ACCOUNTS
of chemical research

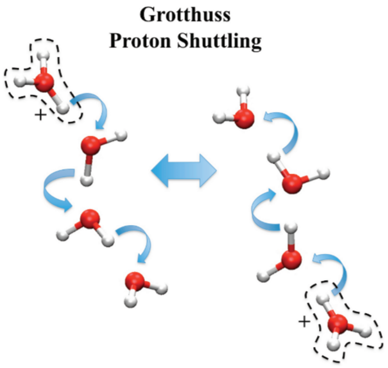
The Curious Case of the Hydrated Proton

CHRIS KNIGHT AND GREGORY A. VOTH*

Department of Chemistry, James Franck Institute, Institute for Biophysical Dynamics, and Computation Institute, University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637, United States

RECEIVED ON MAY 18, 2011

CONSPECTUS



Understanding the hydrated proton is a critically important problem that continues to engage the research efforts of chemists, physicists, and biologists because of its involvement in a wide array of phenomena. Only recently have several unique properties of the hydrated proton been unraveled through computer simulations. One such process is the detailed molecular mechanism by which protons hop between neighboring water molecules, thus giving rise to the anomalously high diffusion of protons relative to other simple cations. Termed Grotthuss shuttling, this process occurs over multiple time and length scales, presenting unique challenges for computer modeling and simulation. Because the hydrated proton is in reality a dynamical electronic charge defect that spans multiple water molecules, the simulation methodology must be able to dynamically readjust the chemical bonding topology. This reactive nature of the chemical process is automatically captured with ab initio molecular dynamics (AIMD) simulation methods, where the electronic degrees of freedom are treated explicitly. Unfortunately, these calculations can be prohibitively expensive for more complex proton solvation and transport phenomena in the condensed phase. These AIMD simulations remain extremely valuable, however, in validating empirical models, verifying results, and providing insight into molecular mechanisms.

In this Account, we discuss recent progress in understanding the solvation and transport properties of the hydrated excess proton. The advances are based on results obtained from reactive molecular dynamics simulations using the multistate empirical valence bond (MS-EVB) methodology. This approach relies on a dynamic linear combination of chemical bond topologies to model charge delocalization and dynamic bonding environments. When parametrized via a variational force-matching algorithm from AIMD trajectories, the MS-EVB method can be viewed as a multiscale bridging of ab initio simulation results to a simpler and more efficient representation. The process allows sampling of longer time and length scales, which would normally be too computationally expensive with AIMD alone.

With the MS-EVB methodology, the statistically important components of the excess proton solvation and hopping mechanisms in liquid water have been identified. The most likely solvation structure for the hydrated proton is a distorted Eigen-type complex ($H_9O_4^+$). In this state, the excess proton charge defect rapidly resonates between three possible distorted Eigen-type structures until a successful proton hop occurs. This process, termed the "special-pair dance", serves as a kind of preparatory phase for the proton hopping while the neighboring water hydrogen-bonding network fluctuates and ultimately rearranges to facilitate a proton hop.

The modifications of the solvation structure and transport properties of the excess proton in concentrated acid solutions were further investigated. The Eigen-type solvation structure also possesses both "hydrophilic" and "hydrophobic" sides, which accounts for the affinity of the hydrated proton for the air–water interface. This unusual "amphiphilic" character of the hydrated proton further leads to the metastable formation of contact ion pairs between two hydrated protons. It also engenders a surprisingly constant degree of solubility of hydrophobic species as a function of acid concentration, which contrasts with a markedly variable solubility as a function of salt (such as NaCl or KCl) concentration.

1. Introduction

The issue of proton solvation and transport remains a challenging problem that continues to provide surprises and promises to have features still to be discovered. Although it is commonly taught that the hydrated proton exists as the classical hydronium cation, H_3O^+, it is more appropriately described as a delocalized electronic charge defect spanning multiple molecules. The spread of this

www.pubs.acs.org/accounts
10.1021/ar200140h

charge defect blurs the identity of the excess "proton" among several likely candidates, each of which corresponds to a different classical hydronium-like character and chemical bond arrangement. It is this charge delocalization and dynamic chemical bonding that is at the heart of the interesting solvation and transport properties of the hydrated proton. One consequence of this behavior is that the mobility of the excess proton is larger than other cations of similar size and charge. Unraveling the details of the mechanism for this anonymously high diffusion, and other chemical processes, is fundamental to understanding proton solvation and transport in a wide range of materials and condensed phase environments.

The transport of delocalized protonic charge defects is a complicated process involving the coordinated rearrangement of several water molecules over which the charge density is distributed. For the hydrated proton, this diffusion process involves two components: the excess proton hopping, or shuttling, between molecules (Figure 1) and a vehicular component involving the translational diffusion of the hydrated proton solvation structure. The time scales for the hopping and vehicular components are both intimately coupled to the dynamics of the water hydrogen-bond (H-bond) network. The proton shuttling mechanism of protons between water molecules was first discussed in a paper by Grotthuss over two centuries ago, and it has since been termed the "Grotthuss mechanism".[1,2] In this mechanism, the proton is transferred from one water molecule to an adjacent water molecule without significant rearrangement of the center of masses (Figure 1). The excess proton diffusion process thus occurs over multiple length and time scales, a proper statistical sampling of which is one of the main challenges to computationally modeling this process in a complex condensed phase environment. Thus, any employed model for the simulation of proton transport must be able to accurately account for the shuttling of protons between molecules (i.e., "chemical diffusion") and the dynamic evolution of the chemical bonding topology and be computationally tractable to sample the long time and length scales necessary.

In this Account, recent progress on understanding the solvation and transport of the hydrated excess proton from computer simulation will be discussed. This will begin with a brief review of the reactive multistate empirical valence bond (MS-EVB) methodology developed for these studies and its applications. This will be followed by discussion on the formulation of the MS-EVB model through a multiscale bridging of the model to condensed phase ab initio molecular dynamics simulations.[3−5] The results from several studies on the proton solvation and transport properties will then be presented.

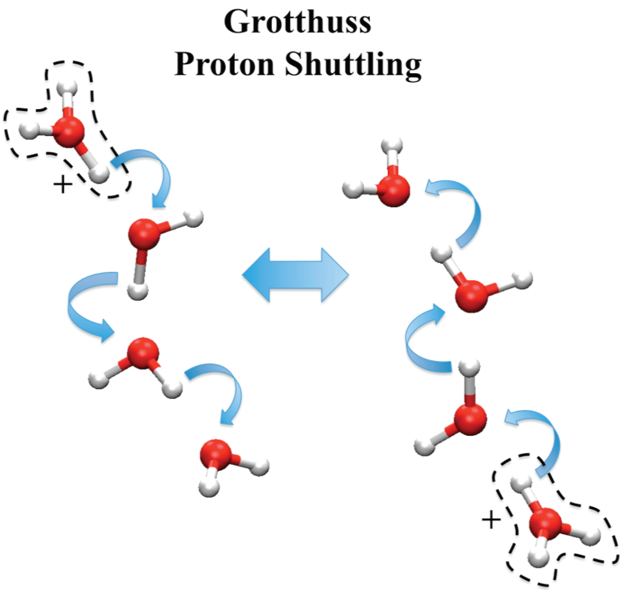


FIGURE 1. Illustration of the Grotthuss shuttling process for the excess proton in a small water wire. The excess protonic charge defect can be transported significant distances with only a small shift in the center of mass for each molecule.

2. Computer Modeling of Hydrated Protons

2.1. Reactive Molecular Dynamics. The modeling of complex chemical processes, such as proton transport, is impossible with traditional fixed-topology force fields, which lack the ability to describe the formation and cleavage of chemical bonds. One possible description of chemical reactions and bond making/breaking processes requires high-level electronic structure methods that explicitly treat the electrons. Although advanced algorithms and cutting-edge high-performance computing machines have enabled the ab initio molecular simulation of condensed phase systems, these calculations are still prohibitively too expensive to properly sample the large time and length scales for the chemical processes of interest. It should be stressed, though, that these ab initio simulations are still quite valuable for the parametrization and validation of empirical models as well as in providing insight into molecular mechanisms.

To properly model the diffusion of the hydrated proton, an empirical model must be able to describe the charge delocalization across several molecules and be sufficiently flexible to account for the dynamic evolution of the H-bond network. One promising route to the simulation of these complex processes is the reactive multistate molecular dynamics (MS-MD) simulation methodology, which uses a combination of multiple bonding topologies to describe the chemically reactive system. The MS-EVB method is one example of an MS-MD algorithm that has been quite successful in the modeling of proton transport processes in a variety of condensed phase systems.[6−10] Only a brief review of the MS-EVB methodology is discussed here. The reader is referred to the literature and references cited therein for other MS-MD approaches (e.g., refs 11−13).

The MS-EVB method is a multistate generalization of the original EVB[11,14] algorithm; the former dynamically identifies those variable bonding topologies that result from considering all possible reactions with a reactive species and its immediate environment. In an MS-EVB simulation, the system is represented as a linear combination of this collection of chemical bonding topologies, as illustrated in Figure 2 for the simple case of a gas-phase Eigen cation, $H_9O_4^+$. The selection process is repeated for each of the newly generated reactive species until the likelihood for a successful reaction has negligible probability. For the case of the hydrated excess proton in bulk water, this typically corresponds to three or four proton hops away from the initial hydronium cation, where the local H-bond network is not yet prepared to solvate the excess proton. These bonding topologies form a basis with which a quantum-like Hamiltonian matrix can be constructed and diagonalized. The coefficients of the ground state eigenvector serve as the corresponding weights for the chemical bonding topologies. For each bonding topology, a molecular mechanics force field is used to evaluate the corresponding diagonal element of the Hamiltonian matrix. The off-diagonal couplings serve as the mechanism for transitioning from one bonding topology to another. After the Hamiltonian matrix has been constructed and diagonalized at each MD time step, the coefficients from the ground state eigenvector are used with the Hellman−Feynman theorem to calculate the force on each atom, which are then used to integrate Newton's equations of motion.

The set of molecules which correspond to the classical hydronium cation in each MS-EVB state form a reactive complex where the chemical bonding topology is variable and defined by the MS-EVB weights. Within the MS-EVB framework, the extent of delocalization of the protonic charge defect[15] can be ascertained by examining the relative weight for each of the bonding topologies. With these weights, one can construct a coordinate to describe the center of excess charge (CEC) distribution as the weighted average of the position of the classical hydronium in each MS-EVB state.[8] This CEC coordinate proves useful in the calculation of the potential of mean force, for example, for the deprotonation of amino acids[16] and in rationalizing unexpected phenomena, such as the formation of contact ion pairs in acidic solutions,[17,18] as discussed below.

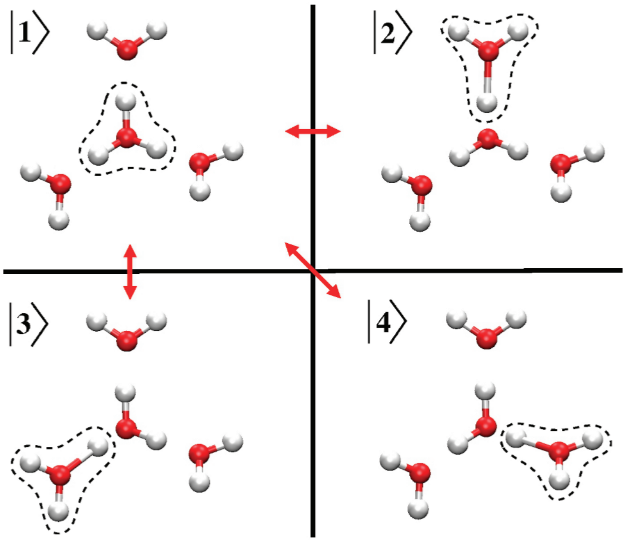


FIGURE 2. A description of the hydrated proton and the Grotthuss proton shuttling process is achieved in MS-EVB simulations by considering a collection of chemical bonding topologies. The classical hydronium for each topology is highlighted in this figure for the case of a gas phase Eigen cation, $H_9O_4^+$, and transitions between bonding topologies as a result of a successful proton hop are indicated with arrows.

For systems involving multiple excess protons, the self-consistent iterative (SCI) MS-EVB algorithm[19] can be utilized. In this iterative algorithm, the ground state eigenvector for each reactive complex is calculated in the effective field of all other reactive complexes. The loop over all reactive complexes corresponds to a single step in the iterative calculation and is continued until self-consistency has been reached with respect to all reactive complexes. The SCI-MS-EVB algorithm has been successfully applied to aqueous hydrochloric solutions,[18,19] as discussed below, and the concentrated environment of proton exchange membranes.[20,21]

2.2. Force Matching Reactive Models. It is critically important that any force field constructed be properly validated against high-level, accurate computational and experimental results. The validation and parametrization of reactive EVB models to ab initio methods is commonly achieved with high-level Schrödinger wave function methods, such as MP2 with a large basis set, on a representative set of configurations.[22] For MS-EVB models describing the hydrated proton, the proton transfer barriers in several water clusters were used to calculate a potential energy surface (PES) which was used to fit the MS-EVB model parameters for the off-diagonal couplings, short-ranged repulsions, and nonbonded hydronium–water interactions.[6–8,10] The intramolecular model for the classical hydronium cation was also determined from gas-phase ab initio calculations. A previously defined water model, such as the classical simple point charge flexible (SPC/Fw) model, can be used to define the remaining interactions. One potential issue with this procedure of parametrizing models in the gas phase is that of transferability to the condensed phase environment of interest. For the case of the reactive amino acid models, the issue of transferability was resolved by fitting MS-EVB parameters in a second round of parametrization to reproduce the solution pK_a values.[16] In another study, issues of transferability were further reduced by using a QM/MM procedure to calculate the minimum energy path for the deprotonation of zinc-bound water in the HCA-II system.[23]

It is becoming possible to apply ab initio molecular dynamics (AIMD) simulations to small condensed phase systems that are representative of larger systems of interest due to recent advances in algorithms and computational hardware. However, these calculations are limited in the number of atoms contained in the AIMD system, and it can often be computationally too expensive to carry out these simulations for sufficiently long times to properly sample the environmental degrees of freedom or to calculate thermodynamic and dynamic properties with sufficient statistical accuracy. Also, until one is capable of simulating condensed phase systems with high-level Schrödinger wave function methods, such as MP2, one is also limited by the accuracy of the present density functionals. It will therefore prove invaluable to have a flexible and systematic algorithm to reliably make a multiscale connection between accurate electronic structure calculations and the parametrization of models to describe complex reactive processes. These empirical models should reproduce the thermodynamic and dynamic properties of the original high-level AIMD calculation at a significantly reduced computational cost. With these models in hand, one can then in principle sample the long time and length scales necessary to explore complex phenomena in condensed phase environments.

A rigorous and flexible route to developing reactive force fields is to use force matching algorithms and reference data directly from ab initio condensed phase simulations.[24–29] In these algorithms, a fitting function is constructed as the squared difference between the forces on atoms calculated from the high-level accurate method and the effective interactions of the empirical model. This function is then variationally minimized with respect to the model parameters to generate a model that best reproduces the forces from the original, high-level calculation. This method is sufficiently flexible that only those portions of the model one is interested in can be parametrized while the remaining interactions can be defined with previously developed models. This flexibility allows for the reactive models to be constructed in stages by first developing a nonreactive model and then parametrizing the reactive portion of the model separately.[30]

The force matching procedure for reactive empirical force fields was successfully used to develop a reactive model for the hydrated excess proton.[30] The reference data for this model was generated from a Car–Parrinello molecular dynamics simulation[31] using the HCTH/120 density functional.[32] The first stage of development for this reactive model was the construction of a nonreactive model for the hydrated classical hydronium cation, H_3O^+, using those configurations from the trajectory for which the cation solvation structure was largely characterized as a symmetric Eigen cation. The hydronium–water interactions were then each fit as a sum of pairwise spline functions whose parameters were determined as the linear least-squares solution to the fitting function.[26,27] This initial model describing the solvation of the classical hydronium cation was then used as the molecular mechanics force field to describe the chemical bonding topologies in an MS-EVB simulation. The remaining reactive, proton hopping, portions of the model were defined using the functional forms for the off-diagonal couplings and short-ranged repulsions in the MS-EVB3 model.[10] A new fitting residual, now a nonlinear function with respect to the MS-EVB model parameters, was constructed and minimized using a distribution of configurations sampled from the entire ab initio trajectory.[30]

The resulting force-match MS-EVB model qualitatively reproduced the thermodynamic and dynamic properties of the original Car–Parrinello simulation at a fraction of the computational cost. One particularly important property calculated from these simulations was the potential of mean force along a proton transfer reaction coordinate where the force-matched MS-EVB model was in excellent agreement with the AIMD simulations. Good agreement with the MS-EVB3 model, parametrized with high-level gas phase ab initio calculations, was observed with the force-matched MS-EVB model being in better agreement with experiment. These results suggest that the optimal parameters for reactive empirical models can be directly determined from condensed phase AIMD simulations. As more accurate ab initio methodologies become computationally tractable for condensed phase simulations, force matching algorithms can then be utilized to significantly extend the time and length scales of these reactive simulations to explore complex phenomena.

3. Hydrated Excess Proton

3.1. Special-Pair Dance. At the heart of understanding the mechanism for the anonymously high diffusion of the aqueous excess proton is a critical understanding of the solvation structure and the role played by the local water H-bond network. To investigate the mechanism for proton shuttling between water molecules, equilibrium, conditional, and time-dependent radial distribution functions were calculated using several simulation methodologies.[33] The focus of this study was to statistically characterize the behavior of the hydrated proton and any structural changes that occurred during those times between proton transfer events. Classical and quantum MS-EVB simulations with two different models as well as AIMD simulations with two different density functionals were analyzed. The mechanism for proton transport in water does not occur within a single step. The "Eigen–Zundel–Eigen" (EZE) mechanism, suggested in earlier studies,[2,3] was statistically validated with several simulation methodologies, including AIMD simulations, which ensured the EZE mechanism was independent of any single simulation methodology. These findings for the EZE mechanism for proton transport were also supported by photoelectron spectroscopy results.[34,35]

The structure of the solvated proton is best described as a distorted, nonsymmetric Eigen cation,[15,33] with one H-bond considerably shorter than the others at any given instant, as illustrated in Figure 3. This distorted structure, the "resonating" state of the hydrated proton, is seen when the oxygen–oxygen radial distribution function (rdf) between the classical hydronium and water is decomposed into contributions from waters in the solvation structure. While in this resting state, thermal fluctuations cause the identity of the short H-bond to rapidly change among the three possible strong H-bonds with the hydronium cation shown in Figure 3. This process, termed the "special-pair dance", is the preparatory stage for proton transport with rapid partner exchanges, randomizing the proton hop direction, until the final partner is found and a successful proton transfer occurs.[4,5,33] This special-pair dance was statistically probed by tracking the identity of the special water over the course of the simulations. The final partner was found to be that water in the first solvation shell that accepted only a single H-bond, as opposed to two H-bonds typical of water molecules in the bulk. Configurations similar in character to the Zundel cation correspond to the transition state for proton transfer and only exist at times near a proton transfer event. There is considerable electronic charge transfer that occurs from the water molecule to the hydronium cation along the special pair strong H-bond.[15]

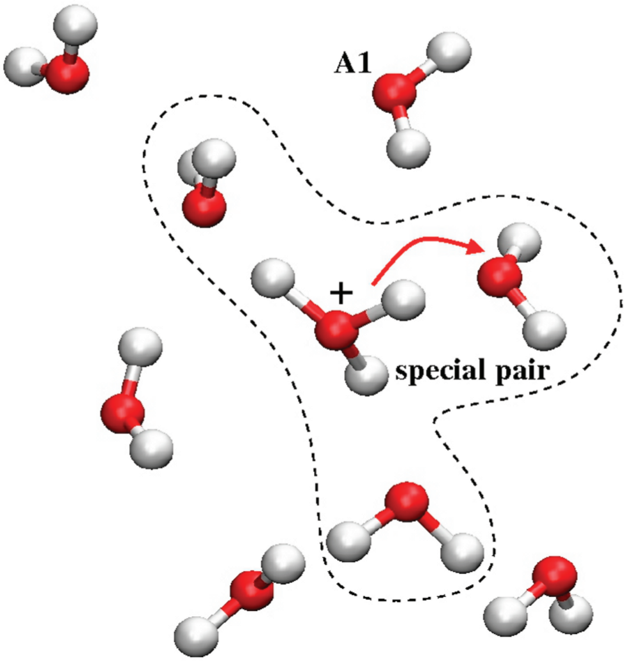


FIGURE 3. Illustration of a distorted Eigen-type complex near the end of a special-pair (SP) dance session, where a successful partner has been found. The special partner, to whom the arrow points, accepts a H-bond from only a single water molecule (labeled A1) in its first solvation shell.

The time evolution of the proton transfer event was well captured with time-dependent rdf's, where the transition from Eigen to Zundel was observed.[33] This partner exchange process occurs on a 50 fs time scale compared to the overall proton transport process, which occurs over several picoseconds. Evidence for proton transport predominantly going through the EZE mechanism was also justified when analyzing radial distribution functions at times just before and after successful proton transfer events. In the oxygen–oxygen rdf's between hydronium and water, it was observed that the first peak splits into two peaks, characteristic of an Eigen-to-Zundel transition, which then coalesced back into a single peak representative of the Eigen complex. The mechanism for proton transport is a cooperative, diffusive process and does not involve the correlated proton hopping along chains of several water molecules. These qualitative findings were independent of the simulation details, such as the water model, classical or quantum nuclear dynamics, or electronic density functional, despite quantitative differences between methods, such as a factor of 2−3 in the proton transfer rate. The proton transfer frequency was higher in quantum simulations due to the lowering of the free energy barrier separating the Eigen−Zundel distorted configurations. A successful decomposition of the conditional rdf's into two separate contributions corresponding to distorted Eigen and Zundel cations was possible for the classical simulations, but the distinction was not as clear for the quantum simulations where the identities were blurred. The statistics required to fully understand these processes were primarily made possible using the computationally efficient MS-EVB models to extend the time scales beyond what is possible with AIMD methods alone.

3.2. Kinetics of Proton Migration. The special-pair dance is indicative of the intimate coupling between motion of the excess proton and the surrounding H-bond network.[4,5,33] To understand the dynamic evolution of the H-bond network and its influence on the proton transport process, the "history independent" pair correlation function was calculated from long-time simulations with the MS-EVB methodology.[36] This correlation function describes the probability of a bound pair at some initial time and whether the species are still bound at some time in the future. This is the probability of the species being bound at some time irrespective of its history, which for the case of proton transport involves the many proton-hopping attempts during the special-pair dance.

It was found that all features of this correlation function could be described with a reversible diffusion model with a distance-dependent diffusivity describing the binding probability of a reversible geminate pair: $C \Leftrightarrow A + B$. When a fixed diffusion coefficient was used, it was observed that the correlation functions decayed too fast at intermediate times as compared with the simulation results. The diffusion coefficients for this study were calculated from the mean-squared displacement (MSD) for the center of excess charge. The time behavior of the MSD is divided into roughly two regions. There is an initial increase of the MSD in the subpicosecond regime that corresponds to the rapid reassignment of the most likely proton acceptor in the special-pair dance. The expected linear time behavior of the MSD was only observed in the long time limit, beyond 15 ps. The time variation of the diffusion was attributed to a dependence on the distance from the initial classical hydronium cation. The diffusion is impeded at short distances due to strong H-bonds in the first solvation shell of the hydronium cation.[37] Beyond the first solvation shell, as the strength of the H-bonds approach that of bulk water, the linear time dependence of the MSD should be observed. Using the limiting diffusion coefficients for short and long times, the entire time dependence for the MSD was well captured by a simple model, which was then used to obtain an expression for a distance-dependent diffusion.

Calculation of the distance-dependent diffusion constant, which was nonlinear, indicates that the motion of the proton is intimately coupled with nearby water molecules, which suggests that large clusters of waters are involved in the proton transfer process.[38] This implies that water molecules in the second solvation shell of the hydronium cation also play important roles in the shuttling of protons. This was confirmed in recent terahertz time-domain dielectric relaxation experiments[39] under acidic conditions which found that those waters in the first solvation shell are strongly bound, with strong H-bonds, and those in the second shell participate at least kinetically in the proton transfer process. The data indicate that two proton hops must occur before the local environment of the initial molecule is bulklike. The long time behavior $t^{-3/2}$ of the correlation function was observed out to 500 ps, in agreement with the theoretical result for a reversible geminate pair. It was presently only possible to obtain the long time behavior of the correlation function from the MS-EVB simulations as the AIMD simulations would have been prohibitively expensive and only the early time behavior converged.

3.3. Structure and Dynamics of Strong Acidic Solutions. The interactions between multiple hydrated protons are expected to be more complicated than the electrostatic interactions between simple cations because of the intimate coupling to the H-bond network and the dynamically delocalized nature of the excess proton charge defects. One would expect that two hydrated protons would repel one another due to the strong electrostatic force between two similarly charged species. As discussed below, this is found to not always be the case as the contact ion pair formed from two hydrated protons is rather quite stable in some situations.

The influence on proton solvation and transport properties when additional excess protons are present has been investigated by simulating concentrated HCl solutions[17,18] (0.43−3.26 M) with the SCI-MS-EVB methodology.[19] In these simulations, it was observed that the hydrated protons actually formed metastable contact ion pairs, with the hydronium lone-pair sides pointing toward one another. This behavior arises at least in part from the unusual "amphiphilic" behavior of the hydrated excess protons.[40] This amphiphilic behavior is mostly due to the directional H-bond asymmetry of the hydronium cation with water molecules in the first solvation shell. The formation of three

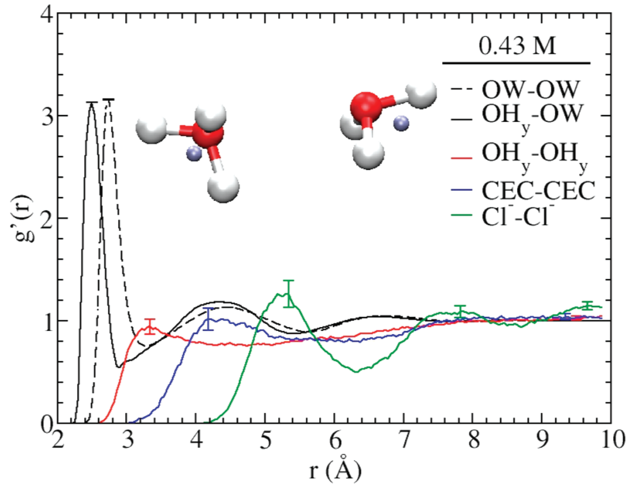


FIGURE 4. Radial distribution functions for a 0.43 M acid solution containing 256 H_2O and 2 dissociated HCl molecules (Figure 1 of ref 18). The labels OW, OHy, CEC, and Cl correspond to a water oxygen, hydronium-like oxygen, excess proton center of excess charge, and chloride ion, respectively. Also shown is an illustrative example of the hydrated proton contact ion pair, where the centers of excess charge, smaller blue spheres, are displaced away from one another.

strong H-bonds, in the Eigen-type complex, gives rise to a hydrophilic character. The "hydrophobic" character arises from the repulsion of H-bonds that are donated to the hydronium on the lone pair side due to the net positive charge of the cation and the resulting disruption of the water H-bond network. To minimize the disruption on the local H-bond network, the hydrated protons can point their lone pair sides toward one another, thus forming contact ion pairs. The presence of this region on the lone pair electron side of the hydronium cation also has the consequence of enhancing the concentration of protons at the air–water interface for acidic solutions, which is supported by surface-selective spectroscopic experiments, such as second harmonic generation.[40−42] The lone pair side of the hydronium is preferentially oriented toward the vapor to minimize the local H-bond disruption.[40,41] This same preferred orientation is also observed when the hydrated cation is in the presence of an ideal hydrophobic interface,[41] which again acts to minimize the disruption on the local H-bond network.

The stability of these Eigen cation contact ion pairs formed by similarly charged species is in part due to a reduced electrostatic repulsion due to delocalization of the excess protonic charge defect over surrounding water molecules (Figure 4).[17,18] The center of excess charges for both Eigen cations are repelled away from one another by ~1.0 Å, effectively reducing the electrostatic repulsion and allowing the contact ion pair to form, as shown in Figure 4. At the lowest concentrations studied, the average lifetime of the hydrated proton contact ion pairs was about 14 ps, which contrasts with an average proton Grotthuss hopping time of 1−2 ps in dilute acid solutions. This result is consistent with an estimate calculated from AIMD simulations of a 1 M HCl solution.[18] The average lifetime decreased to about 5 ps for the largest HCl concentration examined. Although there was an increase in the frequency of ion pairings with increasing HCl concentration, the decreased averaged lifetime was likely due to an increased charge repulsion, which destabilized the ion pairs.

The (meta)stability of the hydrated proton contact ion pairs in solution will lead to changes in the transport properties of the charged proton defect relative to the infinitely dilute case. The diffusion coefficient for each of the hydrated protons was calculated from the long-time slope of the MSD for the center of excess charge. Over the concentration range investigated, the diffusion of both the excess protons and chloride ions was found to decrease with increasing acid concentration,[18] which is consistent with experimental observations. To gain more insight into the molecular mechanism for the proton transport process, the diffusion coefficient for the excess proton was partitioned into vehicular, proton hopping, and the contribution from the correlation between the two processes, which may be positive or negative on average. The total diffusion of the excess proton is the sum of these three contributions. At lower concentrations, the vehicular component is nearly unchanged and the proton hopping component accounts for the majority of the decrease in total diffusion. At the higher concentrations, all components to the proton diffusion were found to decrease with increasing HCl concentration, which is consistent with nuclear magnetic resonance (NMR) experiments.[43] The calculated number of proton hopping events, successful or unsuccessful, was effectively constant with respect to concentration. This indicates that there are fewer successful proton hopping events with increasing concentration. At the higher concentrations, the protons tend to "rattle" between the same water molecules, thus decreasing the Grotthuss hopping component to the long-ranged diffusion of the excess protons. The correlation between the hopping and vehicular components was negative for all concentrations studied, which indicates that the two diffusion processes, vehicular and hopping, can to some degree oppose each other. This surprising effect was also first observed in simulations of the acidic environment of the proton exchange membrane Nafion.[20]

3.4. Hydrophobic Interactions. To gain further insight into the molecular mechanism by which hydrophobic molecules have their solubility changed by the presence of salts and addition of acid, a series of aqueous solutions of neopentane was investigated.[44] Several systems at varying acid and salt concentrations were used to probe the role of the excess protons and salts on the aggregation/dispersion properties of hydrophobic molecules. These systems contained molar ratios of 1, 2, and 4 HCl/NaCl molecules per neopentane molecule. The results from these simulations were compared to those from aqeuous NaCl solutions. The salting out of neopentane was observed for all salt systems as an increase in the first peak of a radial distribution function between neopentane molecules corresponding to an increased association. The degree of the salting out effect increased with salt concentration, as one would have expected. Phase separation was observed in the 4:1 NaCl/neopentane solution with mostly water and NaCl forming one phase and neopentane the other phase. Additional simulations with KCl salt solutions supported the general conclusions from the NaCl solutions. In the acidic solutions, no increase in the hydrophobic aggregation was observed with increasing HCl concentration, leading to a largely unchanged solubility of neopentane with acid concentration. The solubility of the hydrocarbon molecules was thus found to be much more sensitive to the salt concentration than the acid concentration, in agreement with the available experimental data.

In acidic solutions, the hydrophobic neopentane molecules were found to prefer to be adjacent to the hydrated protons rather than other water molecules in the system. The formation of these pairs may be a general feature of these systems and explain the increased solubility of hydrophobic molecules in acidic solutions. This stabilization with the hydrated proton has the effect of inhibiting aggregation of the neopentane molecules. It was found that the hydronium cations were preferentially oriented with its lone-pair electrons pointed toward the hydrophobic molecule, which is again rooted in the amphiphilic nature of the hydrated proton discovered in our earlier work.[40]

4. Future Outlook

Despite what its name may imply, the hydrated excess proton is much more complicated than other similarly sized, simple cations. The intimate coupling of the hydrated proton to water molecules and, in turn, of the resulting electronic charge defect to the local H-bond network leads to unique and sometimes unexpected properties. An increasingly detailed understanding of a number of complex phenomena demands that the solvation properties and the molecular level mechanism for the transport of the hydrated proton continue to be unraveled. The research highlighted here has provided an important foundation for understanding proton solvation and transport in aqueous systems. As computational resources continue to become increasingly more powerful, empirical reactive simulation methodologies, such as MS-EVB, will also prove crucially important to extend ab initio simulation methodologies to study complex condensed phase environments of interest to a broad spectrum of scientific fields including chemistry, biology, and materials science.

BIOGRAPHICAL INFORMATION

Chris Knight received his B.S. in Chemistry in 2003 from Eastern Michigan University. In 2009, he received his Ph.D. in Chemistry from The Ohio State University under the supervision of Sherwin J. Singer. In 2009, he joined the Voth research group, where his postdoctoral research and longer-term interests include the efficient simulation of reactive processes in condensed phase environments and high performance computing.

Gregory A. Voth is the Haig P. Papazian Distinguished Service Professor of Chemistry at the University of Chicago. He is also a Professor of the James Franck Institute and the Institute for Biophysical Dynamics, as well as a Senior Fellow of the Computation Institute and a Senior Scientist at Argonne National Laboratory. He received a Ph.D. in Theoretical Chemistry from the California Institute of Technology in 1987 and was an IBM Postdoctoral Fellow at the University of California, Berkeley from 1987 to 1989. He is the author or co-author of more than 350 peer-reviewed scientific articles and has mentored approximately 150 postdoctoral fellows and graduate students. His research interests include: multiscale theory and simulation of biomolecular and soft matter systems; proton and charge transport processes in chemistry, biology, and materials science; computer simulation and modeling of complex liquids and solvation phenomena; and high performance scientific computing.

This research has been supported by the National Science Foundation (NSF grants CHE-0719522 and CHE-1036464). Computational resources were supported in part by the National Science Foundation through TeraGrid resources and in part by a grant of computer time from the DOD High Performance Computing Modernization Program Supercomputing Resource Centers. We are grateful to the present and former members of the Voth group and to our collaborators.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: gavoth@uchicago.edu.

REFERENCES

1 Grotthuss, C. J. T. d. Sur la décomposition de l'eau et des corps q'uelle tient en dissolution à l'aide de l'électricité galvanique. *Ann. Chim. (Paris)* **1806**, *58*, 54–74.

2 Agmon, N. The Grotthuss mechanism. *Chem. Phys. Lett.* **1995**, *244*, 456–462.

3 Marx, D.; Tuckerman, M. E.; Hütter, J.; Parrinello, M. The nature of the hydrated excess proton in water. *Nature* **1999**, *397*, 601–604.

4 Chandra, A.; Tuckerman, M. E.; Marx, D. Connecting Solvation Shell Structure to Proton Transport Kinetics in Hydrogen-Bonded Networks via Population Correlation Functions. *Phys. Rev. Lett.* **2007**, *99*, 145901.

5 Berkelbach, T. C.; Lee, H.-S.; Tuckerman, M. E. Concerted Hydrogen-Bond Dynamics in the Transport Mechanism of the Hydrated Proton: A First-Principles Molecular Dynamics Study. *Phys. Rev. Lett.* **2009**, *103*, 238302.

6 Schmitt, U. W.; Voth, G. A. Multistate Empirical Valence Bond Model for Proton Transport in Water. *J. Phys. Chem. B* **1998**, *102*, 5547–5551.

7 Schmitt, U. W.; Voth, G. A. The computer simulation of proton transport in water. *J. Chem. Phys.* **1999**, *111*, 9361–9381.

8 Day, T. J. F.; Soudackov, A. V.; Čuma, M.; Schmitt, U. W.; Voth, G. A. A second generation multistate empirical valence bond model for proton transport in aqueous systems. *J. Chem. Phys.* **2002**, *117*, 5839–5849.

9 Swanson, J. M. J.; Maupin, C. M.; Chen, H.; Petersen, M. K.; Xu, J.; Wu, Y.; Voth, G. A. Proton Solvation and Transport in Aqueous and Biomolecular Systems: Insights from Computer Simulations. *J. Phys. Chem. B* **2007**, *111*, 4300–4314.

10 Wu, Y.; Chen, H.; Wang, F.; Paesani, F.; Voth, G. A. An Improved Multistate Empirical Valence Bond Model for Aqueous Proton Solvation and Transport. *J. Phys. Chem. B* **2008**, *112*, 7146.

11 Warshel, A. *Computer Modeling of Chemical Reactions in Enzymes and Solutions*; John Wiley and Sons: New York, 1991.

12 Higashi, M.; Truhlar, D. G. Efficient Approach to Reactive Molecular Dynamics with Accurate Forces. *J. Chem. Theory Comput* **2009**, *5*, 2925–2929.

13 Song, L.; Mo, Y.; Gao, J. An Effective Hamiltonian Molecular Orbital-Valence Bond (MOVB) Approach for Chemical Reactions as Applied to the Nucleophiic Substitution Reaction of Hydrosulfide Ion and Chloromethane. *J. Chem. Theory Comput.* **2009**, *5*, 174–185.

14 Warshel, A.; Weiss, R. M. An Empirical Valence Bond Approach for Comparing Reactions in Solution and in Enzymes. *J. Am. Chem. Soc.* **1980**, *102*, 6218–6226.

15 Swanson, J. M. J.; Simons, J. Role of Charge Transfer in the Structure and Dynamics of the Hydrated Proton. *J. Phys. Chem. B* **2009**, *113*, 5149.

16 Maupin, C. M.; Wong, K. F.; Soudackov, A. V.; Kim, S.; Voth, G. A. A Multistate Empirical Valence Bond Description of Protonatable Amino Acids. *J. Phys. Chem. A* **2006**, *110*, 631–639.

17 Wang, F.; Izvekov, S.; Voth, G. A. Unusual “Amphiphilic” Association of Hydrated Protons in Strong Acid Solution. *J. Am. Chem. Soc.* **2008**, *130*, 3120–3126.

18 Xu, J.; Izvekov, S.; Voth, G. A. Structure and Dynamics of Concentrated Hydrochloric Acid Solutions. *J. Phys. Chem. B* **2010**, *114*, 9555–9562.

19 Wang, F.; Voth, G. A. A linear-scaling self-consistent generalization of the multistate empirical valence bond method for multiple excess protons in aqueous systems. *J. Chem. Phys.* **2005**, *122*, 144105.

20 Petersen, M. K.; Voth, G. A. Characterization of the Solvation and Transport of the Hydrated Proton in the Perfluorosulfonic Acid Membrane Nafion. *J. Phys. Chem. B* **2006**, *110*, 18594–18600.

21 Feng, S.; Voth, G. A. Proton Solvation and Transport in Hydrated Nafion. *J. Phys. Chem. B* **2011**, *115*, 5903–5912.

22 Muller, R. P.; Warshel, A. Ab Initio Calculations of Free Energy Barriers for Chemical Reactions in Solution. *J. Phys. Chem.* **1995**, *99*, 17516–17524.

23 Maupin, C. M.; McKenna, R.; Silverman, D. N.; Voth, G. A. Elucication of the Proton Transport Mechanism in Human Carbonic Anhydrase II. *J. Am. Chem. Soc.* **2009**, *131*, 7598–7608.

24 Ercolessi, F.; Adams, J. B. Interatomic Potentials from First-Principles Calculations: the Force-Matching Method. *Eruophys. Lett.* **1994**, *26*, 583–588.

25 Tangney, P.; Scandolo, S. An ab initio parameterized interatomic force field for silica. *J. Chem. Phys.* **2002**, *117*, 8898–8904.

26 Izvekov, S.; Parrinello, M.; Burnham, C. J.; Voth, G. A. Effective force fields for condensed phase systems from ab initio molecular dynamics simulation: A new method for force-matching. *J. Chem. Phys.* **2004**, *120*, 10896–10913.

27 Izvekov, S.; Voth, G. A. Effective Force Field for Liquid Hydrogen Flouride from Ab Initio Molecular Dynamics Simulation Using the Force-Matching Method. *J. Phys. Chem. B* **2005**, *109*, 6573–6586.

28 Akin-Ojo, O.; Song, Y.; Wang, F. Developing ab initio quality force fields from condensed phase quantum-mechanics/molecular-mechanics calculations through the adaptive force matching method. *J. Chem. Phys.* **2008**, *129*, 064108.

29 Song, Y.; Akin-Ojo, O.; Wang, F. Correcting for dispersion interaction and beyond in density functional theory through force matching. *J. Chem. Phys.* **2010**, *133*, 174115.

30 Knight, C.; Maupin, C. M.; Izvekov, S.; Voth, G. A. Defining Condensed Phase Reactive Force Fields from ab Initio Molecular Dynamics Simulations: The Case of the Hydrated Excess Proton. *J. Chem. Theory Comput.* **2010**, *6*, 3223–3232.

31 Car, R.; Parrinello, M. Unified Approach for Molecular Dynamics and Density-Functional Theory. *Phys. Rev. Lett.* **1985**, *55*, 2471–2474.

32 Boese, A. D.; Doltsinis, N. L.; Handy, N. C.; Sprik, M. New generalized gradient approximation functionals. *J. Chem. Phys.* **2000**, *112*, 1670–1678.

33 Markovitch, O.; Chen, H.; Izvekov, S.; Paesani, F.; Voth, G. A.; Agmon, N. Special Pair Dance and Partner Selection: Elementary Steps in Proton Transport in Liquid Water. *J. Phys. Chem. B* **2008**, *112*, 9456–9466.

34 Winter, B.; Faubel, M.; Hertel, I. V.; Pettenkofer, C.; Bradforth, S. E.; Jagoda-Cwiklik, B.; Cwiklik, L.; Jungwirth, P. Electron Binding Energies of Hydrated H_3O^+ and OH^-: Photoelectron Spectroscopy of Aqueous Acid and Base Solutions Combined with Electronic Structure Calculations. *J. Am. Chem. Soc.* **2006**, *128*, 3864–3865.

35 Kirchner, B. Eigen or Zundel Ion: News from Calculated and Experimental Photoelectron Spectroscopy. *ChemPhysChem* **2007**, *8*, 41–43.

36 Chen, H.; Voth, G. A.; Agmon, N. Kinetics of Proton Migration in Liquid Water. *J. Phys. Chem. B* **2010**, *114*, 333–339.

37 Markovitch, O.; Agmon, N. Structure and Energetics of the Hydronium Hydration Shells. *J. Phys. Chem. A* **2007**, *111*, 2253–2256.

38 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.* **2005**, *122*, 014506.

39 Tielrooij, K. J.; Timmer, R. L. A.; Bakker, H. J.; Bonn, M. Structure Dynamics of the Proton in Liquid Water Probed with Terahertz Time-Domain Spectroscopy. *Phys. Rev. Lett.* **2009**, *102*, 198303.

40 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.

41 Iuchi, S.; Chen, H.; Paesani, F.; Voth, G. A. Hydrated Excess Proton at Water-Hydrophobic Interface. *J. Phys. Chem. B* **2009**, *113*, 4017–4030.

42 Petersen, P. B.; Saykally, R. J. On the Nature of Ions at the Liquid Water Surface. *Annu. Rev. Phys. Chem.* **2006**, *57*, 333–364.

43 Dippel, T.; Kreuer, K. D. Proton transport mechanism in concentrated aqueous solutions and solid hydrates of acids. *Solid State Ionics* **1991**, *46*, 3–9.

44 Chen, H.; Xu, J.; Voth, G. A. Unusual Hydrophobic Interactions in Acidic Aqueous Solutions. *J. Phys. Chem. B* **2009**, *113*, 7291–7297.