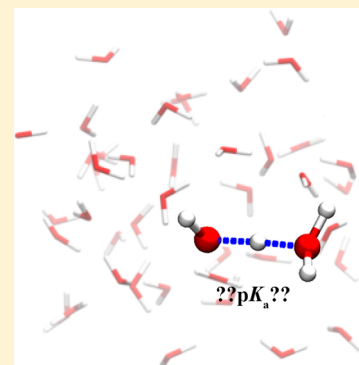


# First-Principles Calculation of Water $pK_a$ Using the Newly Developed SCAN Functional

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## Supporting Information

**ABSTRACT:** Acid/base chemistry is an intriguing topic that still constitutes a challenge for computational chemistry. While estimating the acid dissociation constant (or  $pK_a$ ) could shed light on many chemistry processes, especially in the fields of biochemistry and geochemistry, evaluating the relative stability between protonated and nonprotonated species is often very difficult. Indeed, a prerequisite for calculating the  $pK_a$  of any molecule is an accurate description of the energetics of water dissociation. Here, we applied constrained molecular dynamics simulations, a noncanonical sampling technique, to investigate the water deprotonation process by selecting the OH distance as the reaction coordinate. The calculation is based on density functional theory and the newly developed SCAN functional, which has shown excellent performance in describing water structure. This first benchmark of SCAN on a chemical reaction shows that this functional accurately models the energetics of proton transfer reactions in an aqueous environment. After taking Coulomb long-range corrections and nuclear quantum effects into account, the estimated water  $pK_a$  is only 1.0  $pK_a$  unit different from the target experimental value. Our results show that the combination of SCAN and constrained MD successfully reproduces the chemistry of water and constitutes a good framework for calculating the free energy of chemical reactions of interest.



Acid/base chemistry is an intriguing topic and draws extensive attention from both experimental and computational chemistry research<sup>1</sup> because of its great impact on catalysis,<sup>2</sup> drug design,<sup>3</sup> and other related fields. One area that requires accurate predictions of acidity, or  $pK_a$  (the acid dissociation constant), is that of mineral oxide surfaces, which are frequently covered with hydroxyl (M–OH) groups; these form crucial hydrogen bonds,<sup>4</sup> and their protonation states affect the structure and dynamics of interfacial water or solutes.<sup>5</sup> Besides the  $pK_a$  of minerals, biochemists are interested in the  $pK_a$  of amino acids due to the functional consequences of protonation/deprotonation events. For instance, the protonation and deprotonation of histidine is a key component in the gating of the M2 channel of the influenza A virus.<sup>6,7</sup> The  $pK_a$  of histidine in bulk water<sup>8,9</sup> and in the His-Trp motif on the M2 protein<sup>10</sup> have been previously analyzed and found to be in qualitative agreement with experiments.

Together with experimental measurements, ab initio molecular dynamics (AIMD) simulations can be used to determine the  $pK_a$ . The weak acid dissociation of water is a rare event on the time scales sampled by typical molecular simulations; therefore, noncanonical sampling techniques are essential to calculate the free energy of the OH bond breaking. The latter can be then easily connected to  $pK_a$ , the

macroscopic observable that characterizes acidity. For example, Leung et al. and Sulpizi et al. pointed to a bimodal acidity model of amorphous silica/water interfaces, which is in agreement with experimental SHG measurements.<sup>11,12</sup> Recently, the free energy perturbation (FEP) method<sup>13</sup> has been used to study how the quartz/water interface affects the  $pK_a$  of an interfacial organic acid molecule, an issue not easily addressable by experiments.<sup>14</sup>

While the FEP method is a mature approach for predicting the  $pK_a$ , it can only provide the free energy difference between the initial and final states, neglecting the reaction path, which, by contrast, can be obtained by calculating the potential of mean force (PMF) as a function of appropriately chosen reaction coordinates. Multiple-dimension PMF surfaces have already been used to study weak acid dissociation.<sup>15</sup>

The Helmholtz free energy for the deprotonation can be obtained from the PMF:<sup>9</sup>

$$K_c^{-1} = c_0 \int_0^{R_c} e^{-\beta w(r)} 4\pi r^2 dr \quad (1)$$

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$$pK_a = -\log K_c \quad (2)$$

where  $K_c$  is the acid dissociation constant,  $c_0$  is the standard concentration,  $R_c$  is the distance cutoff for the integral, and  $w(r)$  is the PMF. This method is approximate in that it neglects zero point energy and tunneling effects, which have been shown to contribute significantly to the  $pK_a$ .<sup>9</sup> Moreover, eq 1 assumes that the absolute value of the free energy,  $w(r)$ , is known for all  $r$  values between 0 and  $R_c$  (the reference state being when  $H^*$  and its conjugate base are at infinite separation). This implies that the potential of mean force ought to be calculated from  $r = 0$  up to any distance at which  $w(r)$  is insignificantly different from zero. This constraint results in a severe limitation, given the long-range nature of the interaction between the reactants (hydronium and hydroxide ions) and the limited system size of a typical AIMD simulation.

A commonly adopted strategy to mitigate this problem is to focus on the  $pK_a$  of the species of interest relative to water:<sup>9</sup>

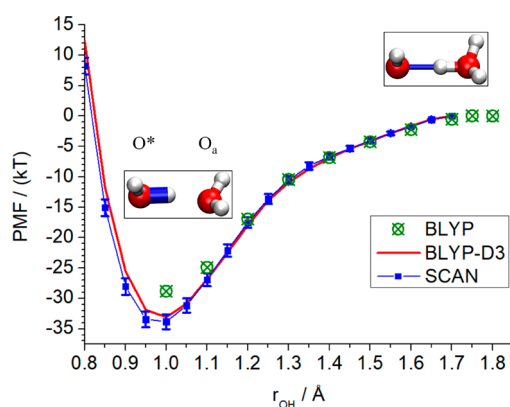
$$\frac{K_c}{K_w} = \frac{\int_0^{R_c} e^{-\beta w_{\text{water}}(r)} r^2 dr}{\int_0^{R_c} e^{-\beta w_{\text{acid}}(r)} r^2 dr} \quad (3)$$

where  $K_w$  is the water ionization constant,  $10^{-14}$ . Despite these challenges, in this paper we attempt to estimate the absolute  $pK_a$  of water. To this end, we model the long-range part of the potential of mean force as a screened Coulombic interaction between the hydroxide and the hydronium ions.

Most of the AIMD studies of OH bond breaking have been based on a density functional theory level, given the acceptable compromise between accuracy and computational cost that this approach provides. However, widely used GGA functionals, such as BLYP and PBE predict an overstructured water: hydrogen bonds are stronger and water–water distances are shorter than the experimentally derived values.<sup>16</sup> The dynamics of water are not satisfactory either; diffusion coefficients of the proton or hydroxide ion predicted by DFT-MD are not in agreement with experiments.<sup>17</sup> The hybrid functional PBE0 with the Tkatchenko–Scheffler van der Waals (VDW) corrections predicts reasonably accurate diffusion coefficients of  $H_3O^+$  and  $OH^-$ , but its large computational cost makes it unsuitable for large-scale MD simulations.<sup>17</sup> The recently developed meta-GGA functional, strongly constrained and appropriately normed (SCAN),<sup>18</sup> shows good performance in calculating covalent and noncovalent interactions of many systems.<sup>19</sup> MD simulations using SCAN successfully predicted the structure,<sup>16</sup> dynamics,<sup>20</sup> and the IR spectra<sup>21</sup> of bulk water, as well as water vibrations near  $TiO_2$ ,<sup>22</sup> alumina,<sup>23</sup> and vapor<sup>24</sup> interfaces. It is, thus, of great interest to know if SCAN describes quantitatively the chemistry of water and, in particular, the thermodynamics and kinetics of water autoionization.

We calculated the PMF of water autoionization employing constrained MD, by selecting the distance of the OH bond from the dissociated water, hereafter referred to as  $O^*-H^*$ , as the reaction coordinate ( $r_{OH}$ ). We varied  $r_{OH}$  from 0.8 to 1.7 Å in increments of 0.05 Å. We then used semiquantitative corrections for nuclear quantum effects (NQE) and the long-range Coulomb interaction energy.

We obtained an absolute water  $pK_a$  that is only 1.0  $pK_a$  unit different from the target value, i.e., in better agreement with experiments compared to results previously obtained with other functionals, such as BLYP.<sup>25,26</sup> First, we calculate the short-range interaction of water autoionization by looking at



**Figure 1.** PMF of water autoionization. Results of “BLYP-D3” and “SCAN” are calculated in this work and “BLYP” is from previous reports.<sup>25,26</sup> The insets show the molecular structures of the reactants ( $r_{OH} = 1.0$  Å) and products states ( $r_{OH} = 1.7$  Å for SCAN and BLYP-D3). The free energy of the products state is set to 0. The blue cylinder in the molecular structures highlights the  $O^*-H^*$  bond kept constrained.

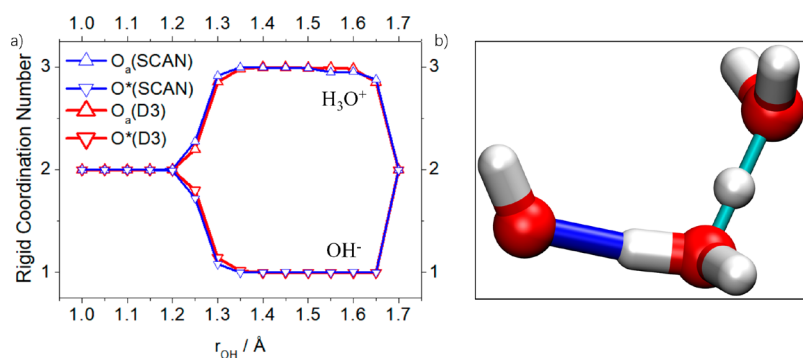
the PMF versus  $r_{OH}$  (Figure 1). Although previous simulations using the SCAN functional predicted an average length of water OH bonds is 0.98 Å,<sup>20</sup> we find a relatively flat PMF (within error bars) between  $r_{OH} = 0.95$  and 1.00 Å. When  $r_{OH} \geq 1.7$  Å, since the proton has been already transferred to  $H_3O^+$ , the major contribution to the free energy comes from the long-range interaction between  $OH^-$  and  $H_3O^+$ , which we modeled as a screened Coulomb interaction between two point charges. This allows us to compare the PMF at  $r_{OH} = 1.0$  Å with that of the dissociated states, when  $OH^-$  and  $H_3O^+$  are infinitely far apart. A direct comparison of free energy between  $r_{OH} = 1.0$  and 1.7 Å by SCAN (Figure 1) results in a free energy difference of 33.83  $kT$ , where  $k$  is the Boltzmann constant and  $T$  is 300 K, corresponding to 14.69  $pK_a$  units:

$$pK_a = \frac{|\Delta F|}{kT \times 2.3026} \quad (4)$$

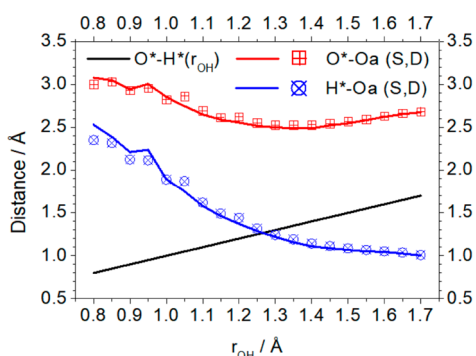
AIMD simulations describe how the water molecule becomes a  $OH^- - H_3O^+$  pair, and to get the full  $pK_a$  of water, the free energy for the separation of such a pair to infinity needs to be estimated as well. Here we use a crude approach by treating the ion pair as charges and by estimating their interaction using a Coulombic form:

$$E_c = -\frac{1}{4\pi\epsilon_r\epsilon_0} \times \frac{e^2}{2.68} \times \frac{1}{10^{-20}kT} \quad (5)$$

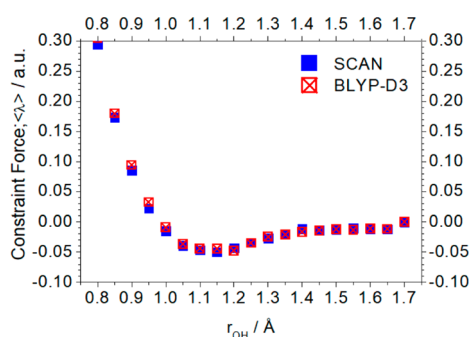
where  $\epsilon_0$  is the vacuum permittivity,  $\epsilon_r$  is the relative permittivity of water ( $\sim 78$ ), and  $e$  is the elementary charge. The point charges are located on the  $O^*$  of  $OH^-$  and  $O_a$  of  $H_3O^+$  atoms with charges  $-1e$  and  $+1e$ , respectively; we find that when  $O^*$  and  $H^*$  is constrained at 1.7 Å, the average distance between  $O^*$  and  $O_a$  is 2.68 Å. We estimate the Coulomb contribution as the energy required to increase the distance between two opposite charges from 2.68 Å to infinity. The contribution from Coulomb interactions is 3.0  $kT$ , corresponding to 1.3  $pK_a$  units. We note that using a MS-EVB type model, the free energy for separating an amino acid anion from the hydronium moiety is about 2 kcal/mol,<sup>27</sup> corresponding to 1.5  $pK_a$  units, i.e. comparable to our estimations.



**Figure 2.** (a) Average coordination number of  $O^*$  and  $O_a$  as a function of the proton transfer reaction coordinate. Coordination numbers of 1 and 3 correspond to  $OH^-$  and  $H_3O^+$ , respectively. (b) Molecular configuration from a simulation at  $r_{OH} = 1.65 \text{ \AA}$ , in which the extra proton forms a Zundel ion. The blue line highlights the constrained  $O^*-H^*$  bond, while the cyan one indicates that the distance between  $O_a$  and its nearest oxygen is less than  $2.43 \text{ \AA}$ , one of the hallmarks of the Zundel ion.<sup>35</sup>

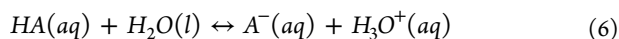


**Figure 3.** Average bond length of  $O^*-O_a$  and  $H^*-O_a$  with respect to  $r_{OH}$ . Red and blue lines are the results from SCAN simulations (marked as “S”); the square and circle symbols are the results from BLYP-D3 simulations (marked as “D”). The black curve is  $r_{OH}$ , as well as the distance of  $O^*-H^*$ .



**Figure 4.** Average constraint force (in atomic units) for each window.

To select the correct reference value we have to take into consideration NQEs. Markland and co-workers use the  $pK_a$  of  $D_2O$  and  $T_2O$ , to estimate the pH of classical water (i.e. with nuclei of infinite-mass).<sup>28</sup> According to the estimate, the pH is 1.5 units higher than the canonical  $pH = 7$  value, corresponding to an increase of 3 units of the  $pK_a$ .<sup>28</sup> The following reaction is used to calculate the  $pK_a$ :

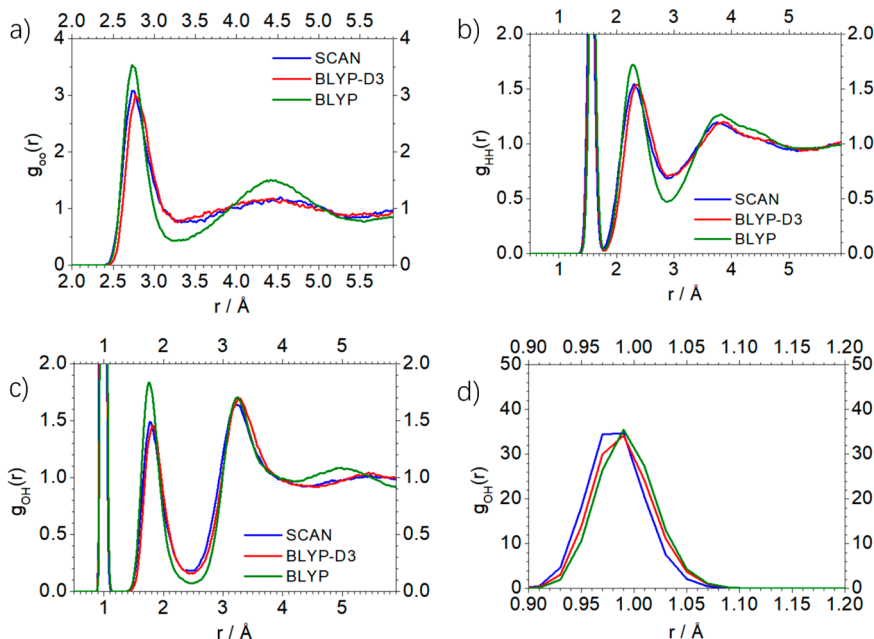


$$pK_a = -\log \frac{a(H_3O^+)a(A^-)}{a(HA)a(H_2O)} \quad (7)$$

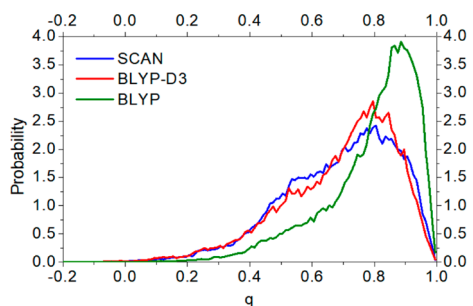
It is important to remind the reader that the value 15.7, reported in many textbooks, comes from the incorrect assumption that  $a(HA) = [HA] = [H_2O] = 55 \text{ mol/L}$ . The first problem with this identification between activity and concentration is that, while acceptable in the limit of infinite dilution, it is certainly not valid for a 55 M solution. More in detail, not all the water molecules can be identified as “reactants” since the vast majority of them are mere spectators to the reaction and thus should be considered “solvent” rather than “solute”. In analogy with what is done for calculating the  $pK_a$  of any other acid, the activity of the solvent,  $a(H_2O)$ , should be assumed to be 1 (i.e., pure water, or, in other words, a large enough system that practically all the waters are available for hydrating solutes) and the activity of the reactive water,  $a(HA)$ , can be approximated with the analytic concentration at standard conditions (i.e., 1 M). Only this definition of the water  $pK_a$  makes it homogeneous and therefore comparable with the  $pK_a$  of other acids.<sup>29</sup> In our simulations, only 1 water is allowed to dissociate (which should be treated as solute) and other 54 water molecules are “solvent”, corresponding to the 1 M concentration. With these assumptions, we take as a reference the  $pK_a$  value of 14.<sup>29</sup> As a result, with the 3  $pK_a$  units from NQEs, the target  $pK_a$  value is chosen as 17.

Notably, our calculations, including short-range and long-range interaction of the  $H^+-OH^-$  pair, predict a  $pK_a$  for water of 16.0, i.e. 1.0  $pK_a$  unit lower than the target value. The difference is likely due to the imperfect definition of the reaction coordinate and the oversimplified model accounting for long-range Coulomb interactions. Nevertheless, when compared with the predictions from other functionals, namely BLYP<sup>25,26</sup> and HCTH,<sup>9</sup> SCAN gives the best agreement and shows significant improvement over previous computational estimates. The PMF contribution of water dissociation by BLYP-D3 is 14.36  $pK_a$  units, 0.33  $pK_a$  units lower than that of SCAN. Albeit modest, this improved description of the chemistry of water suggests that SCAN is a promising tool to study chemical reactions, the breaking and forming of covalent bonds. We carried out additional simulations using the coordination number as the reaction coordinate<sup>30–34</sup> and obtained quantitatively consistent results (Figure S1); this further confirms SCAN’s accuracy in predicting the water  $pK_a$ .

We also analyze how the proton  $H^*$  leaves the water to reveal the mechanism of water autoionization. First, we compare the coordination number of the two water oxygens involved in the reaction as a function of the reaction



**Figure 5.** Radial distribution function. (a), (b), and (c) are  $g_{OO}(r)$ ,  $g_{HH}(r)$ , and  $g_{OH}(r)$ , respectively. (d) Close up of the first peak of  $g_{OH}(r)$  showing the distribution of water OH bond length. Note that the water OH bond length follows this series:  $|\text{OH}|_{\text{SCAN}} < |\text{OH}|_{\text{BLYP-D3}} < |\text{OH}|_{\text{BLYP}}$ .



**Figure 6.** Tetrahedral order parameter probability distribution function. Trajectories used for this calculation are simulations in which  $r_{\text{OH}}$  is constrained at 1.0 Å.

coordinate  $r_{\text{OH}}$  (Figure 2). Here, the “rigid coordination number” is defined by assuming that each hydrogen atom belongs to its nearest oxygen.<sup>25</sup> Both simulations (based on SCAN or BLYP-D3) predict the following stages: (1)  $1.0 \text{ \AA} < r_{\text{OH}} < 1.25 \text{ \AA}$ , in this region, both waters have a coordination number of 2, indicating that the  $\text{O}^*-\text{H}^*$  covalent bond has not yet started to break; (2)  $1.25 \text{ \AA} < r_{\text{OH}} < 1.35 \text{ \AA}$ , the coordination numbers of  $\text{O}^*$  and  $\text{O}_a$  change abruptly to 1 and 3, respectively, indicating that the proton transfer has happened and, in place of the two neutral water molecules, a  $\text{OH}^--\text{H}_3\text{O}^+$  pair appears; (3)  $r_{\text{OH}} > 1.4 \text{ \AA}$ , the proton is completely transferred to  $\text{O}_a$  and, as  $r_{\text{OH}}$  keeps increasing, a positive–negative charge-pair is created that persist up to  $r_{\text{OH}} = 1.7 \text{ \AA}$ . Beyond  $r_{\text{OH}} = 1.7 \text{ \AA}$ , proton transfer events will shuttle the excess proton away from the original pair, transforming the  $\text{OH}^--\text{H}_3\text{O}^+$  into a water–water pair. It is worth mentioning that, in the limited time span of our simulations, when the  $\text{OH}^--\text{H}_3\text{O}^+$  pair forms, the coordination number of  $\text{OH}^-$  is constantly 1 (exception for  $r_{\text{OH}} = 1.7 \text{ \AA}$ ), indicating that no proton transfer on  $\text{OH}^-$  is observed; however, from  $r_{\text{OH}} > 1.55 \text{ \AA}$ , the coordination number of  $\text{O}_a$  is slightly lower than 3, due to proton transfer events from the hydronium ion to neighboring waters. Visual inspection of the trajectory at  $r_{\text{OH}}$

= 1.55 and 1.6 Å shows that one proton dangles between  $\text{O}_a$  and an oxygen near it forming a Zundel cation, whenever it lies in the middle of the two oxygens. However, the Zundel ion is only observed in a small fraction of all the configurations, consistent with an average coordination number very close to 3. The fact that proton transfer events involve more frequently hydronium than hydroxide ions is consistent with recent independent computational work.<sup>17</sup>

The geometry of the  $\text{OH}^--\text{H}_3\text{O}^+$  pair can be used to describe the process of water autoionization as well. As  $\text{H}^*$  unbinds from  $\text{O}^*$ , the  $\text{H}^*-\text{O}_a$  distance decreases, indicating that as the  $\text{O}^*-\text{H}^*$  bond becomes weaker, the interaction between  $\text{H}^*$  and  $\text{O}_a$  becomes stronger. When  $r_{\text{OH}} \approx 1.3 \text{ \AA}$  and  $r_{\text{OH}} = r_{\text{H}^*\text{O}_a} = 1/2 \times r_{\text{O}^*\text{O}_a}$ , the  $\text{H}^*$  lies in the middle between two oxygens. At  $r_{\text{OH}} = 1.4 \text{ \AA}$ , the  $\text{O}^*-\text{O}_a$  distance reaches the global minimum (Figure 3); from here, the proton transfer has occurred and charges start to separate, consistent with the results of coordination numbers. The profile of the constraint force (Figure 4) also confirms this picture: it reaches the global minimum at  $r_{\text{OH}} = 1.15 \text{ \AA}$ , which corresponds to an inflection point of the PMF. Past this point, the PMF starts to deviate significantly from a harmonic well and the “bond” between  $\text{O}^*$  and  $\text{H}^*$  starts to weaken. From  $r_{\text{OH}} = 1.4 \text{ \AA}$ , the constraint force is approximately constant at a small negative value until  $r_{\text{OH}} = 1.7 \text{ \AA}$ , the largest distance explored in our simulations. The evolution of the coordination number, the geometry structure, and constraint force predict one same fact that the  $\text{O}^*-\text{H}^*$  bond break begins at  $r_{\text{OH}} = 1.2 \text{ \AA}$  and is finally broken at  $r_{\text{OH}} = 1.4 \text{ \AA}$ .

The radial distribution functions (RDFs) also show how different functionals affect the PMF of water autoionization. We compared  $g_{\text{OO}}(r)$ ,  $g_{\text{OH}}(r)$ , and  $g_{\text{HH}}(r)$  together with the distribution of the tetrahedral order parameter (as defined in ref 36) from simulations based on SCAN, BLYP, and BLYP-D3 (Figure 5). These are calculated on the constrained MD simulations trajectories at  $r_{\text{OH}} = 1.0 \text{ \AA}$  (the reactant state). For the three RDFs, the results from SCAN are similar to those from BLYP-D3. Since our simulations are carried out at 300 K



(and not at 330 K as is customary to mimic NQEs), we did observe an overstructured first shell and, consequently, more pronounced peaks and minima compared to experiments.<sup>37</sup> Relatively speaking, SCAN and BLYP-D3 predict a less ordered water structure compared to BLYP as apparent from both the  $g_{\text{OO}}(r)$  and tetrahedral order parameter distribution (Figure 6). It is worth mentioning that the water OH bond length predicted by SCAN is slightly shorter than the BLYP one (Figure Sd), which may be one of the reasons why BLYP underestimates the water  $\text{p}K_{\text{a}}$  and overestimates the strength of the hydrogen bond network. We believed that correct RDFs, and more generally, the accurate structure of the first solvation shell, are essential to reproduce the correct chemical bond energy.

This work also shows that BLYP-D3 predicts a similar free energy for water autoionization and water structures of bulk water. However, a recent paper shows that BLYP-D3 fails to predict the free-OH vibration at water/air interfaces,<sup>24</sup> in addition, the accuracy of BLYP for metals is questionable.<sup>38</sup> These issues limit BLYP's application to solid/water interfaces for which SCAN shows good results.<sup>22,23</sup> Having established that SCAN reproduces well the energetics of water dissociation, our results might be of crucial relevance for researchers working in related fields, such as water splitting near solid/water interfaces or the calculation of the  $\text{p}K_{\text{a}}$  of OH groups on mineral surfaces.

In conclusion, using AIMD and, in particular, Car-Parrinello MD,<sup>39</sup> we calculated the PMF of water autoionization with the recently developed density functional SCAN; we used constrained MD and selected the  $\text{O}^*-\text{H}^*$  distance as the reaction coordinate. From the PMF, we estimated the short-range contribution to the free energy of water autoionization, which turned out to be  $33.8kT$ , corresponding to  $14.69 \text{ p}K_{\text{a}}$  units. We then estimated the long-range Coulomb interactions to account for  $3.0kT$ , making the total  $\text{p}K_{\text{a}}$  of water  $16.0$ ,  $1.0 \text{ p}K_{\text{a}}$  unit lower than  $17$ , the estimated target value for a perfect water model devoid of nuclear quantum effects.<sup>28</sup> This work shows that SCAN outperforms other functionals such as BLYP in describing the chemical reaction of water dissociation. While the addition of an empirical VDW correction (BLYP-D3) constitutes an improvement, the results based on SCAN are the closest to the target value. The approach used in this work can be easily applied to similar protonation/deprotonation reactions, and our results constitute a reference for calculating the relative  $\text{p}K_{\text{a}}$  of small organic molecules or minerals at aqueous interfaces. Since this work demonstrates that the SCAN functional successfully describes the chemistry of water OH bond breaking, a good performance is also expected for other chemical reactions, in particular for the prediction of free energy barriers and transition states in an aqueous environment.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.jpcllett.9b02913>.

Simulation details, including those using OH distance or smoothed coordination number as collective variables, further comparison of these two CVs (PDF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) Agmon, N.; Bakker, H. J.; Campen, R. K.; Henchman, R. H.; Pohl, P.; Roke, S.; Thämer, M.; Hassanali, A. Protons and Hydroxide Ions in Aqueous Systems. *Chem. Rev.* **2016**, *116*, 7642–7672.
- (2) Jencks, W. P. General Acid-Base Catalysis of Complex Reactions in Water. *Chem. Rev.* **1972**, *72*, 705–718.
- (3) Chen, Y.-L.; Doltsinis, N. L.; Hider, R. C.; Barlow, D. J. Prediction of Absolute Hydroxyl  $\text{p}K_{\text{a}}$  Values for 3-Hydroxypyridin-4-Ones. *J. Phys. Chem. Lett.* **2012**, *3*, 2980–2985.
- (4) Wang, R.; DelloStritto, M.; Remsing, R. C.; Carnevale, V.; Klein, M. L.; Borguet, E. Sodium Halide Adsorption and Water Structure at the  $\alpha$ -Alumina(0001)/Water Interface. *J. Phys. Chem. C* **2019**, *123*, 15618–15628.
- (5) Tuladhar, A.; Piontek, S. M.; Borguet, E. Insights on Interfacial Structure, Dynamics, and Proton Transfer from Ultrafast Vibrational Sum Frequency Generation Spectroscopy of the Alumina(0001)/Water Interface. *J. Phys. Chem. C* **2017**, *121*, 5168–5177.
- (6) Carnevale, V.; Fiorin, G.; Levine, B. G.; DeGrado, W. F.; Klein, M. L. Multiple Proton Confinement in the M2 Channel from the Influenza A Virus. *J. Phys. Chem. C* **2010**, *114*, 20856–20863.
- (7) Liang, R.; Li, H.; Swanson, J. M. J.; Voth, G. A. Multiscale Simulation Reveals a Multifaceted Mechanism of Proton Permeation through the Influenza A M2 Proton Channel. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, *111*, 9396.
- (8) Ivanov, I.; Klein, M. L. Deprotonation of a Histidine Residue in Aqueous Solution Using Constrained Ab Initio Molecular Dynamics. *J. Am. Chem. Soc.* **2002**, *124*, 13380–13381.
- (9) Ivanov, I.; Chen, B.; Raugei, S.; Klein, M. L. Relative  $\text{p}K_{\text{a}}$  Values from First-Principles Molecular Dynamics: The Case of Histidine Deprotonation. *J. Phys. Chem. B* **2006**, *110*, 6365–6371.
- (10) Bankura, A.; Klein, M. L.; Carnevale, V. Proton Affinity of the Histidine-Tryptophan Cluster Motif from the Influenza A Virus from Ab Initio Molecular Dynamics. *Chem. Phys.* **2013**, *422*, 156–164.
- (11) Leung, K.; Nielsen, I. M. B.; Criscenti, L. J. Elucidating the Bimodal Acid-Base Behavior of the Water-Silica Interface from First Principles. *J. Am. Chem. Soc.* **2009**, *131*, 18358–18365.
- (12) Pfeiffer-Laplaid, M.; Costa, D.; Tielens, F.; Gaigeot, M. P.; Sulpizi, M. Bimodal Acidity at the Amorphous Silica/Water Interface. *J. Phys. Chem. C* **2015**, *119*, 27354–27362.

- (13) Sulpizi, M.; Sprik, M. Acidity Constants from Vertical Energy Gaps: Density Functional Theory Based Molecular Dynamics Implementation. *Phys. Chem. Chem. Phys.* **2008**, *10*, 5238–5249.
- (14) Parashar, S.; Lesnicki, D.; Sulpizi, M. Increased Acid Dissociation at the Quartz/Water Interface. *J. Phys. Chem. Lett.* **2018**, *9*, 2186–2189.
- (15) Park, J. M.; Laio, A.; Iannuzzi, M.; Parrinello, M. Dissociation Mechanism of Acetic Acid in Water. *J. Am. Chem. Soc.* **2006**, *128*, 11318–11319.
- (16) Chen, M.; Ko, H.-Y.; Remsing, R. C.; Calegari Andrade, M. F.; Santra, B.; Sun, Z.; Selloni, A.; Car, R.; Klein, M. L.; Perdew, J. P., et al. Ab Initio Theory and Modeling of Water. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, 10846.
- (17) Chen, M.; Zheng, L.; Santra, B.; Ko, H.-Y.; DiStasio, R. A., Jr; Klein, M. L.; Car, R.; Wu, X. Hydroxide Diffuses Slower Than Hydronium in Water Because Its Solvated Structure Inhibits Correlated Proton Transfer. *Nat. Chem.* **2018**, *10*, 413–419.
- (18) Sun, J.; Ruzsinszky, A.; Perdew, J. P. Strongly Constrained and Appropriately Normed Semilocal Density Functional. *Phys. Rev. Lett.* **2015**, *115*, 036402.
- (19) Sun, J.; Remsing, R. C.; Zhang, Y.; Sun, Z.; Ruzsinszky, A.; Peng, H.; Yang, Z.; Paul, A.; Waghmare, U.; Wu, X.; et al. Accurate First-Principles Structures and Energies of Diversely Bonded Systems from an Efficient Density Functional. *Nat. Chem.* **2016**, *8*, 831.
- (20) Zheng, L.; Chen, M.; Sun, Z.; Ko, H.-Y.; Santra, B.; Dhuvad, P.; Wu, X. Structural, Electronic, and Dynamical Properties of Liquid Water by Ab Initio Molecular Dynamics Based on SCAN Functional within the Canonical Ensemble. *J. Chem. Phys.* **2018**, *148*, 164505.
- (21) Xu, J.; Chen, M.; Zhang, C.; Wu, X. First-principles Study of the Infrared Spectrum in Liquid Water from a Systematically Improved Description of H-bond Network. *Phys. Rev. B* **2019**, *99*, 205123.
- (22) Calegari Andrade, M. F.; Ko, H.-Y.; Car, R.; Selloni, A. Structure, Polarization, and Sum Frequency Generation Spectrum of Interfacial Water on Anatase TiO<sub>2</sub>. *J. Phys. Chem. Lett.* **2018**, *9*, 6716–6721.
- (23) DelloStritto, M. J.; Piontek, S. M.; Klein, M. L.; Borguet, E. Effect of Functional and Electron Correlation on the Structure and Spectroscopy of the Al<sub>2</sub>O<sub>3</sub>(001)–H<sub>2</sub>O Interface. *J. Phys. Chem. Lett.* **2019**, *10*, 2031–2036.
- (24) Ohto, T.; Dodia, M.; Xu, J.; Imoto, S.; Tang, F.; Zysk, F.; Kühne, T. D.; Shigeta, Y.; Bonn, M.; Wu, X.; et al. Accessing the Accuracy of Density Functional Theory through Structure and Dynamics of the Water–Air Interface. *J. Phys. Chem. Lett.* **2019**, *10*, 4914–4919.
- (25) Trout, B. L.; Parrinello, M. Analysis of the Dissociation of H<sub>2</sub>O in Water Using First-Principles Molecular Dynamics. *J. Phys. Chem. B* **1999**, *103*, 7340–7345.
- (26) Trout, B. L.; Parrinello, M. The Dissociation Mechanism of H<sub>2</sub>O in Water Studied by First-Principles Molecular Dynamics. *Chem. Phys. Lett.* **1998**, *288*, 343–347.
- (27) Nelson, J. G.; Peng, Y.; Silverstein, D. W.; Swanson, J. M. J. Multiscale Reactive Molecular Dynamics for Absolute pKa Predictions and Amino Acid Deprotonation. *J. Chem. Theory Comput.* **2014**, *10*, 2729–2737.
- (28) Ceriotti, M.; Fang, W.; Kusalik, P. G.; McKenzie, R. H.; Michaelides, A.; Morales, M. A.; Markland, T. E. Nuclear Quantum Effects in Water and Aqueous Systems: Experiment, Theory, and Current Challenges. *Chem. Rev.* **2016**, *116*, 7529–7550.
- (29) Silverstein, T. P.; Heller, S. T. pKa Values in the Undergraduate Curriculum: What Is the Real pKa of Water? *J. Chem. Educ.* **2017**, *94*, 690–695.
- (30) Davies, J. E.; Doltsinis, N. L.; Kirby, A. J.; Roussev, C. D.; Sprik, M. Estimating pKa Values for Pentaoxyphosphoranes. *J. Am. Chem. Soc.* **2002**, *124*, 6594–6599.
- (31) Doltsinis, N. L.; Sprik, M. Theoretical pKa Estimates for Solvated P(OH)<sub>5</sub> from Coordination Constrained Car–Parrinello Molecular Dynamics. *Phys. Chem. Chem. Phys.* **2003**, *5*, 2612–2618.
- (32) Sandmann, N.; Bachmann, J.; Hepp, A.; Doltsinis, N. L.; Müller, J. Copper(II)-mediated Base Pairing Involving the Artificial Nucleobase 3H-imidazo[4,5-f]quinolin-5-ol. *Dalton Trans.* **2019**, *48*, 10505–10515.
- (33) Sprik, M. Coordination Numbers as Reaction Coordinates in Constrained Molecular Dynamics. *Faraday Discuss.* **1998**, *110*, 437–445.
- (34) Sprik, M. Computation of the pK of Liquid Water Using Coordination Constraints. *Chem. Phys.* **2000**, *258*, 139–150.
- (35) Stoyanov, E. S.; Stoyanova, I. V.; Reed, C. A. The Structure of the Hydrogen Ion (H<sub>aq</sub><sup>+</sup>) in Water. *J. Am. Chem. Soc.* **2010**, *132*, 1484–1485.
- (36) Errington, J. R.; Debenedetti, P. G. Relationship between Structural Order and the Anomalies of Liquid Water. *Nature* **2001**, *409*, 318.
- (37) Skinner, L. B.; Huang, C.; Schlesinger, D.; Pettersson, L. G. M.; Nilsson, A.; Benmore, C. J. Benchmark Oxygen-Oxygen Pair-Distribution Function of Ambient Water from X-Ray Diffraction Measurements with a Wide Q-Range. *J. Chem. Phys.* **2013**, *138*, 074506.
- (38) Rappoport, D.; Crawford, N. R. M.; Furche, F.; Burke, K. Approximate Density Functionals: Which Should I Choose? In *Encyclopedia of Inorganic Chemistry*, 2009 DOI: 10.1002/0470862106.ia615.
- (39) Car, R.; Parrinello, M. Unified Approach for Molecular Dynamics and Density-Functional Theory. *Phys. Rev. Lett.* **1985**, *55*, 2471–2474.