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Application of the SCC-DFTB method to neutral and protonated water clusters and bulk water

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Abstract

The self-consistent charge density functional tight-binding (SCC-DFTB) method has been actively employed to study proton transfer processes in biological systems. Recent studies in the literature employing SCC-DFTB reported that the method favors the Zundel form of the hydrated proton over the Eigen form, both in gas-phase water clusters and in bulk water, in disagreement with both higher-level calculations and experimental data. In this work, we explore the performance of SCC-DFTB for protonated gas-phase water clusters and bulk water (the latter both with and without an excess proton) with a modified O-H repulsive potential reported in our earlier work and with on-site third-order expansion of the DFT energy. Our results show that, with the proper set of published parameters, SCC-DFTB does correctly favor the Eigen form of the hydrated proton compared to the Zundel form, both in gas-phase clusters and in the bulk; the amphiphilic character of the hydrated proton discussed in the literature has also been observed. The analyses do, however, bring forth remaining limitations in terms of the solvation structure around the hydrated proton as well as the structure of bulk water, which can guide future improvements of the method.

I. INTRODUCTION

Water-mediated proton transfer plays a crucial role in many biological processes¹ as well as in important industrial applications such as fuel cells². The fact that proton transfer inherently involves bond-breaking and bond-making calls for the use of a quantum mechanics (QM) based method for modeling the process at the microscopic level. However, high-level QM methods severely limit the amount of conformational sampling, which has been shown to be particularly important for a meaningful analysis of proton transfers in biomolecules^{3–6} and in bulk aqueous solution^{7,8}. Approximate QM methods are, therefore, very useful for studying such reactive processes since they allow the access to larger system sizes and longer time scales, while maintaining a level of accuracy appropriate to many questions of interest^{6,9–13}.

Among the available approximate QM methods, the self-consistent charge density functional tight-binding (SCC-DFTB)^{14,15} method is an approximate density functional theory (DFT) that has been found useful in a number of biomolecular proton transfer problems. Compared to the rather specifically parameterized generations of MS-EVB model^{3,7}, which have been

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SUPPORTING INFORMATION

Additional calculation results for the $H^+(H_2O)_5$ and discussions on the results for $H^+(H_2O)_{22}$ are included. These materials are available free of charge from <http://pubs.acs.org>.

particularly successful in modeling proton transfers in various systems, the advantage of the SCC-DFTB framework is its generality, as demonstrated in several recent applications that discussed the potential involvement of hydroxide (“proton hole”) in long-range proton transfers¹⁶, the “intermolecular proton bond” model for proton storage site in the proton pump bacteriorhodopsin¹² and the role of proton transfers in phosphate hydrolysis^{17,18}.

The applicability of SCC-DFTB method to molecular systems has been tested by several independent benchmark studies^{19–21}, which found that it gives, in general, similar energetics as other NDDO methods, but somewhat better geometries and vibrational frequencies. To determine whether an approximate (QM) method provides a meaningful description for a particular problem, however, it is important to carry out additional benchmark calculations most relevant to the system or problem in hand. In the context of proton transfer processes in biomolecules, we have focused on proton affinities^{15,22}, hydrogen-bonding interactions¹⁵, proton transfer barriers in small clusters^{5,16} as well as microscopic pK_a values^{23–25}. Carrying out these benchmark calculations also motivated our systematic attempts to improve the SCC-DFTB based QM/MM framework, including both SCC-DFTB itself^{9,15,26} and the treatment of long-range^{23,27,28} as well as short-range²⁹ interactions in QM/MM calculations. In particular, as described in more details in **Computational Methods**, a modification to the second-order kernel involving hydrogen, γ_{OH} , was introduced to improve hydrogen bonding interactions, and third-order terms in the DFT energy expansion were found essential for systematically improving proton affinities.

In several recent studies, additional benchmark calculations for testing the applicability of SCC-DFTB to proton transfer problems have been carried out. Choi et al.³⁰ focused on protonated water clusters in the gas phase while Maupin et al.³¹ focused on the behavior of bulk water in the absence and presence of an excess proton; in an earlier study, Hu et al.³² also examined the structural properties of bulk water with a linear-scaling implementation of SCC-DFTB. Although slightly different variants of SCC-DFTB have been used, these studies highlighted several limitations of SCC-DFTB, some of which (e.g., too weak hydrogen bonding interaction with the original parameterization of SCC-DFTB^{14,33}) have been documented in the literature. One trend that consistently emerged from both studies^{30,31} is that the SCC-DFTB methods used thereof favor the Zundel form of the hydrated proton over the Eigen form in both gas and condensed phases, in disagreement with high level QM calculations and available experimental data. Schematic diagrams displaying the qualitative difference between the Zundel ($H_5O_2^+$) and Eigen ($H_9O_4^+$) forms of the hydrated proton can be found elsewhere, e.g., Fig. 1 in Ref³⁴, but as a brief qualitative explanation of the difference: the Eigen form consists of a central hydronium cation that forms hydrogen bonds with neighboring waters, whereas the Zundel form consists of a central water dimer that share equally the excess proton between them. In the aforementioned studies^{30,31}, potential of mean force (PMF) calculations showed³¹ that SCC-DFTB overestimates the stability of Zundel over Eigen by ~ 1 kcal/mol as compared to CPMD simulations using the HCTH/120 gradient-corrected exchange-correlation energy functional. As a result, it was observed that proton transport in water occurs through a Zundel-Zundel mechanism at the SCC-DFTB level, rather than the Eigen-Zundel-Eigen mechanism, which is believed to be the correct mechanism based on MS-EVB^{35–37}, CPMD simulations^{35,37–39} and related spectroscopic measurements^{40,41}.

In our opinion, the behavior of an excess proton in bulk water is not the most compelling benchmark for proton transfers in biomolecules. In a biomolecular environment, the pK_a 's for sites relevant to proton transfers are much more heterogeneous compared to bulk water, and this has two important consequences. First, the degree of delocalization for the excess proton is likely much reduced in biomolecules relative to bulk water, thus making benchmark calculations using small clusters much more relevant. Second, proton transfer

rates are expected to be closely related to pK_a differences (e.g., in a multi-state Marcus framework⁴²), thus the impact of an error of ~ 1 kcal/mol for the relative stability of Zundel and Eigen ions needs to be judged in the context of pK_a values for titratable groups along proton transfer pathways.

Nevertheless, considering the fundamental importance of water as a solvent, these recent studies^{30,31} provided valuable benchmarks for testing the general applicability of the SCC-DFTB framework to chemical reactions in solution and biomolecules. Along this line, we note two limitations of these benchmark studies. First, both studies used the standard repulsive potentials^{14,43}, which are important parameters in SCC-DFTB. In our studies of proton transfer in carbonic anhydrase⁹, cluster models revealed that using the improved γ_{OH} function with the standard second order SCC-DFTB gave too low proton transfer barriers, especially when the transition state involved multiple proton transfers. As an empirical fix to the problem, the O-H repulsive potential was modified by adding a perturbative Gaussian function in the range of O-H distances found in typical proton transfer barriers. We expect that this modification of the O-H repulsive potential plays an important role in determining the relative stability of the Zundel/Eigen configurations, although this remains to be shown quantitatively.

Secondly, we note that the bulk studies of Maupin et al.³¹ employed only second-order SCC-DFTB, with both the standard and modified γ_{OH} functions. Our previous benchmark calculations¹⁵ of small water clusters indicated empirically that the description of hydrogen-bonding interactions is further improved when both the on-site third-order terms and modified γ_{OH} function are used. Whether this carries over to condensed phase and improves bulk properties is an interesting issue worth exploring.

Motivated by these considerations, we carry out calculations for both the gas-phase and condensed phase systems explored in recent studies^{30,31} with the revised O-H repulsive potential published in Ref.⁹. We also compare results from SCC-DFTB with second-order and third-order on-site (diagonal) terms. We hope these calculations help further elucidate the value and limitation of SCC-DFTB in (bio)molecular applications that involve water and excess proton(s).

In the following, we first briefly review SCC-DFTB so as to clearly define the various parameterizations of the methodology tested here; the benchmark systems and simulation details are also summarized in Sect.II. In Sect.III, we present results and compare them to those from previous studies. Finally, we make a few concluding remarks in Sect.IV.

II. COMPUTATIONAL METHODS

A. The SCC-DFTB method

We provide a brief overview of the SCC-DFTB^{14,15} method to clearly define the various parameterizations tested in this work. For further details, original references^{14,15} and recent review articles^{9,26,44,45} should be consulted with. The standard SCC-DFTB method involves a second order expansion of the DFT total energy functional with respect to the charge density fluctuations around a given reference density ρ_0 . The energy is expressed as

$$E^{SCC} = \sum_{i\mu\nu} c_{\mu}^i c_{\nu}^i H_{\mu\nu}^0 + \frac{1}{2} \sum_{\alpha\beta} \gamma_{\alpha\beta} \Delta q_{\alpha} \Delta q_{\beta} + \frac{1}{2} \sum_{\alpha\beta} V[\rho_0^{\alpha}; \rho_0^{\beta}; R_{\alpha\beta}], \quad (1)$$

where $c_{\mu/\nu}^i$ are the Linear Combination of Atomic Orbital (LCAO) coefficients, $H_{\mu\nu}^0$ the Hamiltonian matrix with reference density, $\Delta q_{\alpha/\beta}$ the Mulliken charges on atom α/β and $V[\rho_0^O; \rho_0^H; R_{\alpha\beta}]$ the repulsive potential. The use of valence only minimal basis functions and approximations to electronic integrals makes the method particularly efficient, about 2–3 orders of magnitude faster than typical implementation of DFT methods.

In its original implementation, the $\gamma_{\alpha\beta}$ function, which describes the interaction between atomic partial charges $\Delta q_{\alpha}; \beta$, has the following form

$$\gamma_{\alpha\beta} = \frac{1}{R_{\alpha\beta}} - S_{\alpha\beta}, \quad (2)$$

which reduces to Coulombic form at long-range and, in the case of identical atom pairs ($\alpha = \beta$), chemical hardness at short-range. The particular functional form of $\gamma_{\alpha\beta}$ ¹⁴ presupposes an inverse relation of atomic size and chemical hardness, which does not hold well for the hydrogen atom²⁶. To correct for this physical limitation, an empirical modification was made by including a damping term for γ_{XH} , where X is a heavy (non-hydrogen) atom. This systematically improves the description of hydrogen-bonding interactions by SCC-DFTB, as demonstrated by small water clusters and other hydrogen-bonding clusters¹⁵. The specific form of γ_{XH} after such “hydrogen-bonding correction” is as follows,

$$\gamma_{XH} = \frac{1}{R_{XH}} - S_{XH} \exp \left[- \left(\frac{U_X + U_H}{2} \right)^\zeta R_{XH}^2 \right], \quad (3)$$

where ζ is the only empirical and element-independent parameter, and $U_{X;H}$ is the Hubbard parameter, which is related to the atomic chemical hardness.

Another physically motivated improvement to SCC-DFTB is to include third-order terms in the Taylor expansion of charge fluctuations; this allows the chemical hardness (thus size) of an atom to depend on its charge. Since on-site (diagonal) third-order terms are particularly straightforward to include, they have been implemented first¹⁵ and the complete third-order version has been implemented⁴⁶ as this work was in progress. Test calculations on a fairly broad set of biologically relevant molecules suggest that including the third-order terms, even only the on-site terms, improves calculated proton affinities substantially^{15,46}; this is expected because losing a proton leads to a significant change in the size of the deprotonation site. With the on-site third-order terms in the expansion, an additional contribution to the total energy is included,

$$E^{3rd} = \frac{1}{6} \sum_{\alpha} U_{\alpha}^d \Delta q_{\alpha}^3, \quad (4)$$

where U_{α}^d is the charge derivative of the atomic Hubbard parameter $U_{\alpha}; U_{\alpha}^d$, which depends only on element type, can be either calculated or parameterized^{15,26,46}.

Finally, as mentioned in the Introduction, empirical calculations found that the standard OH repulsive potential, $V[\rho_0^O; \rho_0^H; R_{OH}]$ (see Eq.1), needs to be modified for a better description of

proton transfer barriers. More specifically, as reported in previous work⁹, the OH repulsive potential was modified as follows

$$U_{OH}^{Rep}(R) = U_{OH}^{Rep, std}(R) + a_1 \exp \left[-\frac{(R - a_2)^2}{a_3} \right] S(R), \quad (5)$$

To ensure that the Gaussian perturbation has the largest effect for O-H distances typically found in the barrier region so that hydrogen bonding energies are not spoiled, a switching function $S(R)$ (which differs from $S_{\alpha\beta}$ in Eqs.2,3) was used. The parameters a_1 , a_2 , a_3 and parameters in the switching function were optimized for DFTB2- γ^h using a genetic algorithm and the training set included binding energies, geometries, vibrational frequencies and proton transfer barriers for small gas phase clusters⁹.

In the rest of the paper, we will use the following notations⁴⁶ to denote the different variants of SCC-DFTB tested in this work. Standard second order SCC-DFTB¹⁴ as expressed in Eq.1 will be denoted as ‘DFTB2’. The “hydrogen-bonding correction”, as expressed by the modified γ_{XH} of Eq.3, is denoted by ‘ γ^h ’. For the third-order methods, the notation ‘DFTB3-dia’ will be used to denote the on-site third-order version of SCC-DFTB (set 5 in Table 2 of Ref.¹⁵), which involves adding Eq.4 to Eq.1; to be consistent with our more recent work⁴⁶, we note that the modified γ_{XH} is included in DFTB3-dia. In calculations where the modified O-H repulsive potential (Eq.5) is utilized, its usage will be indicated by the ‘gaus’ keyword; absence of ‘gaus’ indicates use of the standard O-H repulsive potential¹⁴. In all our DFTB2- γ^h (+gaus) calculations, the value of ζ (see Eq.3) is set to 4.50 whereas in the DFTB3-dia(+gaus) calculations, it is set to 4.95; in the recent study of bulk water (with/without an excess proton) with DFTB2- γ^h , Maupin et al.³¹ employed a value of 4.50 for ζ and reported that using a value of 4.88 did not lead to any significant changes.

B. Potential energy surface of the protonated water dimer

The structure of $H_5O_2^+$ is first optimized at the MP2/aug-cc-PVDZ⁴⁷ level, which gives an O-O distance of 2.399 Å. Keeping the terminal water molecules fixed at this MP2-optimized geometry, the shared proton is displaced along the line joining the two O atoms, with the O-O distance constrained to be 2.4, 2.54 and 2.6 Å, respectively. The energy profiles at the MP2/aug-cc-PVDZ level are compared to single point energies calculated with the different SCC-DFTB methods (see Sect.III for the list of SCC-DFTB methods tested).

C. Protonated water clusters $H^+(H_2O)_6$ and $H^+(H_2O)_{22}$

In the recent work of Choi et al.³⁰, SCC-DFTB was applied to eleven isomers of $H^+(H_2O)_6$ and thirteen isomers of $H^+(H_2O)_{22}$ as examined in their previous work⁴⁸. The same isomers that they studied are re-optimized with the different SCC-DFTB variants using CHARMM^{33,49}. The Zundel/Eigen character (see below) and the relative energies of the optimized structures (with respect to the most stable isomer *at the MP2 level*) from the different SCC-DFTB methods are compared to MP2 results.

While Choi et al. also accounted for dispersion interactions with an empirical formulation⁵⁰ in their calculations³⁰, we do not do so in this work. Since a major goal of this paper is to investigate the performance of the SCC-DFTB method for bulk water (with and without an excess proton), for which previous studies^{31,32} have not considered dispersion, we also do not include dispersion in this work.

D. The “magic” cluster $H^+(H_2O)_{21}$

The most stable isomer of the protonated water cluster, $H^+(H_2O)_{21}$, optimized with the ASP potential^{51,52} and available in the Cambridge Cluster Database⁵³ is used as the starting structure for our studies on this cluster. A conjugate gradient optimization is performed for the ASP potential optimized structure with the DFTB2 and DFTB3-diag+gaus methods. These optimized structures are then used as starting structures for gas-phase MD simulations with the respective SCC-DFTB methods. The simulations use the Andersen thermostat⁵⁴ with a re-selection probability of 0.02 and are carried out at temperatures of 50 K, 100 K, 145 K, 195 K and 245 K. Each simulation uses a time step of 0.5 fs and is 40 ps long, of which the last 25 ps are used for analysis. These calculations are carried out with DFTB+⁵⁵.

E. Bulk water, with and without an excess proton

The program CHARMM is used to classically equilibrate a box of 128 modified TIP3P water molecules. The equilibration involves a 500 ps long simulation in the NVE ensemble followed by a 1 ns long simulation in the NPT ensemble. Both the NVE and NPT simulations use periodic boundary conditions; electrostatics are treated by Particle Mesh Ewald (PME) while the potential shift method with a cutoff of 7.5 Å is used for Lennard-Jones interactions. Both simulations are carried out at 300 K and with a time step of 1 fs and the use of the SHAKE algorithm for constraining all bonds involving hydrogen. For the NPT simulation, the pressure is maintained at 1 atm using the extended system pressure/temperature control algorithm implemented in CHARMM⁵⁶. The entire equilibration procedure yields a cubic box of side 15.665 Å and density of 0.995 g/mL (experimental density = 0.997 g/mL⁵⁷). For the excess hydrated proton simulations, a proton is randomly added to this classically equilibrated box of water molecules and further equilibration at the SCC-DFTB level is carried out as described below.

All SCC-DFTB simulations for bulk water with and without an excess proton are carried out with the DFTB+ code⁵⁵. In all these simulations, SCC-DFTB convergence criteria of 10^{-6} atomic units is used. The electrostatics are treated by the supercell sampling method using the $2 \times 2 \times 2$ Monkhorst-Pack scheme.

For neutral bulk water, the classically equilibrated box is subjected to further equilibration at the SCC-DFTB level by running a 50 ps long NVT trajectory at 300 K using an Andersen thermostat with a re-selection probability of 0.2 and a time-step of 1 fs. Post equilibration, production run is carried out in the NVE ensemble with a time-step of 0.5 fs. A single 50 ps long trajectory is used to collect data for analysis; this is sufficient since all properties get averaged over a large number of water molecules.

For the bulk water simulations with an excess proton, two independent trajectories in the NVT ensemble are generated *for calculation of structural and thermodynamic properties*. The two trajectories are started from different initial coordinates as well as different velocity seeds. Both trajectories are 100 ps long and the last 75 ps are used for analysis. For these trajectories, an Andersen thermostat with a re-selection probability of 0.2 is used to maintain the temperature at 300 K. A time-step of 1 fs is used.

For calculation of the hydronium diffusion coefficient, three independent trajectories are initiated with different velocity seeds from three uncorrelated snapshots taken from the NVT simulations of the hydrated excess proton. These trajectories are run for 75–82 ps in the NVE ensemble with a time-step of 0.25 fs. Each of these three trajectories is then divided into two; one trajectory comprising of the first 35 ps and the other one comprising of the last 35 ps. So the analysis is done on 6 independent 35 ps long trajectories. The multiple time-origin method is used for enhanced statistics.

III. RESULTS AND DISCUSSIONS

A. Potential energy surface of the protonated water dimer

Fig. 1a–c show, for $H_5O_2^+$, the change in energy as the proton is displaced along the line joining the O atoms of the two water molecules, at fixed O–O distances of 2.4 Å, 2.54 Å and 2.6 Å respectively.

At an O–O distance of 2.4 Å, while both MP2 and SCC-DFTB predict a barrierless proton transfer from one water molecule to the other, the energy rises more sharply with the SCC-DFTB methods than with MP2 as the proton moves away from the midpoint between the O atoms. However, DFTB3-diag(+gaus) does show slight improvement over the second-order methods.

When the O atoms are separated by 2.54 Å, MP2 predicts a proton-transfer barrier of ~0.5 kcal/mol. With the standard O–H repulsive potential, both second-order and third-order SCC-DFTB, with/without the γ^h correction, predict a barrierless process. With the modified O–H repulsive potential, the barrier rises to ~0.5 kcal/mol with DFTB2- γ^h +gaus and ~1.2 kcal/mol with DFTB3-diag+gaus. It is worthwhile to mention here that the parameters for the Gaussian perturbation in the modified O–H repulsive potential were so developed that the O–H repulsive potential is changed only for O–H distances between ~1 Å and ~1.5 Å. That at an O–O distance of 2.54 Å, DFTB3-diag+gaus gives a barrier a bit too high, in part, stems from the fact that this method with the original O–H repulsive potential gives improved energetics for the proton movement away from the midpoint between the O atoms. Since the bump in the repulsive potential depends only on the precise value of the O–H distance, at all O–H distances, both DFTB2- γ^h and DFTB3-diag energies are bumped up by the same amount. However, since the DFTB3-diag energy is lower than DFTB2- γ^h as the proton localizes onto the oxygen atoms, the computed barrier for proton transfer becomes higher with DFTB3-diag+gaus.

Finally, at the O–O separation of 2.6 Å, while DFTB3-diag gives an appreciable barrier unlike at smaller O–O distances, it still under-estimates the barrier compared to MP2. On the other hand, use of the modified O–H repulsive potential in DFTB2- γ^h +gaus and DFTB3-diag+gaus leads to barriers substantially higher (by ~1–2 kcal/mol) compared to MP2. We note, on the other hand, previous studies^{58,59} have reported that the more reliable CCSD(T) gives a barrier 0.3–0.4 kcal/mol higher than MP2 with the use of the cc-PVTZ basis set. Pavese et al.⁵⁹ also reported that for an O–O distance of 2.6 Å, the CCSD(T) barrier is further raised by 0.3–0.4 kcal/mol by the addition of diffuse functions. Hence, overall, the CCSD(T) barrier would be quite close to the barrier from DFTB2- γ^h +gaus.

Hence, although the use of the modified repulsive potential tends to overestimate the proton-transfer barrier in $H_5O_2^+$, including this contribution is essential for eliminating the bias towards the Zundel structure. It is noted that the DFTB3-diag+gaus method predicts minima in the 2.6 Å potential energy curve at O–H distances such that the proton is further away from the mid-point between the O atoms, predicting an equilibrium geometry which is slightly more Eigen in character than that predicted by MP2.

Although the results above would lead one to speculate that DFTB3-diag+gaus would over-tilt the Eigen-Zundel balance in favor of Eigen while the bias towards Eigen is more reasonable with DFTB2- γ^h +gaus, we show below that for larger protonated water clusters and for bulk water with an excess proton, DFTB3-diag+gaus in fact predicts a better Eigen-Zundel balance than DFTB2- γ^h +gaus. This is possibly related to the fact that the training set for developing the Gaussian perturbation in the O–H repulsive potential included only small gas-phase systems. For example, that even DFTB2- γ^h +gaus gives a barrier higher than

expected at O-O distance of 2.6 Å is because the training set included proton-transfer barrier in $H_5O_2^+$ only at an O-O separation of 3 Å.

B. Protonated water clusters $H^+(H_2O)_6$ and $H^+(H_2O)_{22}$

Choi et al.³⁰ used the DFTB2 and DFTB3-diag methods with dispersion correction to study the protonated water clusters $H^+(H_2O)_6$ and $H^+(H_2O)_{22}$. Using the original O-H repulsive potential, they reported that both SCC-DFTB methods are biased towards Zundel structures compared to MP2. We carry out similar calculations with the DFTB2, DFTB2- γ^h +gaus, DFTB3-diag and DFTB3-diag+gaus methods without dispersion correction to test whether use of the modified O-H repulsive potential shows an improvement in the Eigen-Zundel balance in various isomers of these two clusters. Since for $H_5O_2^+$, proton transfer barriers from DFTB2- γ^h are very similar to those from DFTB2, we do not expect DFTB2- γ^h to perform any better than DFTB2 for the larger clusters. Hence we do not test DFTB2- γ^h for these clusters.

The criteria for classifying a structure as Zundel/Eigen are not unambiguous. Choi et al.³⁰ used the OO distance to categorize structures as Zundel or Eigen (Zundel, $R_{OO} < 2.46$ Å; Eigen, $R_{OO} > 2.49$ Å; intermediate, $2.46 \text{ Å} < R_{OO} < 2.49 \text{ Å}$). On the other hand, Maupin et al.³¹ used $\delta = |\vec{r}_{O_0H} - \vec{r}_{O_{1x}H}|$ as the basis for classification (Zundel, $\delta \leq 0.1$; Eigen, $\delta \geq 0.2$; intermediate, $0.1 < \delta < 0.2$). Here, O_0 corresponds to the “hydronium oxygen” (the oxygen most closely associated with the excess proton) and O_{1x} is the “special pair” nearest oxygen to O_0 ³⁵. We use both R_{OO} and δ based criteria for the Zundel/Eigen classification; Zundel is denoted as ‘Z’, eigen as ‘E’ and intermediate as ‘E-Z’.

Tables I and II show the results for $H^+(H_2O)_6$. In the column for each method in Table I, the three sub-columns stand for the energy relative to isomer VI (which is the most stable isomer at the MP2 level, along with isomer V), the E/Z classification based on R_{OO} and the E/Z classification based on δ , respectively. It is clear that DFTB3-diag+gaus gives significant improvement in relative energies and the E/Z balance over the other SCC-DFTB methods. For example, both DFTB2 and DFTB3-diag overestimate the Zundel character of several isomers, while the situations improves significantly at both second and third-order levels once the Gaussian perturbation potential is included. In terms of RMSE in the relative energies, DFTB3-diag+gaus and DFTB2- γ^h +gaus give comparable results of ~1 kcal/mol. We note that at both levels, there are isomers that have lower energies than isomers V/VI, which are the lowest minima at the MP2 level; the energy differences (both relative to isomers V/VI and relative to the MP2 results), however, are less than 1 kcal/mol.

Fig. 2a,b show the MP2/aug-cc-PVDZ optimized structures⁴⁸ of a low-energy Eigen isomer (isomer VII) and a low-energy Zundel isomer (isomer IX) respectively of $H^+(H_2O)_6$. Fig. 2a indicates that DFTB3-diag+gaus predicts longer hydrogen bonds than MP2 around the Eigen core, which is also found in bulk results (see Sect.III E). The bond lengths and bond angles of the central hydronium are not shown in this figure because they are quite similar from the two methods. The three hydronium bond lengths are 1.008, 1.008 and 1.024 Å from DFTB3-diag+gaus while the corresponding MP2 values are 1.010, 1.011 and 1.034 Å. Also, the DFTB3-diag+gaus bond angles are 106°, 112° and 112° while the corresponding MP2 values are 105°, 111° and 112°. The fact that DFTB3-diag+gaus predicts slightly shorter O-H bonds and slightly larger H-O-H angles for the central hydronium in this water cluster is also observed in an isolated H_3O^+ , as shown in Fig. 2c.

For isomer IX, Fig. 2b shows that DFTB3-diag+gaus predicts a very symmetrical structure for this Zundel cluster, unlike MP2. Also, shorter hydrogen bonds within the Zundel core and larger H-O-H bond angles for the water molecules sharing the excess proton are observed with DFTB3-diag+gaus. Fig. 2d shows that the general trends are very similar in

an isolated $H_5O_2^+$. How much these subtle differences in the bond length and bond angle values highlighted in Fig. 2 affect the energies of the different isomers of $H^+(H_2O)_6$ is not clear. However, as discussed in later sections, a more clear picture emerges concerning how DFTB3-diag+gaus differs from high-level methods and available experimental data in the overall local solvation pattern around an excess proton.

Tables III and IV summarize results for different isomers of $H^+(H_2O)_{22}$. The relative energies are calculated with respect to isomer A. Here, DFTB3-diag+gaus does not show improvement in relative energies over DFTB3-diag but the E/Z balance predicted by DFTB3-diag+gaus is in much better agreement with MP2 results; by comparison, DFTB2- γ^h +gaus gives the correct E/Z balance for only 9 out of 13 cases. Still, DFTB3-diag predicts the wrong global minimum compared to MP2 (see Supporting Information for structures and additional discussions).

It is clear from the results for the two clusters that the high barriers for proton transfer in $H_5O_2^+$ with DFTB3-diag+gaus do not spoil its ability to describe the E/Z balance in large protonated water clusters. While one might argue that the high proton transfer barriers with DFTB3-diag+gaus are responsible for predicting Eigen character of all the isomers of $H^+(H_2O)_{22}$, it is important to note that this method predicts the same two isomers of $H^+(H_2O)_6$ as having Zundel character as MP2. Hence it seems that DFTB3-diag+gaus provides a proper description of the Zundel/Eigen balance in large protonated water clusters, which is also supported by the bulk results discussed below.

The DFTB2- γ^h +gaus method, which gives more reasonable barriers for proton transfer in $H_5O_2^+$, is unable to give the correct E/Z balance for larger water clusters, possibly reflecting the limitations of the training set for the parametrization of the Gaussian bump in the O-H repulsive potential. Since bulk water calculations are expensive and DFTB3-diag+gaus seems to be the only SCC-DFTB method that provides a satisfactory E/Z balance in large protonated water clusters, we limit ourselves below to this method for describing bulk water with an excess proton.

C. The “magic” cluster $H^+(H_2O)_{21}$

From studies on the protonated water clusters $H^+(H_2O)_6$ and $H^+(H_2O)_{22}$ as described above, we would expect DFTB3-diag+gaus to give a better description than DFTB2 or DFTB2- γ^h for the Zundel-Eigen balance in bulk water with an excess proton. However, before we go on to confirm this, it is useful to check whether a good description of the structural properties and Zundel/Eigen balance in large protonated water clusters is maintained at finite temperature by conducting MD simulations with DFTB3-diag+gaus. To this end, we summarize here results on the so-called “magic” cluster $H^+(H_2O)_{21}$ from DFTB2 and DFTB3-diag+gaus.

Fig. 3a and 4a show the O-O radial distribution function (RDF) for $H^+(H_2O)_{21}$ from DFTB2 and DFTB3-diag+gaus simulations, respectively. Similar CPMD calculations (using the BLYP functional) on this cluster have been reported by Kim et al.⁶⁰. The positions of the peaks from both DFTB2 and DFTB3-diag+gaus show good agreement with those from CPMD-BLYP as reported by Kim and co-workers. Similar to CPMD-BLYP results, the second and third hydration shells (4.1, 4.7 Å) begin merging at 145 K and are indistinguishable at 195 K and 245 K. However, there are some differences to be noted between the RDFs from DFTB2 and DFTB3-diag+gaus. At all temperatures, the first peak in the RDF from DFTB2 is broader than that in the RDF from DFTB3-diag+gaus, implying an over-solvation tendency of DFTB2 which we also notice for neutral bulk water (see below). The first peak is not sharp in the RDF from DFTB2, indicating more Zundel-like

character of the hydrated excess proton, which will be discussed in detail in the section on the excess proton in bulk.

Fig. 3b and 4b show the O-H RDF for $H^+(H_2O)_{21}$ from DFTB2 and DFTB3-diag+gaus methods, respectively. Similar to the O-O RDFs, the O-H RDFs also show good agreement with CPMD-BLYP results in terms of peak positions and temperature dependence.

In Fig. 5, the Zundel/Eigen population in $H^+(H_2O)_{21}$ at different temperatures is shown with both DFTB2 and DFTB3-diag+gaus methods. Kim et al.⁶⁰ reported that with CPMD-BLYP, the hydrated proton remains in the Eigen form below 100 K. With rising temperature, the population of Zundel form increases: from about 1% at 125 K to ~ 20% at 270 K. Results from DFTB3-diag+gaus are in quite good agreement with this, the Zundel form increasing from 0% at 50 K to ~ 27% at 245 K. However, with DFTB2, the Zundel form is already ~ 10% at 50 K and then rises rapidly with increasing temperature until at higher temperatures, the Zundel population becomes higher than the Eigen population. This reflects the tendency of DFTB2 to stabilize the Zundel form more than the Eigen form as we have already seen in previous sections. This also raises the hope that DFTB3-diag+gaus gives a good description of the Zundel/Eigen population in bulk water with an excess proton.

D. Neutral bulk water

Before looking at the performance of DFTB3-diag+gaus for bulk water with an excess proton, it is worthwhile to examine how third-order SCC-DFTB performs for neutral bulk water. Recent studies³¹ applied the DFTB2 and DFTB2- γ^h variants of SCC-DFTB to neutral bulk water but did not test the DFTB3-diag method, which has been shown by Yang et al.¹⁵ to give better binding energies for neutral water clusters than the other two methods. Table V shows binding energies of small neutral water clusters¹⁵. The error in the binding energies is considerably smaller with the use of DFTB3-diag than with DFTB2 and DFTB2- γ^h . Since the bulk properties are likely correlated with the description of hydrogen bonding interactions in water clusters, we expect that DFTB3-diag performs better for bulk water than the second-order variants. Since the Gaussian perturbation applies only to barrier regions with O-H distances around 1.4 Å, we do not expect it to make any major contribution to bulk water properties and therefore include the “gaus” variants only in the next section on hydrated excess proton.

Fig. 6a–c show the O-O, O-H and H-H RDF, respectively, for neutral bulk water calculated with DFTB3-diag, in comparison to the CPMD-HCTH, DFTB2 and DFTB2- γ^h results from Maupin et al.³¹; experimental data⁶¹ are also shown.

The O-O RDF from DFTB3-diag shows a slight improvement over the O-O RDF from DFTB2 and DFTB2- γ^h in the sense that it shows a more pronounced second solvation shell, which is also shifted to slightly smaller distances than the DFTB2 and DFTB2- γ^h methods. Table VI shows that while DFTB2 and DFTB2- γ^h tend to largely overestimate the number of waters in the first solvation shell³¹, DFTB3-diag performs better with the integration of the first solvation shell giving a value of 5.9 compared to the experimental⁶¹ value of 4.7; although this is clearly far from being perfect, the improvement over DFTB2 and DFTB2- γ^h is significant. The O-H RDF and the H-H RDF do not show significant deviations from the results with the other SCC-DFTB methods, which already are in good agreement with experimental and CPMD-HCTH results.

The diffusion coefficient for bulk water, as shown in Table VII, also improves with DFTB3-diag. Compared to the experimental value of 0.23 Å²/ps, the value from DFTB3-diag is 0.38±0.03 Å²/ps, which is a notable improvement over diffusion coefficients of ~1.11 Å²/ps and ~0.65 Å²/ps from DFTB2 and DFTB2- γ^h respectively.

Apart from the binding energies of water clusters, Table VIII shows that DFTB3-diag yields a heat of vaporization of 8.5 kcal/mol, which is closer to the experimental value of 10.5 kcal/mol than the values of ~4 and ~7 kcal/mol from DFTB2 and DFTB2- γ^h respectively. These observations are consistent with the better performance of DFTB3-diag compared to DFTB2 and DFTB2- γ^h in terms of the description of hydrogen bonding interactions (Table V).

E. Bulk water with an excess proton

Since only DFTB3-diag+gaus is able to give a satisfactory description of the Eigen-Zundel balance in large protonated water clusters, we carried out simulations for bulk water with an excess proton using this SCC-DFTB method and compared our results to results for DFTB2 and DFTB2- γ^h from Maupin et al.³¹ as well as to other data cited therein.

Fig. 7 shows the RDF for water oxygen atoms around the hydronium oxygen atom (the hydronium oxygen atom is defined as the oxygen with the nearest three H atoms). This RDF reflects the overall solvation structure of the hydrated excess proton. Comparison to experimental^{62,63} and CPMD-HCTH³¹ results is also shown. The experimental data were obtained by empirical potential structure refinement (EPSR) of neutron diffraction data^{62,63}.

A major improvement that can be seen in the RDF with the use of DFTB3-diag+gaus is a non-bifurcated and sharp first peak whose height agrees well with EPSR and CPMD-HCTH results. With the use of the DFTB2 and DFTB2- γ^h methods, Maupin et al.³¹ reported (as shown in the figure) a bimodal distribution in the first peak and reasoned that this indicates a pre-dominance of Zundel-like structures in solution, with the first subpeak corresponding to the Zundel partner (which is considerably closer than the other water O atoms) and the second subpeak representing the other solvating waters in the first solvation shell. However, with DFTB3-diag+gaus, the non-bifurcated first peak indicates that the Eigen form is favored in solution.

Fig. 8 shows that this peak does not arise from three equivalent hydrogen bonds in the first shell of H_3O^+ . In fact, DFTB3-diag+gaus does predict a distorted Eigen structure for the hydrated excess proton as reported in previous studies³⁵. One of the solvating water molecules, O_{1x} , is closer than the other two, forming a “special pair”³⁵. The other two water molecules hydrogen-bonded to the hydronium hydrogen atoms are O_{1y} and O_{1z} , O_{1y} being closer than O_{1z} . However, it should be noted that the total contribution from these three water molecules does not account for the entire first solvation shell. This reflects the overcoordination of the hydronium as mentioned below.

That the distorted Eigen cation is not a static structure is shown by Fig. 9a,b. The long horizontal segments in the plot of O_0 identity versus frame number indicate long non-transfer intervals in which the excess proton resides on a particular O atom. The O_{1x} identity does not remain fixed during such segments but keeps oscillating between the solvating waters of the hydronium, thus leading to the “special pair dance”³⁵. Compared to DFTB2 and DFTB2- γ^h , the plot of O_0 identity shows very few thick vertical regions, i.e. very few Zundel regions. This reflects the reduced stability of the Zundel form with DFTB3-diag+gaus, further supported by PMF calculations described below. Hence, in short, in agreement with previous studies³⁵, DFTB3-diag+gaus predicts a distorted Eigen form of the hydrated proton, which is a dynamic species.

The first peak of the RDF in Fig. 7 seems to be shifted to the right and broader compared to the experimental (EPSR) and CPMD-HCTH results. It is worthwhile to mention here, as has been mentioned in the literature^{31,37}, that the neutron diffraction experiments^{62,63} were done for highly concentrated HCl solutions and the EPSR used a classical non-dissociable model

of the hydronium ion. The much sharper character of the experimental peak might be because a first shell water molecule of the hydronium ion gets replaced by a Cl^- ion in the experiments (due to the high HCl concentration). The broad first depression for DFTB3-diag+gaus is possibly a reflection of the underlying neutral water radial distribution function discussed above (Fig. 6).

The position of the second solvation shell for DFTB3-diag+gaus is, encouragingly, in good agreement with the EPSR data. The amplitude is improved compared to DFTB2 and DFTB2- γ^h but is lower compared to CPMD-HCTH results. It should be noted here that MS-EVB3³⁷ also has the amplitude and position of the second peak in better agreement with EPSR than with CPMD-HCTH. It has been argued³⁷ that the lack of electronic polarizability in the SPC-Fw model (which is what MS-EVB3 is based on) and the concentration of all the excess charge on the hydronium ion in EPSR underestimate ion-water interactions, leading to a less structured second solvation shell. However, to what degree this is true is not clear since it has been shown^{64,65} that the presence of ions in water does not affect water molecules beyond the first solvation shell. The fact that CPMD-HCTH predicts a higher amplitude of the second solvation peak might be related to the over-structuring of the second solvation peak of the O-O RDF even for neutral water by CPMD-HCTH (see Fig. 6a).

Integration of the first peak yields the coordination number of the hydronium ion as shown in Table IX. While DFTB3-diag+gaus shows slight improvement over DFTB2 and DFTB2- γ^h , it still predicts more than 4 water molecules around the central hydronium compared to 3 from CPMD-HCTH.

Further insight into the solvation structure around the hydronium is provided by the radial distribution function of oxygen atoms around O_{1x} , the “special-pair” partner of the hydronium. Fig. 10a shows that the first solvation peak of $g_{\text{O}_{1x}-\text{O}}$ from DFTB3-diag+gaus is quite different from the CPMD-HCTH result. Instead of two distinct sub-peaks as in CPMD-HCTH, there is a merging of the two sub-peaks in DFTB3-diag+gaus. This is because the distance between the hydronium O and O_{1x} is larger in DFTB3-diag+gaus, evident from the fact that in Fig. 8, the $\text{O}_0 - \text{O}_{1x}$ peak, after decomposition, has a maximum at 2.55 Å, as opposed to ~2.45 Å in CPMD-HCTH³¹. Thus the two sub-peaks partly merge with each other. The second sub-peak is quite higher and broader than that from CPMD-HCTH, suggesting over-solvation. Table IX shows that the integration of the entire first peak for DFTB3-diag+gaus gives a value of 5.4 compared to 3.1 for CPMD-HCTH. The broader first peak also causes the shift of the second peak to longer distances. However, the amplitude of the second-peak is improved compared to DFTB2 and DFTB2- γ^h , probably because of the more structured second solvation shell for neutral water as well (Fig. 6a) when third-order SCC-DFTB is employed.

As shown in Fig. 10b, the first peak of the radial distribution function for oxygen atoms around O_{1y} and O_{1z} is also slightly shifted to longer distances compared to CPMD-HCTH. Similar to the trends seen in $g_{\text{O}_{1x}-\text{O}}$, the peak is also higher and broader. That over-solvation occurs in this case too is reflected by an integrated value of the first peak of 6.1, compared to 3.7 for CPMD-HCTH. The fact that use of third-order SCC-DFTB improves the structure of neutral water leads to a higher amplitude of the second solvation peak, compared to DFTB2 and DFTB2- γ^h .

To confirm that the oversolvation of the hydronium is not due to hydrogen bonds being donated to it from the lone-pair side, we compute the radial distribution of hydrogen atoms around the hydronium O, shown in Fig. 10c. Integration of $g_{\text{O}_0-\text{H}}$ upto 2 Å (region not included in Fig. 10c) gives a value of exactly 3, confirming that no hydrogen bonds are being donated to the hydronium O. $g_{\text{O}_0-\text{H}}$ is negligible upto 2.5 Å, further confirming that

the lone-pair side of the hydronium constitutes a 'hydrophobic face', as has been proposed in the literature⁶⁶. The overall nature of the distribution agrees well with MS-EVB3 data; however, the first peak is higher and broader, in turn shifting the second peak to longer distances. Integration of the first peak gives a value of ~ 16 , opposed to 10–12 for the experimental and MS-EVB3 curves³⁷.

Further evidence for the fact that the hydrogen bonds between the hydronium and its three solvating water ligands are longer for DFTB3-diag+gaus than for other methods like MS-EVB3 is provided by the RDF for the water O atoms around the hydronium H atoms. Fig. 10d shows that while g_{H_0-O} from MS-EVB3 has a shoulder, corresponding to the Zundel form, in the first peak, the first peak for DFTB3-diag+gaus has two distinct sub-peaks, representing the Zundel and Eigen forms. This reflects that for the Eigen form of the hydrated proton, DFTB3-diag+gaus leads to longer $O_0 - H_0 - O$ hydrogen bonds, which is also observed in gas phase clusters (see Fig. 2). Note that the experimental first peak does not show a shoulder corresponding to the Zundel form since a classical non-dissociable model for the hydronium was used in the EPSR calculations. Since the water molecules directly hydrogen-bonding to H_0 are at longer distances, the second shell of water molecules also occurs at longer distances. Oversolvation is again reflected in the much higher first minimum for DFTB3-diag+gaus. The fact that bifurcated hydrogen bonds of H_0 with water molecules are not responsible for the oversolvation around the hydronium generally reflected in all the RDFs is proved by the integration of the DFTB3-diag+gaus curve upto 2 Å, which gives a value of 1.

To gain insight into the nature of the oversolvation of the hydronium, we calculate the spatial distribution function (SDF⁶⁷) of water O atoms around the hydronium O. The principal coordinate frame is defined as in Fig. 11, which shows the SDF of water O atoms around O_0 . At distances less than 2.75 Å, the maximum contribution is from the water molecules hydrogen-bonded to the hydronium H atoms. On the other hand, there is little contribution from water molecules on the lone-pair side of the hydronium. At distances between 2.75 Å and 3.05 Å, contribution from water molecules on the lone-pair side and those in the spaces between the H-bond acceptor water molecules starts becoming appreciable. There is also a significant density of water molecules below the hydronium. For distances between 3.05 Å and 3.5 Å, the population of H-bond acceptor water molecules is negligible. At these distances, there is appreciable contribution from water molecules on the lone-pair side and in the spaces between the H-bond acceptor water molecules. Comparison with the SDFs in Ref.³⁷ shows that for distances between 3.05 Å and 3.5 Å, MS-EVB3 predicts lower water population in the spaces between the acceptor water molecules than DFTB3-diag+gaus. Hence it is possible that the overcoordination behavior around the hydronium with DFTB3-diag+gaus arises partly due to large water population in the spaces between the water molecules hydrogen-bonded to the hydronium.

Careful examination of the various radial distribution functions for the hydrated proton reveals that $g_{H_0-O}(r)$ can be useful in further understanding the origin of the oversolvation. The reason is that in the other RDFs, over-solvation leads to the rise in height of some non-zero minimum. On the other hand, in $g_{H_0-O}(r)$, the minimum between 2 Å and 2.5 Å is almost zero in both the experimental and MS-EVB3 curves while its height is quite significant in the DFTB3-diag+gaus curve. Thus, looking into the spatial distribution of O atoms between 2 Å and 2.5 Å of the hydronium H atoms for DFTB3-diag+gaus can provide a clear picture of the oversolvation. This is made easier by the fact that the experimental, MS-EVB3 and DFTB3-diag+gaus curves, all integrate to 1 upto 2 Å. Fig. 12 shows that within 2 Å of the hydronium H atoms, the sole contribution is from the water molecules directly H-bonded to the hydronium H atoms. Between distances of 2 Å and 2.5 Å from the H_0 atoms, there is large contribution from water molecules below the hydronium and in the

spaces between the H-bond acceptor water molecules, trailing upto the lone-pair side of the hydronium. Hence, overall, it seems that DFTB3-diag+gaus has a tendency to over-estimate the population of water molecules in the so-called “interstitial” sites around the hydronium.

By potential of mean force (PMF) calculations, Maupin et al.³¹ determined the free energy difference between Eigen and Zundel species in solution for the DFTB2 and DFTB2- γ^h methods and also for CPMD-HCTH. Results from similar calculations with the DFTB3-diag+gaus method (along with CPMD-HCTH, DFTB2 and DFTB2- γ^h results from Maupin et al.) are presented in Fig. 13. The reaction coordinate used is the same as the one used by Maupin et al.³¹. More specifically, it is $\delta = |\vec{r}_{O_0H} - \vec{r}_{O_{1x}H}|$ where O_0 and O_{1x} are the same as explained before (in the section on protonated water clusters). As before, $\delta \leq 0.1$ corresponds to Zundel species and $\delta \geq 0.2$ corresponds to Eigen species.

Fig. 13 shows that while CPMD-HCTH predicts the Eigen form to be ~ 0.6 kcal/mol more stable than the Zundel form, both DFTB2 and DFTB2- γ^h place the minimum of the free energy curve at the Zundel species. On the basis of this, Maupin et al.³¹ explained that while CPMD-HCTH (and experiments) support an Eigen-Zundel-Eigen mechanism for proton transport in bulk water, SCC-DFTB predicts a Zundel-Zundel mechanism. However, when the modified O-H repulsive potential is employed as in DFTB3-diag+gaus, the PMF clearly shows a minimum at $\delta \approx 0.5$, which corresponds to the Eigen form of the hydrated proton. The free-energy difference between the Eigen and Zundel forms is ~ 0.4 kcal/mol, in good agreement with the CPMD-HCTH results. The two major differences with the CPMD-HCTH results are in the position of the minimum and in the barrier for the proton transfer between the two species. The occurrence of the minimum of the PMF at larger δ value for DFTB3-diag+gaus possibly arises from the larger distance at which the first solvation peak occurs in the radial distribution function for water O atoms around the hydronium O (see Fig. 7). The DFTB3-diag+gaus method does give a barrier of ~ 0.9 kcal/mol for proton transfer, unlike CPMD-HCTH in which the free energy rises monotonically from the Eigen to the Zundel ion. Still, the DFTB3-diag+gaus results compare favorably with previous work. Wu et al.³⁷ used different versions of the MS-EVB method to estimate the free energy difference between Eigen and Zundel species as well the free energy barrier for proton transfer in solution. Both the (classical) MS-EVB2 and the MS-EVB3 models predict a value of ~ 1 kcal/mol for both quantities, which were close to the estimate of ~ 0.6 kcal/mol by Agmon⁶⁸.

The proton diffusion constant is a property that further illustrates how the excess proton is transported through the hydrogen bond network in bulk water. Table VII shows the diffusion constant of H_3O^+ in bulk water from DFTB3-diag+gaus, compared to published values for other theoretical methods³¹. The value of $0.66 \pm 0.20 \text{ \AA}^2/\text{ps}$ from DFTB3-diag+gaus is lower than the experimental value⁶⁹ of $0.94 \pm 0.01 \text{ \AA}^2/\text{ps}$. It is however, an improvement over the values of 0.36 ± 0.02 , 0.29 ± 0.03 and 0.50 ± 0.05 reported for MS-EVB2, MS-EVB3 and qMS-EVB3 respectively³⁷. However, $D_{H_3O^+}$ is a quantity strongly affected by the underlying water diffusion constant and it is more reasonable to compare, for different methods, the ratio $D_{H_3O^+}/D_{H_2O}$ which reflects the enhancement of proton diffusion through the Grotthuss mechanism^{70,71}. The experimental value for this ratio is an anomalously high 4.09, and CPMD-HCTH gives a value of 3.30; DFTB3-diag+gaus gives a lower ratio of 1.74. The latter is, though, an improvement over DFTB2 and DFTB2- γ^h . For this ratio, MS-EVB calculations³⁷ reported values of 1.02, 1.26 and 2 from MS-EVB2, MS-EVB3 and qMS-EVB3 respectively. The value for qMS-EVB3 was obtained through centroid molecular dynamics (CMD) and accounted for nuclear quantum effects on the proton diffusion. Hence, inclusion of nuclear quantum effects enhances $D_{H_3O^+}$ for MS-EVB3 by a factor of ~ 1.7 and it was argued³⁷ that an improved description of the coherent contribution to quantum tunneling by CMD would further enhance the diffusion constant by a factor of

about 1.3, thus predicting an overall ~ 2 -fold increase in $D_{H_3O^+}$ due to nuclear quantum effects. If we consider a similar enhancement factor for DFTB3-diag+gaus, the $D_{H_3O^+}/D_{H_2O}$ value will be in quite good agreement with the experimental result.

IV. CONCLUDING REMARKS

Due to its higher computational efficiency compared to popular *ab initio* QM methods, SCC-DFTB has become a useful tool in the study of chemical and biological systems^{9,26,44,45}. Since it is semi-empirical in nature, it is important to carefully benchmark its accuracy in the context of the problem under investigation.

In this work, stimulated in part by recent benchmark studies^{30,31}, we explore the applicability of several published SCC-DFTB variants to protonated water clusters and bulk water. We show that significant improvement in the description of the hydrated excess proton in gas-phase clusters and in bulk water can be achieved when SCC-DFTB is used with the inclusion of the third-order term in the DFT energy expansion, coupled to a modified O-H repulsive potential published in our previous work⁹. The use of third-order SCC-DFTB also improves the structural, energetic and dynamical properties of neutral bulk water. The most important result of this work is that, with the proper set of published parameters, SCC-DFTB does favor the Eigen form of the hydrated excess proton over the Zundel form, in the gas phase as well as in bulk, in agreement with high-level calculations and photoelectron spectroscopy experiments. Besides this, we observe a distorted nature of the Eigen cation, with one of the three water ligands involved in a “special pair”³⁵ and the identity of the latter changing rapidly during non-proton-transfer intervals. The Grotthuss enhancement of the proton diffusion is smaller in magnitude compared to experiments, although the inclusion of nuclear quantum effects is expected to improve this, as discussed in recent studies using MS-EVB models. Another encouraging observation is that the hydronium seems to have a “hydrophobic” face on its lone-pair side, giving it an amphiphilic nature as has been proposed in the literature^{66,72}.

There are still remaining limitations of the method. There seems to be a tendency of SCC-DFTB to favor small rings around the hydronium in the gas phase, which affects the relative stabilities of different isomers of gas-phase clusters and translates to over-solvation of the hydronium in the bulk phase. Also, the hydrogen bonds between the hydronium and its three water ligands are predicted to be longer than by experiments and other theoretical methods. The structural feature of bulk water also requires further improvements.

These shortcomings of SCC-DFTB variants that we and others^{30–32} come across can guide future development of the method. Along this line, it is of interest to carry out similar benchmark calculations for the full third-order variant of SCC-DFTB⁴⁶, which also includes non-diagonal third-order contributions and was found to yield even more systematic improvements for both hydrogen-bonding interactions and proton affinities beyond DFTB2 as compared to DFTB3-diag. Recent studies in the literature have also highlighted the effect of including dispersion interactions on the solvation structure of bulk water⁷³. It has been shown that including dispersion effects can lead to increased population in the “interstitial sites” around water molecules and destroy the tetrahedral coordination. While this work does not take dispersion into account in the calculations, this is one issue worth investigating in future work. Moreover, studying the structural and spectroscopic signatures of water interface, with and without an excess proton or hydroxide, will shed further light into the applicability and limitations of SCC-DFTB.

Finally, we note that although it is of great fundamental interest to improve SCC-DFTB for both gas-phase clusters and bulk water properties, whether the limitations we have discussed have a major impact on the study of proton transport in biomolecules is likely very case

dependent. As emphasized in the Introduction, since protein groups involved in proton transport often have much more heterogeneous pK_a values than water in bulk solution, benchmark calculations using cluster models are likely more informative; the other important guideline for setting up a proper computational model is to reproduce experimental pK_a values of relevant groups^{4,25}.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(a) O-O distance: 2.4 Å

(b) O-O distance: 2.54 Å

(c) O-O distance: 2.6 Å

FIG. 1. Potential energy surface of the gas-phase protonated water dimer $H_5O_2^+$ for different values of the O-O distance. Note that the modified γ_{XH} is included in DFTB3-dia and DFTB3-dia+gaus.

(a) Isomer VII of $H^+(H_2O)_6$ (b) Isomer IX of $H^+(H_2O)_6$ (c) Isolated H_3O^+ (d) Isolated $H_5O_2^+$

FIG. 2. MP2/aug-cc-PVDZ optimized structures⁴⁸ of two isomers of $H^+(H_2O)_6$, gas-phase H_3O^+ and gas-phase $H_5O_2^+$. Values without parentheses are from DFTB3-diag+gaus while those in parentheses are from MP2/aug-cc-PVDZ.

FIG. 3. Radial distribution functions at different temperatures for the “magic” cluster $H^+(H_2O)_{21}$ from gas-phase MD simulations using the DFTB2 method: (a) oxygen-oxygen (b) oxygen-hydrogen. The insets provide a magnified view of parts of the main figure.

FIG. 4. Radial distribution functions at different temperatures for the “magic” cluster $H^+(H_2O)_{21}$ from gas-phase MD simulations using the DFTB3-diag+gaus method: (a) oxygen-oxygen (b) oxygen-hydrogen. The insets provide a magnified view of parts of the main figure.

FIG. 5. Population of Zundel and Eigen forms at different temperatures for the “magic” cluster $H^+(H_2O)_{21}$ from gas-phase MD simulations using the DFTB2 and DFTB3-diag+gaus methods.

(a)

(b)

(c)

FIG. 6. Radial distribution functions for neutral bulk water: (a) oxygen-oxygen (b) oxygen-hydrogen (c) hydrogen-hydrogen. The experimental data is from Ref.⁶¹. CPMD-HCTH, DFTB2 and DFTB2- γ^h results are from Ref.³¹.

FIG. 7.

Radial distribution function for water oxygen atoms around the hydronium oxygen in bulk water with an excess proton. O_0 represents the hydronium oxygen atom. The hydronium O is determined by a geometric criterion: it is the oxygen with the closest three H atoms. Experimental EPSR data is from Refs.^{62,63}. The CPMD-HCTH, DFTB2 and DFTB2- γ^h results are from Ref.³¹.

FIG. 8.

The decomposition of the first solvation peak of the hydronium O - water O radial distribution function for bulk water with an excess proton. The data shown is for one of the two independent 75 ps production runs. The curves labeled X, Y and Z represent the contributions of O_{1x} , O_{1y} and O_{1z} respectively (see text for definition). The curve labeled X + Y + Z represents the total contribution from these three atoms and that labeled 'all' represents the $g(r)$ for all the water O atoms.

(a)

(b)

FIG. 9.

The evolution of the identity of (a) O_0 and (b) O_{1x} with time. The data shown is for one 35 ps NVE trajectory. In the plot of O_0 identity versus frame number, the dark, thick vertical regions are indicative of a Zundel species while the long horizontal segments represent non-transfer intervals in which the proton exists as an Eigen species.

FIG. 10.

For (a) and (b), the CPMD-HCTH, DFTB2 and DFTB2- γ^h results are from Ref.³¹. For (c) and (d), experimental EPSR data is from Refs.^{62,63} and MS-EVB3 data is from Ref.³⁷. (a)Radial distribution function for oxygen atoms around O_{1x} in bulk water with an excess proton. O_{1x} is the “special pair” partner of the hydronium oxygen. (b)Radial distribution function for oxygen atoms around O_{1y} and O_{1z} in bulk water with an excess proton. O_{1y} and O_{1z} are farther than O_{1x} from the hydronium oxygen. (c)Radial distribution function for hydrogen atoms around the hydronium oxygen, O_0 , in bulk water with an excess proton. Note that only the RDF beyond 2.0 Å is shown here; the distribution upto 2.0 Å integrates to 3, which corresponds to the three hydronium hydrogens. (d)Radial distribution function for water oxygen atoms around the hydronium hydrogen atoms in bulk water with an excess proton. The hydronium hydrogen atoms are denoted by H_0 .

FIG. 11.

Spatial distribution function (SDF) of water oxygen atoms around the hydronium oxygen atom from DFTB3-diag+gaus calculations. 'r' denotes the radial distance from the hydronium O. The top three figures show the side view of the hydronium while the bottom three figures show the top view of the hydronium. The figure of the hydronium in the middle illustrates the coordinate frame for the SDF. The origin is at the hydronium oxygen. The Z-axis is perpendicular to the plane of the three hydrogen atoms. The vector from the origin to the hydrogen atom hydrogen-bonded to O_{1x} (shown in green) lies in the XZ plane. Only distribution for SDF > 3 is shown.

FIG. 12.

Spatial distribution function (SDF) of water oxygen atoms around the hydronium hydrogen atoms from DFTB3-diag+gaus calculations. 'r' denotes the radial distance from the hydronium H atoms. The left figure shows the side view of the hydronium while the right figure shows the top view of the hydronium. Although the SDF is actually computed around the hydronium oxygen and the hydronium hydrogen atoms have a finite distribution, the use of the same local coordinate axes frame for each snapshot facilitates choosing approximate positions of the H atoms for the SDF illustrated above.

FIG. 13.

Potential of mean force for the hydrated excess proton. The reaction coordinate is $\delta = |\vec{r}_{O_0H} - \vec{r}_{O_{1x}H}|$ where O_0 is the hydronium oxygen and O_{1x} is the “special pair” partner of O_0 . $\delta \leq 0.1$ corresponds to the Zundel form and $\delta \geq 0.2$ corresponds to the Eigen form. The CPMD-HCTH, DFTB2 and DFTB2- γ^h results are from Ref.³¹.

TABLE I

Energies relative to isomer VI (in kcal/mol) and Zundel/Eigen character of low-energy isomers of $H^+(H_2O)_6$ ^a

Isomer	MP2 ^b	DFTB2	DFTB2- γ^b +gaus	DFTB3-diag	DFTB3-diag+gaus
I	0.47 (E)	2.06 (E-Z)	0.01 (E)	1.44 (E)	0.53 (E)
II	0.58 (E)	2.06 (E-Z)	0.01 (E)	1.44 (E)	0.53 (E)
III	0.09 (E)	2.06 (E-Z)	0.01 (E)	0.57 (E)	-0.48 (E)
IV	0.78 (E)	0.78 (Z)	0.21 (E-Z)	0.46 (Z)	-0.03 (E)
V	0.00 (E)	1.34 (Z)	-0.01 (E)	0.59 (E)	-0.40 (E)
VI	0.00 (E)	0.00 (Z)	0.00 (E)	0.00 (Z)	0.00 (E)
VII	0.31 (E)	0.26 (Z)	-0.34 (E-Z)	0.06 (Z)	-0.47 (E)
VIII	0.56 (E-Z)	-0.79 (Z)	-0.92 (Z)	-0.47 (Z)	0.03 (E)
IX	1.75 (Z)	-1.30 (Z)	-1.03 (Z)	-0.20 (Z)	0.09 (Z)
X	1.39 (E)	1.11 (E-Z)	0.86 (E)	1.48 (E)	0.94 (E)
XI	4.01 (Z)	3.94 (Z)	3.07 (Z)	2.86 (Z)	3.28 (Z)

^aIn the column for each method, the three sub-columns indicate the energy relative to isomer VI, Z/E-E-Z classification according to the criterion based on ROO^{30} and Z/E-E-Z classification according to the criterion based on δ^{31} . Note that the modified γXH is included in DFTB3-diag and DFTB3-diag+gaus.

^bThe MP2 relative energies are from Ref.⁴⁸. The MP2 results therein were obtained by single-point calculations with the aug-cc-PVTZ basis set at MP2/aug-cc-PVDZ optimized geometries. The Z/E-E-Z classification is based on the MP2/aug-cc-PVDZ geometries.

TABLE II

Summary of performance of various variants of SCC-DFTB for $H^+(H_2O)_6$ as compared to previous MP2 results⁴⁸

	MP2	DFTB2	DFTB2- γ^b +gaus	DFTB3-dia	DFTB3-dia+gaus
MAXE	0.0	-3.1	-2.8	-2.0	-1.7
RMSE	0.0	1.4	1.1	0.9	0.7
MUE	0.0	1.0	0.7	0.7	0.6
MSE	0.0	0.1	-0.7	-0.2	-0.5
# of E isomers (def 1) ^a	8	0	8	5	9
# of E isomers (def 2) ^b	10	6	8	7	9

^a Criterion based on ROO^{30}

^b Criterion based on δ^{31}

TABLE III

Energies relative to isomer A (kcal/mol) and Zundel/Eigen character of low-energy isomers of $H^+(H_2O)_{22}$ ^a

Isomer	RIMP2 ^b	DFTB2	DFTB2- γ^H +gaus	DFTB3-diag	DFTB3-diag+gaus
A	0.00 (E)	0.00 (Z)	0.00 (E)	(Z)	0.00 (E)
B	9.53 (E)	8.86 (Z)	7.61 (E)	(Z)	6.22 (E)
C	2.94 (E)	0.94 (Z)	0.97 (Z)	(Z)	2.12 (E)
D	7.49 (E)	1.90 (Z)	0.50 (E)	(Z)	0.00 (E)
E	6.56 (E)	4.17 (Z)	2.42 (Z)	(Z)	1.27 (E)
F	5.38 (E)	2.66 (Z)	2.79 (Z)	(Z)	3.35 (E)
G	9.81 (E)	6.93 (Z)	5.61 (E)	(Z)	5.32 (E)
H	2.72 (E)	1.81 (E-Z)	-0.34 (E)	(E-Z)	-1.22 (E)
I	2.45 (E)	1.78 (Z)	-0.58 (E)	(E-Z)	-1.40 (E)
J	0.57 (E)	1.69 (E-Z)	1.07 (E)	(E-Z)	1.00 (E)
K	12.06 (E)	8.02 (Z)	8.16 (E)	(Z)	6.60 (E)
L	3.45 (E)	4.57 (Z)	4.30 (E)	(Z)	3.39 (E)
M	6.87 (E)	3.92 (Z)	3.51 (Z)	(Z)	4.55 (E)

^aIn the column for each method, the three sub-columns indicate the energy relative to isomer A, Z/E-E-Z classification according to the criterion based on ROO^{30} and Z/E-E-Z classification according to the criterion based on δ^{31} .

^bThe RIMP2 relative energies are from Ref.⁴⁸. The RIMP2 results therein were obtained by single-point calculations with the aug-cc-PVTZ basis set at B3LYP/6-31+G(d) optimized geometries. The Z/E-E-Z classification is based on the B3LYP/6-31+G(d) geometries.

TABLE IV

Summary of performance of various variants of SCC-DFTB for $H^+(H_2O)_{22}$ as compared to previous RIMP2 results⁴⁸

	RIMP2	DFTB2	DFTB2- γ^b +gaus	DFTB3-diag	DFTB3-diag+gaus
MAXE	0.0	-5.6	-7.0	-7.2	-7.5
RMSE	0.0	2.6	3.3	3.5	3.8
MUE	0.0	2.1	2.8	2.8	3.0
MSE	0.0	-1.7	-2.6	-2.6	-3.0
# of E isomers (def 1) ^a	13	0	9	0	13
# of E isomers (def 2) ^b	13	3	9	4	13

^a Criterion based on ROO^{30}

^b Criterion based on δ^{31}

TABLE V

Binding energy^a (kcal/mol) of small neutral water clusters

Molecules	high level	DFTB2 ^b	DFTB2- γ^{hb}	DFTB3-diag ^b
$2H_2O$	-4.9 (G3B3)	1.6	0.7	0.2
$3H_2O$	-15.1 (G3B3)	5.5	2.3	0.3
$4H_2O$	-27.4 (G3B3)	10.3	5.5	2.7
$5H_2O$	-36.3 (G3B3)	14.0	7.9	4.2
$6H_2O$ book	-45.6 (CBS)	17.3	9.3	4.4
$6H_2O$ cage	-45.8 (CBS)	17.1	8.1	2.3
$6H_2O$ prism	-45.9 (CBS)	16.9	7.3	1.6
$6H_2O$ ring	-44.9 (CBS)	17.6	10.1	5.6

^aThe binding energy is computed as the energy difference between the complex and the isolated molecules at 0 K in the gas phase. No zero point energy correction has been included.

^bThe numbers are the binding energy differences between various SCC-DFTB models and the corresponding high-level result (i.e., $BE_{SCC-DFTB} - BE_{high-level}$).

TABLE VI

Integrated first *solvation* shell of $g_{O-O}(r)$ and $g_{O-H}(r)$ for neutral bulk water

	Exp ^a	CPMD-HCTH ^b	DFTB2 ^b	DFTB2- γ ^b	DFTB3-diag
$g_{O-O}(r)$	4.7	4.1	8.4	7.1	5.9
$g_{O-H}(r)$	1.7	1.9	1.7	1.9	1.8

^a Reference⁶¹

^b Reference³¹

TABLE VII

Diffusion coefficient ($\text{\AA}^2/\text{ps}$) of oxygen atom in neutral bulk water (D_{H_2O}) and of the hydronium oxygen atom in bulk water with an excess proton ($D_{H_3O^+}$)

	Exp	CPMD-HCTH ^c	DFTB2 ^c	DFTB2- $\gamma^{\mu c}$	DFTB3-diag(+gaus) ^d
D_{H_2O}	0.23 ^a	0.10	1.11 ± 0.04	0.65 ± 0.02	0.38 ± 0.03
$D_{H_3O^+}$	0.94 ± 0.01 ^b	0.33	0.81 ± 0.03	0.90 ± 0.20	0.66 ± 0.20
$D_{H_3O^+}/D_{H_2O}$	4.09	3.30	0.73	1.38	1.74

^aReference^{74,75}

^bReference⁶⁹

^cReference³¹

^dThe Gaussian modification (+gaus) to the O-H repulsive potential is used only for H_3O^+

TABLE VIIIHeat of vaporization, ΔH_{vap} (kcal/mol), for neutral bulk water

Exp ^a	DFTB2 ^b	DFTB2- γ^h	DFTB3-diag
10.50	4.09 $\pm$ 0.04	7.0 $\pm$ 0.08	8.48 $\pm$ 0.02

^aReference⁷⁶^bReference³¹

TABLE IX

Integrated first solvation shell of $g_{O_0-O}(r)$, $g_{O_{1x}-O}(r)$ and $g_{O_{1yz}-O}(r)$ for bulk water with an excess proton

	Exp ^a	CPMD-HCTH ^b	DFTB2 ^b	DFTB2- γ ^{bb}	DFTB3-diag+gaus
$g_{O_0-O}(r)$	2.1	3.0	5.2	5.1	4.5
$g_{O_{1x}-O}(r)$	-	3.1	5.4	5.2	5.4
$g_{O_{1yz}-O}(r)$	-	3.7	6.8	6.4	6.1

^aReference^{62,63}

^bReference³¹