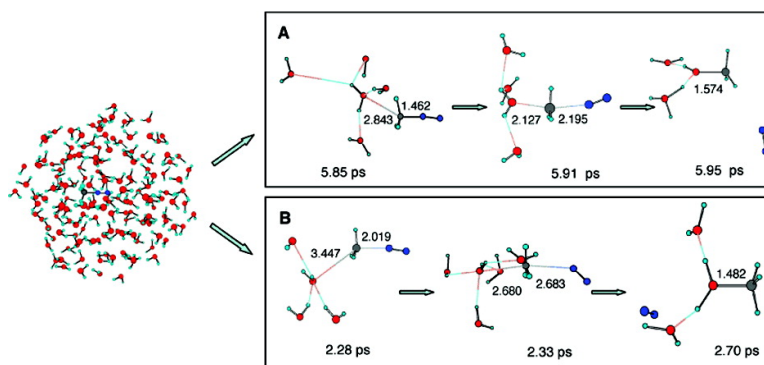


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## How Does an S<sub>N</sub>2 Reaction Take Place in Solution? Full Ab Initio MD Simulations for the Hydrolysis of the Methyl Diazonium Ion

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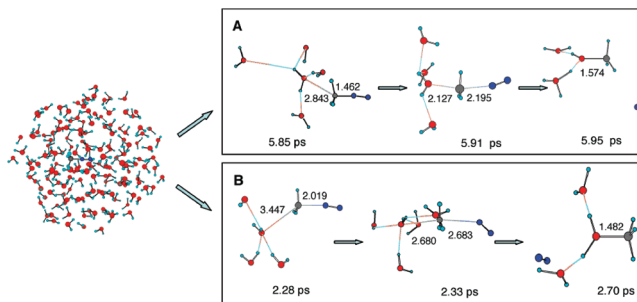
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The traditional reaction mechanism in organic chemistry considers that the hydrolyses of CH<sub>3</sub> substrates (CH<sub>3</sub>-X, X = leaving group) proceed via a concerted pathway, in which the CH<sub>3</sub>-X bond cleavage is facilitated by the H<sub>2</sub>O-CH<sub>3</sub> bond formation. One explanation is that the CH<sub>3</sub> cation is unstable and could never form in solution without an interaction with water molecules. This is known as the enforced concerted mechanism.<sup>1</sup> Such a mechanism is intuitively reasonable, since solvent reorganization is believed to be faster than bonding changes in reacting substrates and hence there is enough time for a solvent molecule to react as a nucleophile. However, recent molecular dynamics (MD) simulation studies suggested cases where dynamic effects cause a behavior that differs from what is predicted by the transition state theory<sup>2-5</sup> and, in particular, a seemingly concerted reaction actually takes place via stepwise processes with bond-cleavage and bond-formation steps occurring successively.<sup>6,7</sup>

An important goal of mechanistic studies of chemical reactions is to see how atoms in reacting molecules behave at the molecular level and to understand why they do so. Reactions in solution have been analyzed computationally using the combined quantum mechanical/molecular mechanical (QM/MM) method, in which a large number of solvent molecules are treated as discrete molecules within the MM framework.<sup>8,9</sup> Although the QM/MM method can treat chemical events in solution at a reasonable computational expense, it has the inherent limitation that nucleophilic participation by solvent molecules cannot be treated by the classical MM scheme. Thus, a full QM method is inevitably required to describe the hydrolysis mechanism of CH<sub>3</sub> substrates. The fragment molecular orbital (FMO)-MD scheme, which treats the whole system in a full QM fashion, makes it possible to deal with solution reaction dynamics with a reasonable number of solvent molecules explicitly with the accuracy of the given QM level.<sup>10-12</sup>

The present article describes the results of full quantum mechanical FMO-MD simulations for the reaction of the methyl diazonium ion, CH<sub>3</sub>N<sub>2</sub><sup>+</sup>, in water, which is one of the most facile S<sub>N</sub>2 reactions known. In addition, the configuration analysis for fragment interaction (CAFI)<sup>13</sup> was applied to obtain the interaction modes and energies for the attacking water molecule and the substrate during the reaction. Since the purpose of this study is to see how the reaction takes place and how the solvent participates in the reaction, the MD simulation has to be started at the reactant state without presupposition, which necessarily makes the reactions rare to occur. One way to observe a rare event is to inject an excess energy on the reaction coordinate mode, that is, the CH<sub>3</sub>-N<sub>2</sub> stretching vibrational mode in the present reaction. However, this



**Figure 1.** Initial droplet structure and structures of substrate and nearby water molecules along type A and B trajectories. Numbers are atomic distances in Å.

poses an artificial perturbation on the reaction and may hinder us from observing the inherent nature of the reaction. Another way to obtain productive trajectories is to run the simulation with larger kinetic energy than in the actual experiment. We took the second choice and ran the simulations of the reaction of CH<sub>3</sub>-N<sub>2</sub><sup>+</sup> in water at higher temperatures.

FMO-MD simulations at HF/6-31G were carried out by using a water droplet model, in which CH<sub>3</sub>-N<sub>2</sub><sup>+</sup> is located at the center of gravity of a sphere consisting of 156 water molecules. The initial structure of CH<sub>3</sub>-N<sub>2</sub><sup>+</sup> was taken from the gas-phase optimized structure at HF/6-31G, which was equilibrated in the water droplet with the substrate structure fixed for 0.5 ps at 300 K, and then for 5.0 ps at 1000 K. We took 15 seeds from these 5-ps initial equilibrations, ran calculations at 700 K, and obtained 10 productive trajectories leading to the substituted products, CH<sub>3</sub>-OH<sub>2</sub><sup>+</sup> + N<sub>2</sub>. Although the number of productive trajectories was small, the results showed reasonable diversity together with some common features. The trajectories can be classified into three groups: tight S<sub>N</sub>2, loose S<sub>N</sub>2, and intermediate types.

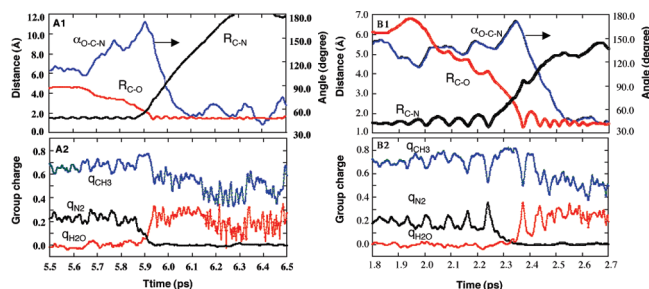
Figure 1 illustrates the initial water droplet, and the structures of CH<sub>3</sub>N<sub>2</sub><sup>+</sup> and nearby water molecules at the transition regions. In Figure 2 are shown the time-dependent changes of geometries and charges along trajectories. Trajectory A, in which the geometrical constraint was turned off at 5.5 ps, shows tight S<sub>N</sub>2-type features, whereas trajectory B, for which the constraint was released at 1.8 ps, exhibits loose S<sub>N</sub>2-type characteristics. Detailed analyses of the time-dependent changes of the mode of interaction between the attacking H<sub>2</sub>O and CH<sub>3</sub>N<sub>2</sub><sup>+</sup>, examined by using the CAFI technique are given in the Supporting Information (Figures S1-S2).

Trajectory A provides a molecular level picture of how the tight S<sub>N</sub>2 reaction takes place. The C-N bond cleavage and the C-O bond formation occur concertedly within ~100 fs around *t* = 5.91 ps (Figure 1A). The transition point where the two atomic distances

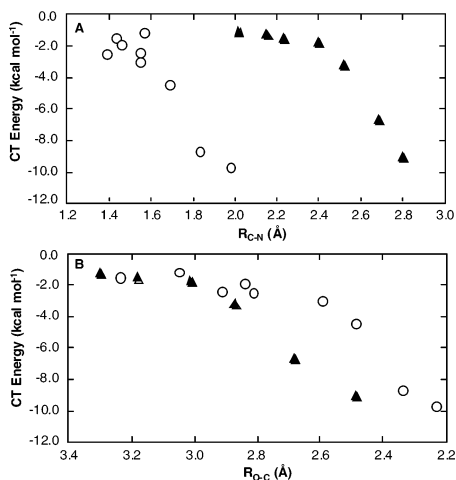
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**Figure 2.** Variations of O–C and C–N atomic distances and O–C–N angle (upper) and group charges (lower) along trajectory A (left) and B (right).



**Figure 3.** Charge transfer interaction energies between attacking H<sub>2</sub>O and CH<sub>3</sub>N<sub>2</sub><sup>+</sup> vs (A) C–N and (B) O–C distances. Open circle is for trajectory A and filled triangle is for trajectory B.

become equal occurs with a tight structure with the distances of 2.15 Å at  $t = 5.90$  ps. The O–C–N angle, which is small and less than 140° before the reaction, rapidly increases when the reaction starts to occur, and becomes 166° at  $t = 5.91$  ps (Figure 2). Thus, the results clearly indicate the synchronicity of the bond formation–bond cleavage processes, consistent with the qualitative picture of the enforced S<sub>N</sub>2 mechanism of the diazonium cation decomposition.<sup>14</sup> Finally, one of the hydrogens originally on the attacking H<sub>2</sub>O molecule starts to move to a neighboring H<sub>2</sub>O when the O–C bond is formed. It is noticeable, however, that the O–C–N angle deviates significantly from the 180° expected for an ideal S<sub>N</sub>2 transition structure. The result suggests that the real picture of an S<sub>N</sub>2 reaction does not necessarily follow the typical and ideal reaction profile as described in chemistry textbooks.

Trajectory B gives basically similar results and shares common features characteristic of concerted S<sub>N</sub>2 processes as described above. The C–N bond cleavage and the O–C bond formation occur concertedly within the ~150 fs time scale (Figure 2). However, trajectory B is different from A in that the transition point, where the two atomic distances become equal, is associated with a much looser structure with the distances of 2.68 Å. It is noticeable that the C–N bond cleavage starts to occur without the attacking H<sub>2</sub>O molecule coming close to the backside of CH<sub>3</sub>–N<sub>2</sub><sup>+</sup>. The trajectory indicates that the reaction proceeds via a two-stage concerted process, and the product CH<sub>3</sub>OH stays in the protonated form for a longer time.

The mode of orbital interaction between the attacking H<sub>2</sub>O and the CH<sub>3</sub> moiety obtained by CFI calculations (Figures 3, S1, and S2) clearly shows the difference between the two trajectories. In trajectory A, one water molecule interacts with a C–H bond of

CH<sub>3</sub>N<sub>2</sub><sup>+</sup> with the C–N bond intact at 5.82 ps, then the water molecule moves toward the backside of the CH<sub>3</sub>–N<sub>2</sub> bond at 5.87 ps, and finally the C–N bond begins to be cleaved at 5.88 ps (Figure S1). In trajectory B, on the other hand, the C–N bond is already partially cleaved when a water molecule interacts with the C–H bond of the CH<sub>3</sub>–N<sub>2</sub><sup>+</sup> molecule at 2.28 ps, and then the lone pair of the water molecule interacts with the p-orbital of the CH<sub>3</sub> moiety after 2.29 ps (Figure S2).

Charge-transfer (CT) interaction between the two fragments increases rapidly when the C–N distance increases to 1.6 Å for trajectory A, whereas for trajectory B the CT becomes large only when  $R_{C-N}$  is 2.4 Å or longer (Figure 3A). Clearly the C–N bond cleavage and O–C bond formation events take place in a two-stage fashion in the latter case. The CT interaction energy is larger for trajectory B than for A at  $R_{C-O} = 2.6$  Å (Figure 3B), because at the same C–O distance the C–N bond is cleaved to a larger extent and hence the CH<sub>3</sub> moiety has more positive charge for trajectory B than A.

Most of other trajectories obtained in the present study exhibit intermediate characters between trajectories A and B. The diversity of the reaction can be seen in Figure S3, in which the ten trajectories are plotted on a two-dimensional reaction map. It was shown that the reaction pathway differs for different reacting molecules, the picture quite different from the well-accepted image of chemical reactions and also from what is commonly obtained from MO studies. An important message is that the chemical reaction does not always proceed through the lowest energy pathway with optimal solvation.

In conclusion, the present simulations for the first time illustrate how the atoms in reacting molecules behave in solution at the molecular level, which was made possible by using full QM simulations with the recently developed FMO-MD methodology.<sup>12</sup>

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**Supporting Information Available:** Figures S1–S3 for the results of CFI calculations, and computational details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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