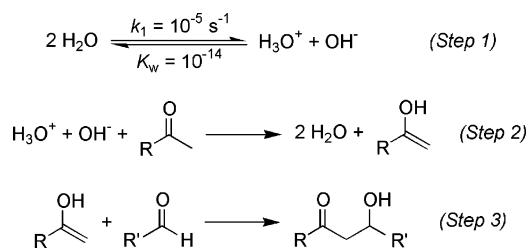# JOC Article

Acid/Base Catalysis by Pure Water: The Aldol Reaction

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The mechanism of aldol reactions in pure water has been studied with density functional calculations (B3LYP/6-311++G(3d,3p)//B3LYP/6-31G(d)). The reaction is a three-step process that involves: (1) water autoionization generates catalytic hydroxide and hydronium ions, (2) hydroxide and hydronium ions rapidly convert donor aldehyde or ketone into enol, and (3) C−C bond formation and proton transfer occur to give the aldol product. This study provides a general basis for understanding acid/base catalysis by pure water.

Introduction

Enzyme-catalyzed reactions frequently involve acid and base-catalyzed processes even at pH 7. This extraordinary catalysis is achieved by a variety of chemical and orientation effects perfected over years of evolution.[1] Uncatalyzed reactions that require acid or base catalysis occur at slow, but not negligible, rates in water.[2] The rates and mechanisms of such reactions are of interest as benchmarks to compare with rates of enzyme-catalyzed processes.[3] This article shows how the autoionization of water can serve as a mechanism for the acid/base catalysis of the aldol reaction, a typical organic reaction that requires acid or base catalysis.

Theoretical investigations of aqueous aldol reactions were recently reported for the reaction of acetone and acetaldehyde.[4] It was proposed that the acetone enol is preformed by an unspecified mechanism, and the enol reacts with acetaldehyde through a two-step mechanism requiring two explicit catalytic water molecules. The rate-determining step involves C−C bond formation, proton transfer from water to acetaldehyde, and C−OH bond formation to give a β-hydroxy-geminal diol intermediate. In the second step, a second water molecule facilitates the cleavage of the C−OH bond via protonation to yield the aldol product, and the two explicit catalytic water molecules are regenerated. Since acetone enol is 9 kcal/mol above acetone,[5] the activation energy is 42 kcal/mol. The necessity to assemble three molecules in the slow step will import an additional large entropic penalty. In any case, the proposed reaction mechanism could not occur at 37 °C.

We have performed density functional calculations with the B3LYP functional to reinvestigate the mechanism of aqueous aldol reaction using two model systems: the reaction of acetaldehyde with acetaldehyde and the reaction of acetaldehyde with acetone. The catalysis of reaction by the spontaneous autoionization of water is proposed as a relatively low energy path for the aldol reaction in pure water. The general mechanism has wide applications to other reactions occurring spontaneously in water.

Background

In 2002, Janda and co-workers discovered that nornicotine, a minor metabolite of nicotine, is capable of

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(2) For example, hydrolysis of carbon dioxide occurs within several seconds in neutral aqueous solution at room temperature, cis−trans isomerization of peptide bonds takes place within a few minutes, and rearrangement of chorismic acid to prephenic acid happens over a period of several hours. (a) Roughton, J. F. W. *J. Am. Chem. Soc.* **1941**, 63, 2930−2934. (b) Grathwohl, C.; Wüthrich, K. *Biopolymers* **1981**, 20, 2623−2633. (c) Andrews, P. R.; Smith, G. D.; Young, I. G. *Biochemistry* **1973**, 12, 3492−3498.

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(5) The 9 kcal/mol energy difference comes from the calculations shown in Scheme 3.

SCHEME 1.   Reaction Mechanisms of the Aldol Reaction of Acetone Enol and Acetaldehyde in THF and in H₂O Proposed by Dickerson et al.[4]
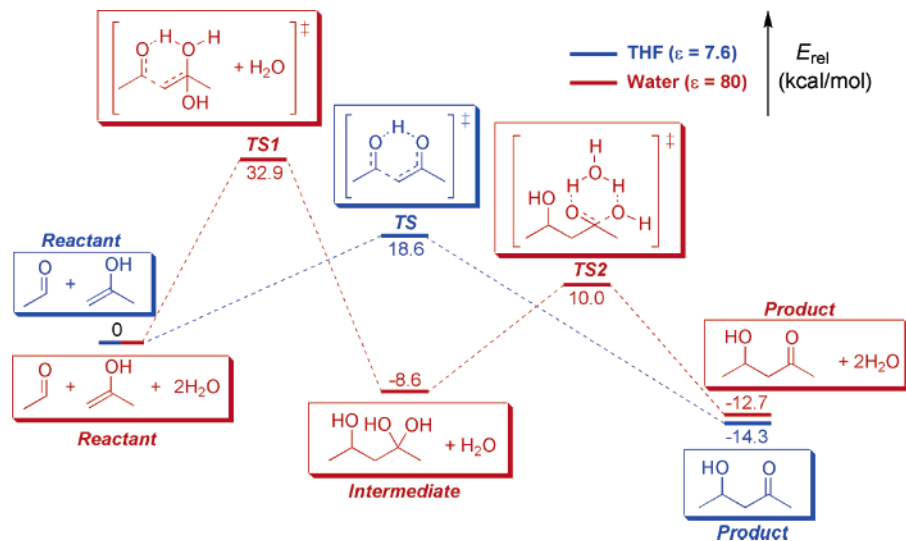
catalyzing aldol reactions under buffered aqueous conditions.[6] Other compounds containing similar functionality (e.g., proline and pyrrolidine) were not competent catalysts.[4] To explore the mechanism of these processes, Dickerson et al. carried out density functional studies using acetaldehyde and acetone as the reactants and a variety of amines as potential catalysts.[4] The studies were performed for THF and water solvents (Scheme 1).

For THF, a single concerted transition state involving acetone enol and acetaldehyde was proposed (blue in Figure 1). In this step, C−C bond formation and proton
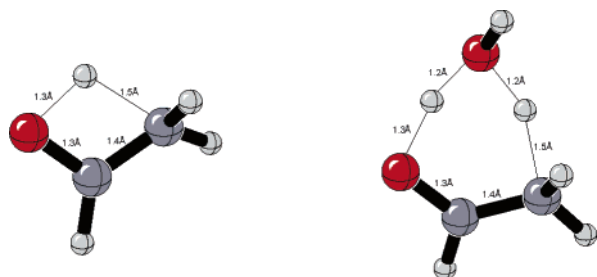

FIGURE 1. Geometries of the transition states for uncatalyzed 1,3-H shift (left) and water-catalyzed 1,3-H shift (right) in acetaldehyde.

transfer occurs concurrently at 18.6 kcal/mol to generate the aldol product. For the aqueous reaction, Dickerson et al. proposed that the reaction occurs through a stepwise mechanism (red in Figure 1). Two explicit water molecules are necessary for proton transfer. In the first step of the reaction, C−C bond formation, proton transfer from water to acetaldehyde, and C−OH bond formation occur simultaneously to give a β-hydroxy-geminal diol intermediate. In the following step, a second water molecule promotes the cleavage of the C−OH bond via proton donation to yield the aldol product, and the two explicit water molecules are regenerated. Formally, each step of the mechanism is catalyzed by a water molecule to complete a six-membered transition state. The activa-

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tion barrier of the aqueous aldol reaction by this mechanism is 32.9 kcal/mol, and the first step is the rate-determining step. On the basis of these calculations, Dickerson et al. proposed that the mechanism of the nornicotine-catalyzed aldol reaction proceeds via a two-step mechanism very similar to the aqueous aldol reaction, except that one reactant is the nornicotine-derived enamine instead of enol.[4]

Although these calculations shed some light on the nornicotine reaction, the mechanism proposed for the aldol reaction in water is unlikely. First, the authors did not include the 9 kcal/mol higher energy of the enol of acetone compared to acetone. Second, it is unclear why the aqueous aldol reaction would take place through the high energy pathway (red in Figure 1), especially when entropy would highly disfavor the red pathway. Third, the authors noted that the uncatalyzed aldol reaction in organic solvent is much faster than that in aqueous solution.

The mechanism by which reaction involving proton transfer occurs in the absence of acid or base catalysts is of general interest. For example, autocatalytic reactions such as the bromination of ketones, in which the catalyst HBr is generated, require some non-HBr dependent reaction to begin the process. Aside from unknown "adventitious catalysts", how might these reactions begin in pure water? In the reaction of specific interest here, Dickerson et al. have proposed reasonable mechanisms based on enol reactant, but the formation of enol requires acid−base catalysis in water or concerted 1,3-H shift of acetone.

Our investigations are relevant to the mechanisms of condensation, dehydration, hydrolysis, decarboxylation, and all other reactions involving proton transfer without added acid or base catalysts.

Results and Discussion

We have considered three possible pathways for the uncatalyzed aldol reaction between two acetaldehyde molecules (Scheme 2). Pathway I involves the direct proton transfer between two acetaldehydes to form

SCHEME 2.   Aqueous Aldol Reaction between Acetaldehyde and Acetaldehyde (B3LYP/6-311++G(3d,3p)// B3LYP/6-31G(d) Calculations Using the CPCM Solvation Model)
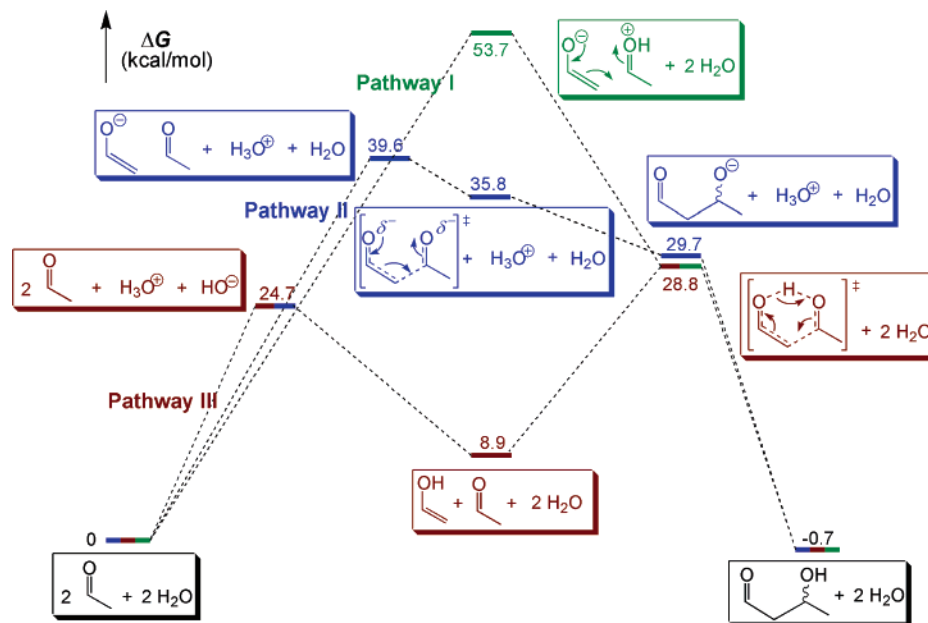
enolate and protonated acetaldehyde. Here, one acetaldehyde acts as acid, and the other as base, to generate an ion pair that is high in energy, even with aqueous solvation. The two water molecules included in the pathway are not directly involved but are present so as to allow direct comparison with pathways II and III. Pathway I requires 53.7 kcal/mol for producing the ion pair in water. Subsequent C−C formation and proton transfer occur without barriers to give the aldol product.

Pathway II involves the deprotonation of acetaldehyde by a water molecule acting as a base; this process requires 39.6 kcal/mol. The enolate then reacts with an acetaldehyde to give deprotonated 3-hydroxybutanal at 29.7 kcal/mol. The activation barrier of C−C bond formation is −3.8 kcal/mol due to the formation of an ion−dipole type of complex between the enolate and acetaldehyde.[7] Finally, protonation by hydronium occurs to give 3-hydroxybutanal. The difference in pathways I and II corresponds to 14.1 kcal/mol, because water is more basic than acetaldehyde; the difference corresponds to a 10 pK_a unit difference. Experimentally, the pK_a of H$_3$O$^+$ is −1.7, and the pK_a of CH$_3$CHOH$^+$ is −10.[8] The 8 pK_a unit difference agrees reasonably well with our calculated results.

In pathway II, we consider water as a base to react directly with acetaldehyde. In fact, water is a poor base for this reaction. The pK_a of H$_3$O$^+$ is −1.7, and the pK_a of acetaldehyde is 17.[8] The equilibrium constant of the direct reaction between water and acetaldehyde to generate enolate and hydronium is 10^{-18},[7] a process that generates lower concentration of hydronium than water autoionization ($K_w = 10^{-14}$). When the substrate to be enolized is a ketone (p$K_a = 26.5$)[8] instead of acetaldehyde, the equilibrium constant of the direct reaction is 10^{-28},[2]

and even lower concentration of hydronium will be generated. Therefore in pathway III, we consider that the reaction initiates with water autoionization.

The familiar pK_a of water is 15.7, which translates to a free energy of 22.0 kcal/mol from $\Delta G = -RT \log K_a$. The rate of forward reaction (water autoionization) at room temperature has been explored both experimentally and theoretically. Experimentally, Eigen and Maeyer show that the process has a barrier of 23.8 kcal/mol;[9] the rate constant for water autoionization is 2.6×10^{-5} s^{-1} according to Burns and Moore and 5.5×10^{-6} s^{-1} according to Chatterjee et al.[10−12] Theoretically, Bakker and Nienhuys used Car−Parrinello molecular dynamics simulations to estimate a barrier of 18.8 kcal/mol,[13,14] Warshel et al. calculated the barrier to be about 16 kcal/mol with their empirical valence bond (EVB) approach,[15] and Cárdenas et al. determined the activation barrier to be 21.2 kcal/mol using ab initio calculations.[16] In our calculations of pathway III, the energy needed for water autoionization is calculated as the energy difference between isolated and solvated hydroxide and hydronium

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SCHEME 3. Aqueous Aldol Reaction between Acetaldehyde and Acetone (B3LYP/6-311++G(3d,3p)//B3LYP/6-31G(d) Calculations Using the CPCM Solvation Model)
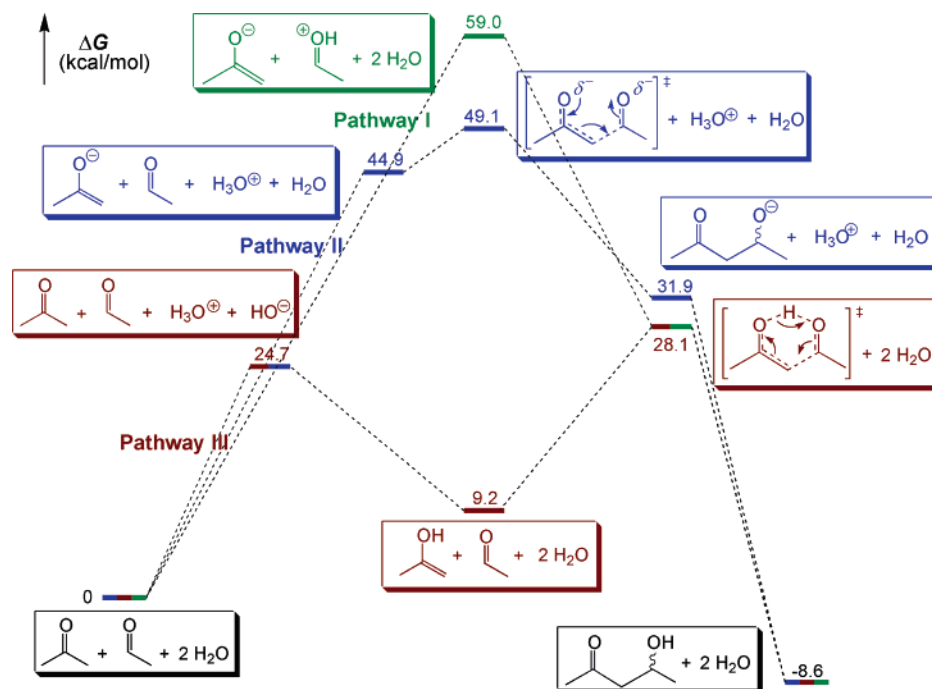
in water ($\Delta G = G_{hydroxide} + G_{hydronium} - 2 \times G_{water}$). The resulting 24.7 kcal/mol is well within the expected range from documented experimental and computed values.

Once hydroxide and hydronium are formed, very efficient general base and general acid catalysis can occur to generate the enol. Deprotonation of acetaldehyde by hydroxide requires 14.9 kcal/mol, and protonation of acetaldehyde by hydronium requires 14.1 kcal/mol. Consequently, the barrierless concerted acid and base catalysis should be much more efficient than the stepwise reaction mechanism. The enol generated then reacts with acetaldehyde to give the final product. This is the step proposed by Dickerson et al. for the THF reaction. With the participation of two water molecules to give H_3O^+ and OH^- as catalysts, pathway III is the lowest in energy ($\Delta G^{\ddagger} = 28.8$ kcal/mol), and the rate-determining step is the reaction of enol with acetaldehyde.

In pathway III, the enol is formed by the catalysis of general acid/base generated from water autoionization. We also investigated the possibility of enol formation from acetaldehyde 1,3-H shift. The transition state for this process is shown in Figure 1. The activation barrier is 70.2 kcal/mol in water. Although the process could be catalyzed by an explicit water molecule, as shown in Figure 1, the activation barrier in water (41.4 kcal/mol) is still higher than that of water autoionization. Adding more water molecules increases the activation barrier due to an additional entropy penalty.

The analogous calculated reaction coordinates for the aqueous aldol reaction between acetaldehyde and acetone are shown in Scheme 3. Upon the change of donor reactant from aldehyde to acetone, the activation barriers of paths I, II, and III become 59.0, 49.1, and 28.1 kcal/mol, respectively. Pathway III is still the most favorable by a large factor. The activation barrier we predict here for the aqueous aldol reaction between acetaldehyde and acetone, 28.1 kcal/mol, is essentially the same as the

activation barrier predicted for the aldol reaction between two acetaldehydes, 28.8 kcal/mol (Scheme 2), and involves the reaction of the enol with aldehyde.

The geometries of the rate-determining transition states in pathway III are shown in Figure 2. TS-A is the
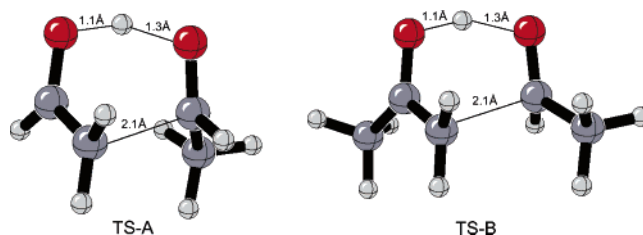

FIGURE 2. Geometries of the transition states for the aldol reaction between acetaldehyde and acetaldehyde (left) and the aldol reaction between acetaldehyde and acetone (right).

transition state for the aldol reaction between acetaldehyde and acetaldehyde, and TS-B is the transition state for the aldol reaction between acetaldehyde and acetone. As shown in Figure 2, C–C bond formation and proton transfer occur concurrently in TS-A and TS-B.

The catalytic role of water for organic reactions has been documented mainly for high-temperature water (HTW), defined as liquid water above 200 °C and supercritical water.[17] The high K_w of HTW facilitates its autoionization and gives rise to high concentrations of H_3O^+ and OH^-. In this article, we have demonstrated that water under normal temperature, such as room temperature, also plays a catalytic role. Although only the aldol reaction is addressed in this article, we expect that autoionization will produce strong acid and base catalysts and provide a mechanism for other organic reactions that occur in water.

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SCHEME 4. Aqueous Aldol Reaction
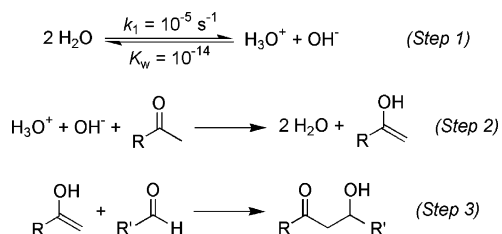
Conclusions

The mechanism of the aqueous aldol reaction is important and fundamental for understanding aldol reactions catalyzed by nornicotine and other analogues. Herein, we performed density functional calculations (B3LYP/6-311++G(3d,3p)//B3LYP/6-31G(d)) to reinvestigate the mechanism of aqueous aldol reaction. Our results predict a multistep process (Scheme 4).

Step 1 of this reaction occurs with a pseudo-first-order of $0.6-2.6 \times 10^{-5}$ s^{-1},[11,12] and the hydronium and hydroxide produced can react with an aldehyde or ketone to promote enolization (step 2). The enol then reacts directly with an aldehyde by an ene-type process to produce the aldol product (step 3).

For the reactions studied here, the rate-determining step is the C–C bond-forming step, a slow process occurring after the keto–enol equilibrium is set up by water autoionization. In other cases of more reactive aldehydes, the formation of enol or enolate could become rate-determining. Formally, water catalyzes the aldol reaction by generating hydroxide and hydronium ions, a concept that can be extended to other reactions that require acid/base catalysis, such as dehydrations, hydrolysis reactions, decarboxylations, and various types of rearrangements.

Experimental Section

Computational Methods. B3LYP/6-31G(d) has been found to be a suitable method and basis set for a variety of reactions.[18] B3LYP/6-31G(d) geometry optimizations were carried out with Gaussian 98[19] for the model systems in the gas phase. Frequency calculations were performed to verify the nature of all the stationary points as either minima or transition states and to compute free energies. Since the reactions of interest are carried out in aqueous solution,[4] solvation calculations were performed at the B3LYP/6-311++G-(3d,3p) level and with the CPCM model.[20] Geometries from gas-phase calculations were used directly.

Supporting Information Available: Cartesian coordinates of all reported structures and the free energies in water. This material is available free of charge via the Internet at http://pubs.acs.org.

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