

## Dissociation Mechanism of Acetic Acid in Water

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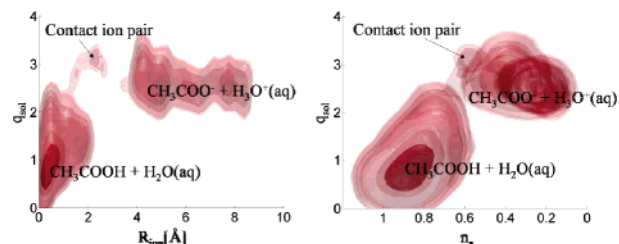
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Understanding the dissociation mechanism of a weak acid in aqueous solution is of great importance not only for acid–base chemistry but also for understanding biological processes. Most theoretical efforts have been so far directed toward the accurate  $pK_a$  estimation of weak acids such as water,<sup>1a,b</sup> biological intermediates,<sup>1c</sup> and amino acid residues.<sup>1d</sup> A detailed microscopic mechanism for weak acid dissociation in solution is available only for the auto-ionization in water.<sup>2</sup> Determining the reaction pathway for the proton dissociation from a weak acid and its subsequent diffusion in solution remains an important challenge due to the long time scale involved in the reaction and, more importantly, to the complex solvent reorganization required.

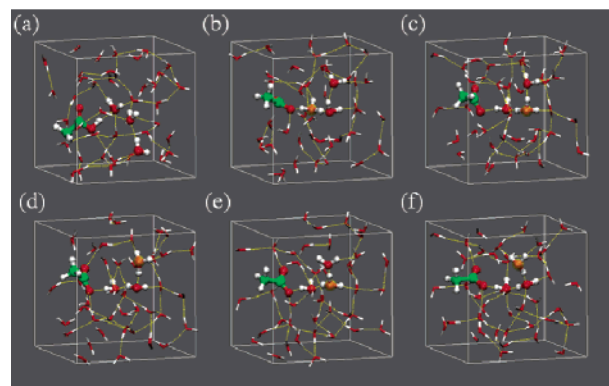
Here, we study the dissociation mechanism of acetic acid, a prototypical weak acid with a  $pK_a$  value of  $\sim 4.8$ , by employing Car–Parrinello (CP)-based metadynamics<sup>3</sup> and transition path sampling.<sup>4</sup> Simulations<sup>5</sup> were performed for a system consisting of a single acetic acid molecule and 43 water molecules in a periodically repeated cubic cell whose size is determined from the experimental density.<sup>6</sup> The HCTH/120<sup>7</sup> density functional was employed because it was reported recently to accurately describe the properties of liquid water.<sup>7a,8,9</sup>

In a preliminary molecular dynamics run at a temperature of 300 K the system remained in its initial state, and no dissociation event was observed. Using metadynamics, we now allow the system to escape the free energy minimum of the reactant and to explore the dissociated product state. This is achieved by biasing the dynamics with a history-dependent term that fills the free energy surface defined by a few pre-chosen collective variables (CVs).<sup>5</sup> To observe the formation of a stable product we had to use three CVs, to keep into account not only the deprotonation of the acetic acid but also the solvation structure of the hydronium ion that is formed and its distance from the acetate ion. The CVs are all defined as differentiable functions of the atomic coordinates, as required for applying CP metadynamics (see Supporting Information for an explicit definition). The CVs are: (1) the number  $n_a$  of hydrogen (H) atoms chemically bonded to the hydroxyl oxygen, (2) the distance  $R_{\text{ion}}$  between the hydronium and the acetate, and (3) the number of H-bonds  $q_{\text{sol}}$  formed by the hydronium. This variable is introduced since a water molecule normally forms four H-bonds, whereas a hydronium ion forms only three, and this makes the structure of their solvation shell very different.

By performing metadynamics with these three variables, the dissociation is observed after approximately 5 ps. The corresponding free energy is depicted in Figure 1 and shows a very well-defined minimum in the reactant region, separated from the product state by a shallow transition area, and a tiny local minimum in between. Some configurations along the metadynamics trajectory are reported in Figure 2.



**Figure 1.** The free energy as a function of the three CVs, projected onto  $q_{\text{sol}}$  and  $R_{\text{ion}}$  (left), and on to  $q_{\text{sol}}$  and  $n_a$  (right). The isosurfaces are at the value of  $-0.5$ ,  $-0.6$ ,  $-1.0$ ,  $-1.5$ ,  $-5.5$ ,  $-8.0$  kcal/mol in order of color strength.

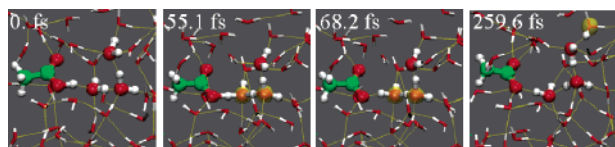


**Figure 2.** Some configurations along the metadynamics trajectory. The acetic acid molecule and the water molecules involved in the dissociation are represented with balls-and-sticks. Other molecules are represented with lines. White, red, and green indicate H, O, and C atoms, respectively. The hydronium oxygen, which has an extra proton within a cutoff radius of  $1.32 \text{ \AA}$ , is marked with a bigger yellow sphere. The dashed yellow line denotes the H-bond.

In the reactant state (Figure 2a) a water molecule is H-bonded to the hydroxyl and to other three water molecules with a tetrahedral coordination. At 4.5 ps, one H-bond in the first solvation shell of this water molecule is broken, forming at 5.5 ps a structure that can accommodate the nascent hydronium ion. At this point, in a concerted manner, the hydroxyl O–H bond is broken, and the proton is released in the solvent, forming a contact ion pair (Figure 2b). This state corresponds to the tiny minimum between reactants and products in Figure 1. The contact ion pair (Figure 2b) is separated from the reactant well by a tiny barrier. In a standard molecular dynamics run, this contact ion pair returned to neutral reactant state within  $\sim 100$  fs. After an additional 0.3 ps of metadynamics, the contact ion pair gets separated, leading to a free hydronium ion (Figure 2c). Denoting by  $L$  the number of H-bonds in the shortest H-bond wire connecting the hydronium ion and the acetate ion, the state in Figure 2c corresponds to  $L = 2$ . The next configuration that is explored (Figure 2d) is characterized by  $L = 3$ . The transition to this configuration is triggered by the breaking of one of the H-bonds formed by the water molecule that accepts

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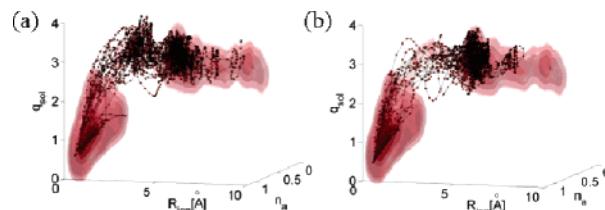
**Figure 3.** Four snapshots of one of the transition paths obtained from TPS, showing the dissociation of the acetic acid without the formation of the (metastable) contact ion pair intermediate.

the proton. Afterward, several other states with  $L > 1$  are explored. Configurations 2e and 2f are, for example, characterized by  $L = 2$  and  $L = 3$ , respectively.  $L = 4$  is the maximum separation between the two ionic species observed during the simulation. We note that due to the finite cell size the reaction cannot proceed toward higher ionic separation. This can influence the relative depth of the product and reactant free energy wells but should not change the reaction mechanism. The transition between states with different  $L$  is always triggered by a solvent fluctuation in which the hydronium recovers the normal solvation structure of a water molecule or the water molecule that accepts the extra proton acquires, due to a fluctuation, the hydronium solvation structure.

More insight on the reaction mechanism is obtained by transition path sampling (TPS).<sup>4</sup> The configurations along the metadynamics trajectory represented in Figure 2 are evolved forward and backward in time with initial velocities generated from a Maxwell distribution at 300 K. The resulting trajectory is accepted as a transition path if it connects reactants and products ( $L > 2$ ) within 0.5 ps. The above shooting procedure is repeated for a randomly chosen configuration along the existing transition path. In this manner, we gathered a total of 21 dynamic transition paths. All transition paths were obtained by using the configuration 2e as the initial shooting configuration, whereas the configurations 2b, 2c, 2d are committed to the reactants and 2f is committed to the products. The saddle point in the free energy surface (Figure 1) is localized between configurations 2b and 2c, while configuration 2e is approximately 0.6 kcal/mol lower in free energy, on the side of the products. This small discrepancy between the TPS and metadynamics results is likely to derive from the relatively short time used to reconstruct the free energy surface by metadynamics.

In 11 of the TPS reactive trajectories, the dissociation takes place through the mechanism predicted by metadynamics and represented in Figure 2: the reaction is initiated by a solvent rearrangement around the water molecule that is H-bonded to the hydroxyl and captures the proton from the acid. From the resulting contact ion pair, a proton is then transferred to the next water molecule, and subsequently, the free ion pair diffuses away. Similar to what is observed in the metadynamics trajectory, a contact ion pair evolves toward a free ionic product state due to a solvent rearrangement.

In 10 of the reactive trajectories obtained by TPS the dissociation takes place through a slightly different channel (Figure 3). The dissociation is not triggered by the breaking of one of the H-bonds formed by the water molecule that is in contact with the hydroxyl. Instead, the proton of the acid is rapidly released into the solution without forming the contact ion pair. During the proton transfer, a Zundel-ion-like complex is temporarily formed, with the extra proton shared by the water molecule in contact with the hydroxyl and one of the water molecules of its solvation shell.



**Figure 4.** CV trajectories of the transition paths, involving (a) the formation of a contact ion pair as indicated by metadynamics and (b) the formation of a Zundel-ion-like proton complex, drawn on top of the free energy surface.

For both the mechanisms observed by TPS the dynamic trajectories are compatible with the free energy surface, as shown in Figure 4. This indicates that the three collective variables used in this work are able to capture, at least qualitatively, the physics of the dissociation process. The trajectories corresponding to the first mechanism (Figure 4a) reside for a significant time in the contact ion pair region before evolving toward reactants or products.

Hence, the contact ion pair is a metastable intermediate also in a dynamical sense. At variance with what is observed in water auto-ionization, in which a key role is played by the H-bond wires, acetic acid dissociation is not necessarily driven by the breaking of the H-bond wire connecting the ions. The dissociation is also triggered by a solvent reorganization around the proton-accepting water.

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**Supporting Information Available:** Computational details of the CPMD, metadynamics setup, mean square displacements (MSD) of the water oxygen atoms. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Our system remained in the liquidlike state during the simulation, as shown by MSD as a function of time (See Figure 1SI).<sup>5</sup>

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