EVB) approach, which allows for the explicit treatment of (Grotthuss) proton shuttling and charge delocalization.

1. Introduction

Few problems in recent years have attracted as much interest as the problem of proton solvation and transport (PS&T) in aqueous media, biomolecular systems, and materials science. It is a topic at the core of our basic scientific knowledge as chemists, one that is introduced to most high school students in their first exposure to (acid−base) chemistry. In biology, the transport and storage of protons forms the basis for much of bioenergetics, enzyme function, and processes as complex as viral replication. In materials science, the electrical current generated from the motion of protons, for example, through polymer electrolyte membranes, provides a critical component of the hydrogen fuel cell—a key target for reducing society's future dependence on fossil fuels. Acidified aerosols in the atmosphere are a key aspect of the air pollution that threatens the health and environmental welfare of millions of people. Yet, despite its importance, to this day a completely conclusive and comprehensive picture of the mechanism by which excess protons are solvated and transported in aqueous, biological, and materials systems does not exist.

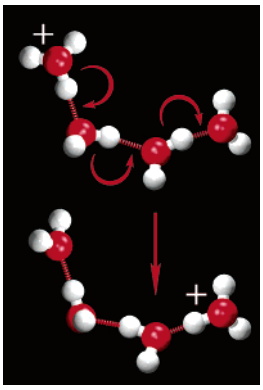

FIGURE 1. The Grotthuss shuttling process for the excess proton in a small chain of water molecules. Note that the chemical bonds and hydrogen bonds are rearranged, thereby moving the excess charge without any (or little) molecular diffusion.

The reason that PS&T is such a challenging problem rests with the fact that both processes are believed to be strongly influenced by the proton shuttle mechanism (see Figure 1). In this mechanism, elements of which date back to an 1806 paper by Grotthuss,[1] the excess protonic charge is shuttled through chains of water molecules. There is no "single" proton. It is like a proton "shell game" in which only the excess protonic charge moves, but numerous protons are involved in the shuttling process. To study this phenomenon either experimentally or through computer simulation, one is confronted with the challenge of dynamically rearranging a chemical bonding topology, that is, chemical bonds are constantly being made and broken. In fact, there is no "hydronium cation" (H_3O^+), as is routinely and incorrectly taught to high school and undergraduate university students, but instead some sort of constantly interchanging "entity" between the limiting cases of the Eigen cation ($H_9O_4^+$) and the Zundel cation ($H_5O_2^+$), both having numerous water molecules dynamically hydrogen-bonded to them in the condensed aqueous phase.

In this Account, our group's long-standing efforts[2−29] to develop and apply a computational methodology to study PS&T will be reviewed. This line of research has born fruit in recent years in the form of a number of published papers on excess PS&T in bulk water,[2−16] at the water liquid−vapor interface,[17] in protonated water clusters,[18,19] in water-filled hydrophobic channels,[19] at the water/lipid bilayer interface,[20] through lipid bilayers,[21] in large transmembrane biomolecular proton channels,[22−28] such as the M2 channel in influenza A,[22−24] the biomimetic LS2 proton channel,[25] the aquaporin channels,[26] and the proton pump cytochrome *c* oxidase,[27] and in hydrogen fuel cell polymer electrolyte membranes.[29] Due to space limitations, the reader is referred to the original articles for more details, while only certain key and interesting results will be described herein. Space also does not allow for an extensive discussion of the relvant experimental results

Gregory Voth is Distinguished Professor of Chemistry and Director of the Center for Biophysical Modeling and Simulation at the University of Utah. He received a B.S. in Chemistry from the University of Kansas (1981) and a Ph.D. in Theoretical Chemistry from the California Institute of Technology (1987). His postdoctoral work was carried out as an IBM Postdoctoral Fellow at the University of California, Berkeley (1987−1989). His group research interests include the theory and simulation of condensed phase dynamical processes, proton and electron transport in biological, solution phase, and materials systems, and the multiscale simulation of biomolecular systems. He has published approximately 250 peer-reviewed scientific publications on these areas of research.

* Fax: (801) 581-4353. Phone: (801) 581-7272. E-mail: voth@chem.utah.edu.

10.1021/ar0402098 CCC: $33.50
Published on Web 02/01/2006

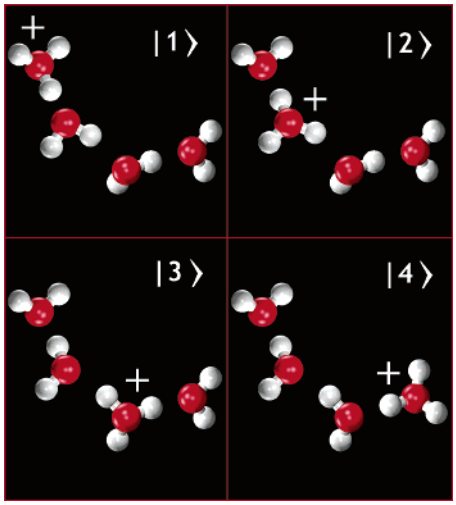

FIGURE 2. The MS-EVB basis states used to describe the Grotthuss shuttling process for the excess proton in the small chain of water molecules depicted in Figure 1. Transitions between these states via the MS-EVB algorithm allow for a continuous and deterministic trajectory describing the Grotthuss shuttling and delocalization process.

and related theoretical/simulation efforts, so here again the reader is referred to our original articles for such information.

2. Computational Methodology

The Multistate Empirical Valence Bond (MS-EVB) Method. The MS-EVB approach explicitly simulates PS&T in molecular dynamics (MD) simulations using all-atom deterministic trajectories as derived from the MS-EVB potential function.[2−11] It can describe excess protons, including the Grotthuss mechanism, in various environments. Standard MD approaches based on empirical (classical) force fields do not have the capability of describing Grotthuss proton shuttling because they generally do not incorporate bond-breaking phenomena. To simulate the Grotthuss process computationally, one must therefore be able to treat a chemical bonding topology that is dynamically changing.

In the MS-EVB approach,[3−5,11] the various possible protonation configurations of the water molecule are modeled by limiting "states" (see Figure 2), which in turn compose the basis states in an overall "Hamiltonian" matrix. These diagonal states are generally empirical potentials that describe all of the relevant bonded and nonbonded interactions for that bonding topology. There are also off-diagonal elements in this matrix that allow for *transitions* to occur between the various states as a function of the instantaneous nuclear configurations, and hence, the chemical and hydrogen-bonding topology varies along with it as a function of time. To help illustrate the MS-EVB concept, shown in Figure 2 are the four MS-EVB states necessary to model the proton shuttle through the small water wire depicted in Figure 1. In the bulk liquid phase, however, many more states are necessary (as many as 20−40 to describe the first three solvation shells of a hydronium ion), and the identity of those states must be allowed to dynamically change in time. Each state contains *all* of the molecules of the condensed phase system but with the excess proton bonded to a different water molecule in each state. Then, for any given nuclear configuration and time step in the MD simulation, the MS-EVB Hamiltonian matrix is diagonalized and the lowest eigenfunction determined. The forces on the nuclei are next calculated using the Hellmann−Feynman theorem for this lowest state and fed into a MD integrator such as Velocity Verlet. The procedure is iterated and a MD trajectory is generated that *includes explicit excess proton delocalization shuttling through the water molecules*.

The MS-EVB method was developed to be compatible with, and transferable to, molecular mechanics (MM) force fields such as AMBER and CHARMM. Furthermore, a (reasonably) systematic approach has been developed to define the parameters of both the diagonal and off-diagonal MS-EVB matrix elements to accurately reproduce various high-level ab initio results for binding energies and proton-transfer barriers,[3,5,11] as well as the bulk phase proton structural, transport, and spectroscopic properties,[3,5,10−12] including nuclear quantum effects.[5,7]

The ground-state MS-EVB vector of state coefficients, $\vec{c} = (c_1, c_2, ..., c_N)$, reflects the delocalization of the excess proton charge over the hydrogen-bond network, with weights of the different EVB states given by the amplitudes c_i^2. The process of PS&T proceeds through the redistribution of these amplitudes at each time step, as well as through the propagation of the nuclear coordinates. The distribution of the first (largest) MS-EVB amplitude, c_1^2, in bulk water is bimodal, with a maximum at $c_1^2 \approx 0.65$, corresponding to an Eigen cation, $H_9O_4^+$. The Zundel cation, with $c_2^2 \approx 0.5$, is somewhat less thermodynamically stable than the Eigen cation in bulk water. The spatial position of the excess proton is defined to be the center of excess of charge (CEC) of the MS-EVB complex:[11]

$$\mathbf{r}_{\mathrm{cec}}(t) = \sum_{i=1}^{N} c_i^2 \mathbf{r}_i(t) \qquad (1)$$

where $\mathbf{r}_i(t)$ are center of charge vectors of the hydronium in the ith MS-EVB state at time t. The (classical) hydronium ion is represented as a simple limit of the MS-EVB model corresponding to a single (1×1) diagonal element of the MS-EVB Hamiltonian. Throughout this Account, the terms "proton" and "hydronium" stand for the CEC of the full MS-EVB model and the single-state MS-EVB model (the "classical" hydronium cation), respectively.

Within any MD simulation methodology, it is important to consider exactly what one should seek to calculate. Proton transport over long length and time scales is rather different from simpler kinetic processes in that it can involve numerous free energy barriers and subtle dynamical effects, for example, long time scale protein conformational changes. In some cases, such as biomolecular proton channels, the first (and perhaps most important) question is an even simpler one, that is, is the channel open or is it closed? Going beyond that question, one should then seek a deeper analysis, which might involve calculating the potential of mean force (PMF) for the

excess protonic charge (which is, as described earlier, characterized as a function of the CEC coordinate). The PMF, in essence, provides a picture of the free energy landscape sampled by an ensemble of excess protons as they diffuse through a confined space such as a proton channel. Ideally, for any biomolecular (and certainly simpler aqueous) system, one should also calculate the actual (dynamical) diffusive behavior of the excess proton, because it is not clear how well more phenomenological approaches based on free energy barriers (PMFs) fit reality.

A few comments are also in order on how our MS-EVB MD simulation methodology relates to the work of other researchers. The original empirical valence bond (EVB) method was developed by Warshel and co-workers[30] to study proton and hydride transfer in enzymes, as well as electron transfer reactions. Generally these applications required a two- or three-state EVB parametrization. The MS-EVB approach represents a nontrivial generalization of these ideas to describe PS&T over much longer distances, involving shuttling through many diffusing water molecules and possibly through ionizable molecular groups such as amino acids. A critical element of the MS-EVB approach is that the identity of the states included in the MS-EVB complex constantly changes in the simulation. These states are selected by virtue of a complex state-searching algorithm to ensure as much continuity in the molecular forces as possible, which in turn to ensures good energy conservation in the MD simulation. Without good energy conservation in a MD simulation, one cannot claim that the trajectory is generating a reasonable ensemble average nor a valid dynamical observable. Furthermore, if good energy conservation does not exist, then it is also not likely to be valid to attach a thermostat to the system in an attempt to generate a canonical (constant temperature) distribution. The key difference, therefore, between the MS-EVB approach and Warshel's original and pioneering EVB method is the feature of the former that the identity of the important EVB states is constantly changing during the dynamics. This is not merely an algorithmic difference, but a key physical one, as the role of molecular diffusion (something common in condensed phase aqueous systems) can also be included in the MS-EVB method. The interplay between molecular diffusion and Grotthuss proton shuttling is critical for understanding the process of PS&T in aqueous, biomolecular, and materials systems.

It should further be noted that Vuilleumier and Borgis[31−35] independently developed their own multistate model for the excess proton in bulk water. Both this and our MS-EVB model are derived from our original two-state EVB model for the excess proton in water.[2] However, there are important differences between their approach and MS-EVB, particularly in the treatment of the off-diagonal matrix elements, the state selection algorithms, and the energy conservation properties. It should also be noted that the second generation MS-EVB model[11] (MS-EVB2) and its underlying algorithm has significantly improved upon some of the initial concepts.

Generalizations of the MS-EVB Method. One relatively straightforward generalization of the MS-EVB approach has been to describe acid dissociation on the same dynamical footing as the PS&T of the excess (dissociated) proton.[6,9,15] The latter extension of the MS-EVB method is quite important, because it allows for the explicit dynamical protonation and deprotonation of acidic groups such as amino acids in proteins. In essence, the fundamental deprotonation step is simply embedded within the water MS-EVB state structure as another EVB state, the latter having the proton bound to the conjugate base.

Although the MS-EVB method has proven to be very successful at describing single excess proton solvation and transport in a variety of systems (i.e., neutral or near-neutral pH conditions), a considerable challenge was faced in expanding the overall methodology to treat systems containing more than one excess proton in the same simulation cell (i.e., low pH conditions) because the number of EVB states would seemingly need to grow exponentially in the power of the number of excess protons, therefore requiring an extremely expensive solution of a large matrix eigenvalue problem at each MD time step. A significantly different approach for multiproton systems was therefore required called the self-consistent iterative MS-EVB (SCI-MS-EVB) method.[13] In this approach, the system is divided into EVB complexes, each consisting of a single excess proton. An MS-EVB problem is solved for each EVB complex within an effective field of the other EVB complexes. The computational cost for an N proton system using the SCI-MS-EVB method scales linearly with respect to the number of excess protons, and the parallelization of the SCI-MS-EVB method over multiple CPUs can also be implemented efficiently.

Ongoing Improvements of the MS-EVB Model. There is also an ongoing effort to increase the accuracy and generality of the MS-EVB methodology. It should be appreciated that the central goal of the original model development was to utilize the approach to study proton translocation phenomena in biomolecular systems. The choice of the underlying water potential energy function for the original MS-EVB and second generation MS-EVB2 models was largely dictated by this goal, that is, a water model that was simple enough for large scale MD simulations and also compatible with existing biomolecular force fields. However, two possibly important physical effects, nuclear quantum effects and electronic polarization, are generally not included in such force fields. One of our original papers[5] showed that quantization of the MS-EVB potential enhances the proton hopping rate to bring it into closer agreement with experiment. However, these small differences (about a factor of 2) are less important relative to the other errors one can make in the force fields for large systems, and the additional cost of incoporating quantum effects, for example, using Feynman path integral techniques, is not presently warranted, especially given the likelihood that much, if not all, of the overall force field would require reparametrization if it were quantized globally. A priority for the immediate future is to incorporate a better empirical potential for the under-

lying water solvent molecules along with a revised MS-EVB parameter set and state-selection algorithm.

The inclusion of electronic polarizibility in the MS-EVB model is certainly another important goal but also a somewhat subtle issue. There is growing evidence that the electronic polarizability of water is necessary for MD simulations that involve interfaces[36] (with and without charged ions) and possibly in the bulk aqueous solvation of ions and charged amino acid groups in proteins.[37] At least some version of the MS-EVB model should eventually incorporate a polarizable water potential as one of its components and, in fact, such an MS-EVB model has recently been published.[38] However, it should be noted that the original MS-EVB potential is already locally polarizable (i.e., within the EVB complex of states), because the charges are dynamically adjusting in the MS-EVB algorithm and, as such, they will respond to external fields or nearby charged ions or molecular groups. There are also already a significant number of parameters to be defined in the model, so the additional parametrization of the polarizability in the EVB complex becomes less "pure" than for bulk water polarizability parametrizations alone. It is also not yet clear to what degree the enhancement in the diffusion comes from the electronic polarization or from the nuclear quantization (or both).

Comparison to Other Simulation Approaches for Proton Solvation and Transport. Perhaps the most notable of the early efforts to study the excess proton in water are those of Parrinello and co-workers[39−41] using the Car−Parrinello MD (CPMD) method. In this approach, the electronic structure at the level of gradient-corrected density functional theory is solved simultaneously with the nuclear dynamics. Innovative ab initio MD approaches such as Car−Parrinello MD (CPMD), in principle, do describe chemical rearrangements that occur in the Grotthuss mechanism, but they are limited to small system sizes (on the order of 100 water molecules or less) and short simulation times (tens of picoseconds). Of more concern is recent work[14,42−44] suggesting that the simple generalized gradient approximation (GGA) density functionals required by the CPMD method may give poor structural and dynamical results for the underlying liquid water, contrary to the reports of earlier simulations in the literature. On a more optimistic note, these issues and the importance water (with and without excess protons) point to an exciting future challenge for both electronic structure theory and ab initio MD methods.

Another approach to simulating PS&T is the Q-HOP model,[45] which utilizes a stochastic hopping algorithm to describe the proton shuttling process. While such algorithms are often useful, they are not deterministic, so the dynamics are not directly derived from an underlying potential energy function, and therefore it is difficult to associate actual physical interactions with the underlying dynamics. Several other ad hoc assumptions must be made to define the stochastic proton hopping probability, so additional errors may be introduced into the simulation results. In other PS&T simulation studies (e.g., ref 46), the PM6 model has been employed. This empirical potential energy function can describe proton shuttling and charge delocalization using deterministic Newtonian dynamics, but it is inaccurate for proton solvation and transport both in bulk water and in protonated water chains. Two other approaches[47,48] to simulate PS&T have involved approximations to the full MS-EVB methodology in which two states are used to transfer an excess proton between water molecules and these two states are then dynamically moved along to the next step. Because they do not contain the full symmetry of problem, these approaches tend to overestimate the population of the Zundel cation[49] and thereby may lead to erroneous conclusions.

3. Highlights from Applications of the Methodology

In this section, key results are summarized from the application of the MS-EVB simulation approach to study PS&T in a variety of systems.[2−29] In general, the guiding philosophy of our work from the beginning has been to study very realistic systems (having as many as tens of thousands of atoms) for long MD times (tens to even hundreds of nanoseconds in total), so as to obtained statistically converged structural and dynamical effects. Generally, this effort has been quite successful and, in many cases, yielded quite interesting and even unexpected results. However, the reader should bear in mind, as with all molecular simulation, that our approach is not perfect and in the future some results may require updating and even revision as increasingly more accurate versions of the methodology (e.g., the underlying MS-EVB method and potential, protein force fields, etc.) are developed.

Proton Solvation and Transport in Bulk Water. As an intrinsically interesting and ongoing application of the MS-EVB methodology, as well as an important step for its validation in conjunction with the simulation of more complex systems, PS&T in bulk water has been studied a great deal in our group. In general, the model reproduces the self-diffusion properties for the hydrated proton, as well as its likely solvation structure (an approximate 65:35 mixture of the Eigen and Zundel cations), infrared spectroscopy, and observed deuterium isotope effects. The second-generation (MS-EVB2) model also incorporates simpler electrostatics and improved energy conservation characteristics via a more advanced EVB state-selection algorithm. The numerical value of the self-diffusion constant from the MS-EVB2 MD simulation with classical (Newtonian) nuclear motion is below the experimental result by a little more than a factor of 2. However, as stated earlier, quantum path integral simulations for the MS-EVB model showed that the quantum effects on the proton transport (PT) rate increase the rate by the factor of 2, consistent with an observed deuterium isotope effect of around 1.4−1.6. Thus, upon quantization, the MS-EVB model gives a result for the excess proton diffusion in good agreement with experiment. Furthermore, the model also predicts a value for the activation energy of 2.7 kcal/mol, in good agreement with the experimental value of 2.5 kcal/mol. (Again, this latter value is slightly lower than the

experimental result because of the small lowering of the activation barrier by quantum effects.)

The calculation of the excess proton diffusion rate raises the interesting and important question of the *mechanism* for Grotthuss-assisted diffusion in bulk water. Agmon[50] first proposed a mechanism in which a hydrogen bond being donated from a second solvation shell water molecule to a water molecule in the first solvation shell of the hydronium cation needs to first break for the excess proton to hop to the latter water molecule. Otherwise, too much electrostatic repulsion from the offending donated hydrogen bond would drive the excess proton back to the originating hydronium species. In turn, a hydrogen bond needs to form to fully solvate the water molecule left behind by the departing excess proton, as its coordination number is approximately four while that of the hydronium cation is around three. This mechanism has analogy to Moses parting the Red Sea and hence Agmon called it the "Moses Mechanism." Ten or so years ago, it was believed this basic mechanism had been confirmed from ab initio molecular dynamics (CPMD) studies,[39−41] but as mentioned earlier, recent work has shown that for the electronic density functional used (the BLYP functional), the excess proton may exhibit substantially reduced diffusion due to an underlying glassy water network.[14] More recent MS-EVB simulations,[12] involving averaging over many Grotthuss hopping events acquired from tens of nanoseconds of trajectory data, have shown that the likely mechanism for the proton hopping in bulk water is significantly more complicated than proposed in the original Moses mechanism, involving a collective reorganization of H-bonds up to three solvation shells away from the central hydronium cation for a successful Grotthuss hop to occur. To this day, it would seem that the precise mechanism for the excess proton mobility in bulk water is not entirely understood. Further studies using increasingly accurate models and statistical analysis are clearly needed.

Proton Transport through Water-Filled Channels. One of the first applications of the MS-EVB model was to study the transport of protons through narrow hydrophobic channels filled with water.[19] This study revealed a significant enhancement of the proton transport rate by a factor of 20 when a hydrophobic channel becomes so narrow that only a single file chain of water can be supported (i.e., a "water wire" or "proton wire"). Subsequently, Dellago et al.[51] used the MS-EVB approach, along with CPMD, to study proton transport through water-filled carbon nanotubes and a found a similarly enhanced proton transport rate.

Protons at Aqueous Interfaces. Our MS-EVB simulations of both protonated water clusters[17,18] and the excess proton at the water liquid−vapor interface[16] have revealed intriguing and important behavior not before known. In all of these studies, it has been found that excess protons seem to have a higher affinity for the interface with low dielectric media (e.g., the vacuum). The apparent reason for this behavior is that the hydronium cation has a directionality to its hydrogen bonding behavior which, despite its overall positive charge, imparts to it an "amphiphilic" character, thus causing it to have the interfacial preference (cf. Figures 3 and 4). The basic effect is also found in simpler classical (non-Grotthuss shuttling) potential models for hydronium[16,36] with and without the electronic polarization effect, ab initio MD studies of water clusters,[17] and studies of the excess proton in water−methanol mixtures (to be published) where the excess proton shows a preference for the low dielectric interface with the methanol methyl groups (Figure 4). There is in addition a growing body of indirect experimental support

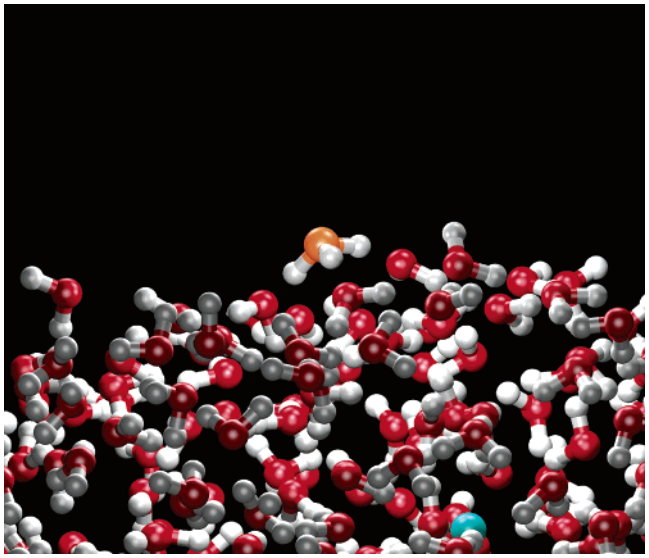

FIGURE 3. A snapshot of the preferred solvated structure of the hydronium cation (orange) at the water liquid−vacuum interface. The lone pair side is seen to point outward away from the bulk water with the three O−H bonds of the hydronium maintaining strong H-bonds to water molecules in the first and second liquid layers. This behavior arises from the predicted "amphiphilic" behavior of the hydronium cation.

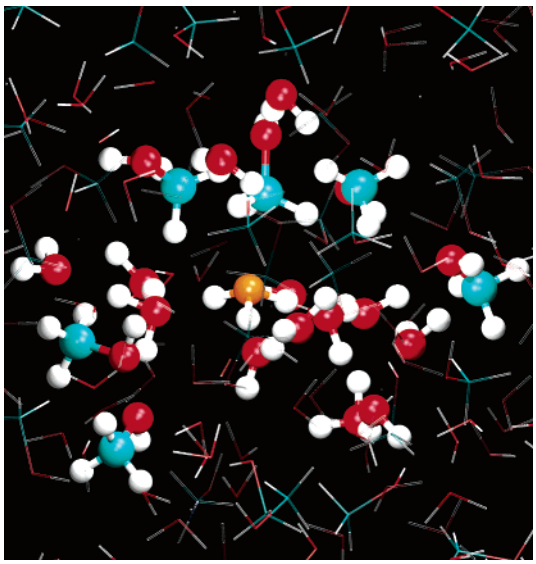

FIGURE 4. A snapshot of the preferred solvated structure of the hydronium cation (orange) at the water−methanol interface. The lone pair side is seen to point away from the bulk water toward the methyl groups (blue) of the methanol. This behavior again arises from the "amphiphilic" nature of the hydronium cation.

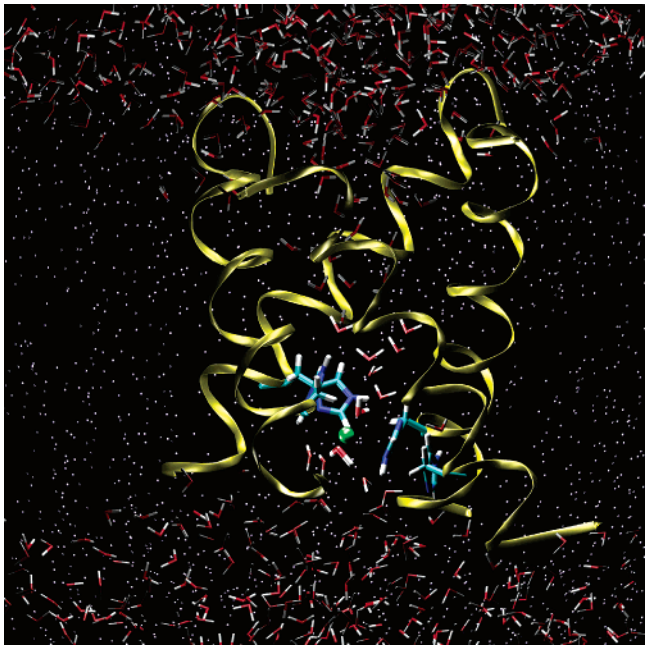

FIGURE 5. A snapshot from an MS-EVB simulation of the M2 proton channel in DMPC lipid bilayer. The excess proton (green ball) is seen shuttling through a "water wire" across the histidine gate region.

for this effect.[36,52] The implications of this discovery, should it stand the test of time and receive additional experimental verification, should prove to be very significant in atmospheric science, biology, acid−base chemistry, and materials science.

Proton Transport in Biomolecular Systems. Perhaps some of the most complex and significant applications of the MS-EVB simulation methodology to date have been for biomolecular systems.[20−28] Below will be highlighted several applications to proton channels, where the simulations have provided some new insight into their function. The reader is referred to our original papers cited below for more references to the relevant experimental and related simulation work.

One such result provided the first MD simulation of explicit proton translocation through the M2 channel of the influenza A virus.[22−24] The M2 channel is a proton selective channel that has been found to play essential roles in the viral life cycle. It is highly proton-selective—at least 10^6-fold more proton conductive than for other cations—and it is low-pH gated, undergoing a 50-fold conductance increase from pH 8.2 to pH 4.5. Clear experimental evidence has suggested that His37, which is highly conserved in all strains of influenza virus and is the only ionizable residue in the transmembrane domain (around pH 6), plays a crucial role. The MS-EVB simulations were carried out on the transmembrane domain of M2 in a fully solvated DMPC bilayer with the assumption that one stable biprotonated His37 might lead to the opening of the channel for protons. Within the time scales reached by the simulations (1 ns for each trajectory), the proton was observed to pass through the channel in three of the seven trajectories (Figure 5). In addition, a temporary opening of the pore at the constrictive region formed by the His37 residues was observed when the excess proton approached this region. This MS-EVB study suggested that one (or maybe two) biprotonated histidine may be sufficient for opening the channel for protons while still keeping it closed for other ions.

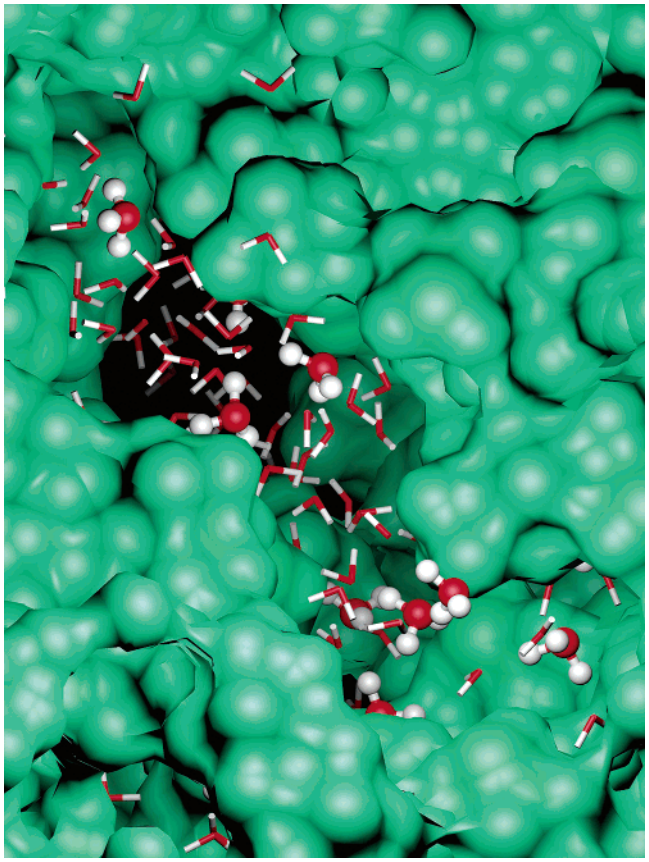

FIGURE 6. A snapshot from an SCI-MS-EVB simulation of 40 excess protons in a hydrophilic pocket of the Nafion polymer electrolyte membrane. The sulfonate groups are not shown for clarity of presentation. The hydrophobic polymer backbone is shown in green, while the excess protons and the water molecules to which they are most strongly bound are shown in ball-and-stick representation.

Another important application of the MS-EVB simulation methodology has been to study proton transport in cytochrome *c* oxidase (CcO),[27] which is in the superfamily of terminal respiratory enzymes found within the inner mitochondrial and bacterial membranes. Although the proton pump channels of CcO from various sources have been characterized and studied extensively by experimentalists, they had never before been studied through computer simulation in which the full proton hopping and transport was *explicitly included*, as in the MS-EVB method. Our simulation study[27] of the important D-channel of CcO revealed that the proton transport in the D-channel is very rapid once the Glu242 residue (bovine heart notation) at the top of the channel is deprotonated, thus lending support to experimental evidence that this residue is a critical step in the proton transport pathway through that channel. Furthermore, an interesting behavior was discovered in that a "proton trap" may exist in the channel where a proton resides "waiting" for the Glu242 residue to deprotonate and hence to then rapidly

reprotonate that residue as a key part of the proton pumping machinery in the enzyme.

Another recent and very interesting application of the MS-EVB methodology has been to study proton selectivity by the biomolecular aquaporin channel GlpF.[26] The aquaporin channels are very important in biology and also extremely interesting in that they allow water to pass through but no cations whatsoever, including protons.

Proton Solvation and Transport in Polymer Electrolyte Membranes (PEM). The computer simulation of proton solvation and transport in PEM such as Nafion is an exceptionally challenging problem given the high acid concentration (as high as 10 M) and the heterogeneous nature of the material. Our first MS-EVB results[29] have indicated key differences between Grotthuss shuttling protons and classical hydronium cations, as is seen, for example, in both the populations of and conversions between the contact ion pairs (CIP) and solvent separated ion pairs (SSIP) of the hydronium cations and sulfonate group anions, and the new SCI-MS-EVB approach[13] for multiple excess protons is presently being applied to Nafion PEM in our group (Figure 6).

4. Conclusions and Future Outlook

In this Account, our more than 10 year effort[2−29] to develop a robust and accurate computer simulation methodology to study proton solvation and transport in a host of realistic and complex systems has been reviewed. This approach has led, for the first time, to an unprecedented understanding of this mysterious and important phenomenon, dating back 200 years to the original work of Grotthuss. In the most general sense, this work also reflects the power and promise of combining new theoretical methodology with increasingly powerful computational resources. The future clearly points to a growing set of applications of the MS-EVB simulation methodology to study PS&T in a variety of contexts, as well as the continued improvement and extensions of the model itself.

I am extremely grateful to the members of the Voth group, past and present, and my other co-authors cited in refs 2−29. Without their remarkable efforts, this body of work would not have been possible. The different aspects of this research have been supported by the National Science Foundation, the National Institutes of Health, the Army Research Office, and the Department of Energy.

References

(1) de Grotthuss, C. J. T. The Grotthuss Mechanism. *Chem. Phys. Lett.* **1995**, *244*, 456−462.
(2) Lobaugh, J.; Voth, G. A. The quantum dynamics of an excess proton in water. *J. Chem. Phys.* **1996**, *104*, 2056−2069.
(3) Schmitt, U. W.; Voth, G. A. A multi-state empirical valence bond model for proton transport in water. *J. Phys. Chem. B* **1998**, *102*, 5547−5551.
(4) Schmitt, U. W.; Voth, G. A. Quantum properties of the excess proton in liquid water. *Isr. J. Chem.* **1999**, *39*, 483−492.
(5) Schmitt, U. W.; Voth, G. A. The computer simulation of proton transport in water. *J. Chem. Phys.* **1999**, *111*, 9361−9381.
(6) Cuma, M.; Schmitt, U. W.; Voth, G. A. A multi-state empirical valence bond model for acid−base chemistry in aqueous solution. *Chem. Phys.* **2000**, *258*, 187.
(7) Schmitt, U. W.; Voth, G. A. The isotope substitution effect on the hydrated proton. *Chem. Phys. Lett.* **2000**, *329*, 36−41.
(8) Day, T. J. F.; Schmitt, U. W.; Voth, G. A. The mechanism of hydrated proton transport in water. *J. Am. Chem. Soc.* **2000**, *122*, 12027−12028.
(9) Cuma, M.; Schmitt, U. W.; Voth, G. A. Multi-state empirical valence bond model for weak acid dissociation in aqueous solution. *J. Phys. Chem. A* **2001**, *105*, 2814−2823.
(10) Kim, J.; Schmitt, U. W.; Grueetzmacher, J. A.; Voth, G. A.; Scherer, N. F. The vibrational spectrum of the hydrated proton: Comparison of experiment, simulation, and normal-mode analysis. *J. Chem. Phys.* **2002**, *116*, 737−746.
(11) Day, T. J. F.; Soudackov, A. V.; Cuma, M.; Schmitt, U. W.; Voth, G. A. A second generation multistate empirical valence bond model for proton transport in aqueous systems. *J. Chem. Phys.* **2003**, *117*, 5839−5849.
(12) Lapid, H.; Agmon, N.; Petersen, M. K.; Voth, G. A. A bond-order analysis of the mechanism for hydrated proton mobility in liquid water. *J. Chem. Phys.* **2004**, *122*, No. 014506.
(13) Wang, F.; Voth, G. A. A linear-scaling self-consistent generalization of the multi-state empirical valence bond model for multiple excess protons in aqueous systems. *J. Chem. Phys.* **2005**, *122*, No. 144105.
(14) Izvekov, S.; Voth, G. A. Ab initio molecular dynamics simulation of aqueous proton solvation and transport revisited. *J. Chem. Phys.* **2005**, *123*, No. 044505.
(15) Maupin, C.; Wong, K. F.; Soudakov, A. V.; Kim, S.; Voth, G. A. A multi-state empirical valence bond description of protonatable amino acids. *J. Phys. Chem. B* **2006**, *110*, 631−639.
(16) Petersen, M. K.; Iyengar, S. S.; Day, T. J. F.; Voth, G. A. The hydrated proton at the water liquid/vapor interface. *J. Phys. Chem. B* **2004**, *108*, 14804−14806.
(17) Iyengar, S. S.; Day, T. J. F.; Voth, G. A. On the amphiphilic behavior of the hydrated proton: An ab initio molecular dynamics study. *Int. J. Mass. Spectrom.* **2005**, *241*, 197−204.
(18) Iyengar, S. S.; Petersen, M. K.; Day, T. J. F.; Burnham, C. J.; Tiege, V. E.; Voth, G. A. The properties of ion−water clusters. I. The protonated 21-water cluster. *J. Chem. Phys.* **2005**, *123*, 084309.
(19) Brewer, M. L.; Schmitt, U. W.; Voth, G. A. The formation and dynamics of proton wires in channel environments. *Biophys. J.* **2001**, *80*, 1691−1702.
(20) Smondyrev, M.; Voth, G. A. Molecular dynamics simulation of proton transport near the surface of a phospholipid membrane. *Biophys. J.* **2002**, *82*, 1460−1468.
(21) Tepper, H. L.; Voth, G. A. Protons may leak through pure lipid bilayers via a concerted mechanism. *Biophys. J.* **2005**, *88*, 3095−3108.
(22) Smondyrev, M.; Voth, G. A. Molecular dynamics simulation of proton transport through the influenza A virus M2 channel. *Biophys. J.* **2002**, *83*, 1987−1996.
(23) Wu, Y.; Voth, G. A. Computational studies of proton transport through the M2 channel. *FEBS Lett.* **2003**, *552*, 23−27.
(24) Wu, Y.; Voth, G. A. *Computer simulations of proton transport through the M2 channel of the influenza A virus*; Kluwer Academic/Plenum Publishers: New York, 2004; Chapter 10.
(25) Wu, Y.; Voth, G. A. A computer simulation study of the hydrated proton in a synthetic proton channel. *Biophys. J.* **2003**, *85*, 864−875.
(26) Ilan, B.; Tajkhorshid, E.; Shulten, K.; Voth, G. A. The mechanism of proton exclusion in aquaporin channels. *Proteins: Struct. Funct. Bioinform.* **2004**, *55*, 223−228.
(27) Xu, J.; Voth, G. A. Computer simulation of explicit proton translocation in cytochrome *c* oxidase: The D-pathway. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 6795−6800.
(28) Voth, G. A. The computer simulation of proton transport in biomolecular systems. *Front. Biosci.* **2003**, *8*, 1384−1397.
(29) Petersen, M. K.; Wang, F.; Blake, N. P.; Metiu, H.; Voth, G. A. Excess proton solvation and delocalization in a hydrophilic pocket of the proton conducting polymer membrane Nafion. *J. Phys. Chem. B* **2005**, *109*, 3727−3730.
(30) Warshel, A. *Computer modeling of chemical reactions in enzymes and solutions*; Wiley: New York, 1991.
(31) Vuilleumier, R.; Borgis, D. Molecular dynamics of an excess proton in water using a non-additive valence bond force field. *J. Mol. Struct.* **1997**, *436*, 555−565.
(32) Vuilleumier, R.; Borgis, D. Quantum dynamics of an excess proton in water using an extended empirical valence bond Hamiltonian. *J. Phys. Chem. B* **1998**, *102*, 4261.
(33) Vuilleumier, R.; Borgis, D. An extended valence bond model for describing proton transfer in H+(H20)n clusters and liquid water. *Chem. Phys. Lett.* **1998**, *284*, 71.
(34) Vuilleumier, R.; Borgis, D. An extended empirical valence bond model for describing proton mobility in water. *Isr. J. Chem.* **1999**, *39*, 457.

(35) Vuilleumier, R.; Borgis, D. Transport and spectroscopy of the hydrated proton: A molecular dynamics study. *J. Chem. Phys.* **1999**, *111*, 4251.
(36) Mucha, M.; Figato, T.; Levering, L. M.; Allen, H. C.; Tobias, D. J.; Dang, L. X.; Jungwirth, P. Unified picture of the surfaces of aqueous acid, base, and salt solutions. *J. Phys. Chem. B* **2005**, *109*, 7617−7623.
(37) Kim, B.; Young, T.; Harder, E.; Friesner, R. A.; Berne, B. J. Structure and dynamics of the solvation of bovine pancreatic trypsin inhibitor in explicit water. *J. Phys. Chem. B* **2005**, *109*, 16529−16538.
(38) Brancato, G.; Tuckerman, M. E. A polarizable empirical valence bond model for proton transport in aqueous solution. *J. Chem. Phys.* **2005**, *122*, No. 224507.
(39) Tuckerman, M.; Laasonen, K.; Sprik, M.; Parrinello, M. Ab initio molecular dynamics simulation of the solvation and transport of hydronium and hydroxyl ions in water. *J. Chem. Phys.* **1995**, *103*, 150−161.
(40) Tuckerman, M. E.; Marx, D.; Klein, M. L.; Parrinello, M. On the quantum nature of the shared proton in hydrogen bonds. *Science* **1997**, *275*, 817.
(41) Marx, D.; Tuckerman, M. E.; Hutter, J.; Parrinello, M. The nature of the hydrated excess proton in water. *Nature* **1999**, *397*, 601.
(42) Asthagiri, D.; Pratt, L. R.; Kress, J. D. Free energy of liquid water on the basis of quasichemical theory. *Phys. Rev. E* **2003**, *68*, 041505.
(43) Grossman, J. X.; Schwegler, E.; Draeger, E. W.; Gygi, F.; Galli, G. Towards an assessment of the accuracy of density functional theory for first principles simulations of water. *J. Chem. Phys.* **2004**, *120*, 300.
(44) VandeVondele, J.; Mohamed, F.; Krack, M.; Hutter, J.; Sprik, M.; Parrinello, M. The influence of temperature and density functional models in ab initio molecular dynamics simulation of liquid water. *J. Chem. Phys.* **2005**, *122*, No. 014515.
(45) Lill, M. A.; Helms, V. Molecular dynamics simulation of proton transport with quantum mechanically derived proton hopping rates (Q-HOP MD). *J. Chem. Phys.* **2001**, *115*, 7993−8005.
(46) Chakrabarti, N.; Tajkhorshid, E.; Roux, B.; Pomes, R. Molecular basis of proton blockage in aquaporins. *Structure* **2004**, *12*, 1−20.
(47) Walbran, S.; Kornyshev, A. A. Proton transport in polarizable water. *J. Chem. Phys.* **2001**, *114*, 10039−10048.
(48) Zahn, D.; Brickman, J. Quantum-classical simulation of proton migration in water. *Isr. J. Chem.* **1999**, *39*, 469−482.
(49) Kornyshev, A. A.; Kuznetsov, A. M.; Spohr, E.; Ulstrup, J. Kinetics of proton transport in water. *J. Phys. Chem. B* **2003**, *107*, 3351−3366.
(50) Agmon, N. The Grotthuss mechanism. *Chem. Phys. Lett.* **1995**, *244*, 456−462.
(51) Dellago, C.; Naor, M. M.; Hummer, G. Proton transport through water-filled carbon nanotubes. *Phys. Rev. Lett.* **2003**, *90*, No. 105902.
(52) Petersen, P. B.; Saykally, R. J. Evidence for an enhanced hydronium concentration at the liquid water surface. *J. Phys. Chem. B* **2005**, *109*, 7976−7980.

AR0402098