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Density Functional Study of the Proline-Catalyzed Direct Aldol Reaction

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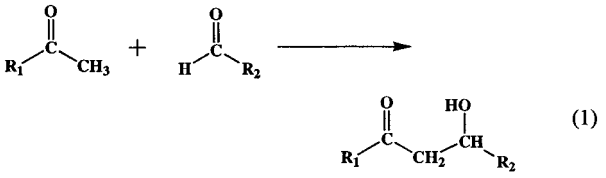
The proline-catalyzed direct aldol reaction between acetone and acetaldehyde has been investigated using density functional theory. Proline catalyzes the reaction according to the enamine mechanism characteristic of the natural class I aldolase enzymes. Although it has been postulated that the rate-limiting step in the proposed mechanism is enamine and/or C−C bond formation, the initial reaction between proline and acetone is accompanied by a very large barrier which may inhibit further progression of the reaction. However, an alternative lower energy reaction pathway is utilized when the ionizing solvent DMSO is present to assist in the formation and stabilization of separated charges. The direct aldol reaction between acetone and acetaldehyde illustrates the catalytic potential of simple organic molecules in asymmetric synthesis.

Introduction

The discovery and development of molecular species that may catalyze chemically important reactions has long been a subject of great research interest. Enzymes, nature's catalysts, enable a robust number of biologically relevant chemical transformations to occur with high catalytic efficiency and stereochemical control. To further the understanding of the fundamentals of molecular recognition and catalysis, notable attention has been directed upon developing catalytic antibodies[1,2] or biocatalysts that rival natural enzymes in efficiency but catalyze an array of chemical reactions. This has resulted in the development of novel biocatalysts for organic transformations such as the aldol reaction.[1]

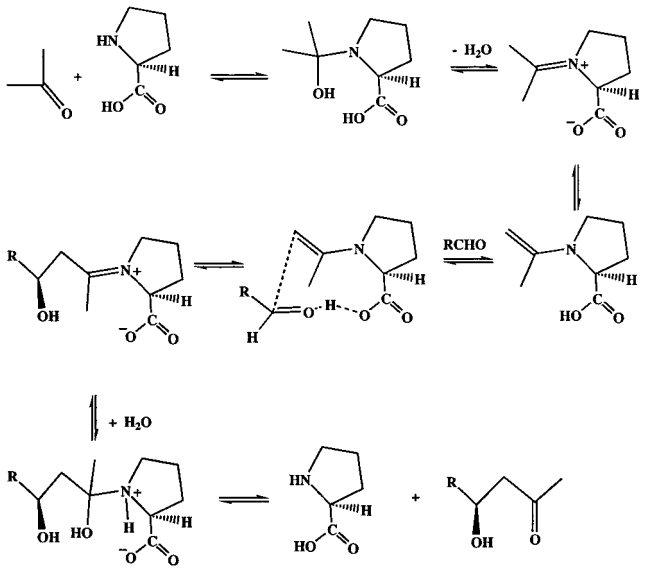


(1)

The aldol reaction, an example of which is shown above, is one of the fundamental chemical mechanisms for the formation of C−C bonds. Consequently, considerable effort has been directed upon the development of catalytic variants of the aldol reaction. Previous approaches have generally utilized transition metal-based catalysts in combination with modified substrates.[3,4] Clearly, a more attractive synthetic alternative would involve the development of a catalyst which would enable the reaction between unmodified carbonyls; the *direct* aldol reaction.

The aldol reaction exists in biological systems and is catalyzed by a powerful group of enzymes referred to collectively as the aldolase enzymes.[5−8] These enzymes are classified depending upon their mode of catalysis. The class II aldolase enzymes catalyze the aldol reaction using a zinc-cofactor. The class I aldolase enzymes, however, utilize an enamine mechanism, the chemistry of which is dependent upon a chemically reactive lysine residue in the active site of the enzyme. Using the catalytic-antibody (reactive immunization) technology, antibodies of the class I aldolase enzymes have been generated[9−15] which are programmed to function by a mechanism analogous to that used by the naturally occurring aldolase enzymes. Although the development of these biocatalysts has demonstrated the importance of the amine group in catalyzing the aldol reaction, it was only recently that the first amine-based asymmetric class I aldolase antibody was reported.

SCHEME 1: Proposed Enamine Mechanism of the Proline-catalyzed Aldol Reaction (Ref 16).



Recently, List et al.[16] reported the catalysis of the aldol reaction between acetone and 4-nitrobenzaldehyde by the simple amino acid L-proline. They proposed a mechanism (Scheme 1) in which the initial interaction between proline and acetone generates an enamine intermediate, which then may react further with an aldehyde to yield the aldol product. In addition, they found that direct asymmetric aldol reaction between acetone and a variety of aldehydes proceeds with good yields and enantioselectivities, a consequence of the chiral nature of the proline catalyst.

Density functional theory calculations are employed in the present study to examine the mechanism by which proline

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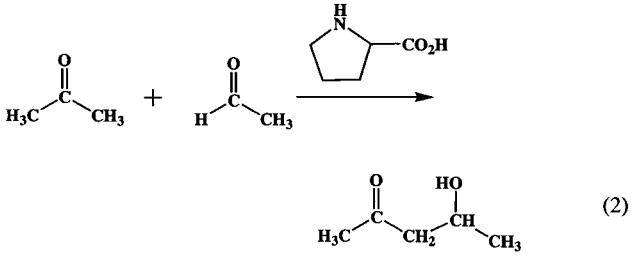
catalyses the direct aldol reaction between acetone and acetaldehyde. Although it is well-known that proline can undergo a variety of reactions with aldehydes, these side reactions were not considered in this theoretical study as they were believed to be suppressed in the original experiment[16] due to the high concentration of acetone used in the reaction mixture. In addition, the effect of solvent on the proposed mechanism has also been investigated.



(2)

Computational Methods

Density functional theory calculations were carried out using the Gaussian 98[17] suite of programs. All geometry optimizations were performed using the B3LYP functional and the 6-31G-(d,p) basis set. The B3LYP functional is composed of Becke's three-parameter hybrid exchange functional (B3),[18,19] as implemented in Gaussian 98,[20] and the correlation functional of Lee, Yang, and Parr (LYP).[21] Harmonic vibrational frequencies and zero-point vibrational energy (ZPVE) corrections were calculated at the same level of theory. Relative energies, obtained by subsequent single point calculations performed at the B3LYP/6-311+G(2df,p) level using the above geometries, were corrected with the appropriate ZPVE, i.e., B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d,p) + ZPVE. This level of theory has been used in our previous studies of catalysis.[22]

The effect of solvent on the enamine mechanism was investigated using the Onsager model.[23] DMSO, with a dielectric constant of 46.7, was utilized as the solvent to model the original reaction conditions. All bond lengths are in angstroms (Å) and energies in kJ mol^{-1}. Optimized structures (Tables S1 and S2) and total energies of all molecules on the nonsolvated and solvated surfaces (Tables S3 and S4) are summarized in the Supporting Information.

Results and Discussion

Initially, acetone interacts with proline in the gas-phase (Figure 1a) via an O···HO bond of 1.763 Å, forming complex **1a**, lying lower in energy by 13.3 kJ mol^{-1}. A formal C−N bond between acetone and proline forms as the proton on the N of proline is transferred simultaneously to the carbonyl oxygen of acetone in transition structure (TS) **1b**, with a barrier of 158.1 kJ mol^{-1}. Substantial energy (124.1 kJ mol^{-1}) is released as the proton is completely transferred, producing complex **1c**. A zwitterionic imine complex **1d** is formed as a water molecule, which interacts with the anionic carboxyl group via a short and strong O$^-$···HO hydrogen bond of 1.314 Å, is generated in complex **1d**, lying 72.1 kJ mol^{-1} higher in energy than the reactants. As the hydrogen bond between the water molecule and the carboxyl group elongates to 1.702 Å, complex **1e** is generated, lying higher in energy by 28.5 kJ mol^{-1}.

Complete removal of the water molecule yields the isolated imine complex **1f**. As illustrated in Figure 1b, the imine complex converts to the enamine analogue by a proton transfer from the methyl group cis to the α-carbon of proline to the carboxyl group. The imine-enamine conversion passes through TS **1g**, with a barrier of 29.9 kJ mol^{-1}, before complete proton-transfer yields the enamine complex **1h**, which is 27.3 kJ mol^{-1} more stable than its imine analogue. This is the structurally and energetically preferred pathway for the tautomerism and the alternate pathway, which involves proton transfer from the methyl group trans to the α-carbon of proline to the carboxyl group, is summarized in Figure S1 of the Supporting Information. Thus, the energetically preferred orientation of the enamine double bond, which is on the substituted side of the pyrrolidine ring, is in contrast to that outlined in the proposed mechanism by List et al.[16] Enamine **1h** may undergo conversion to enamine **1h′** by rotation about the C−N bond. Although the two possible pathways available for rotation, which are summarized in Figure S2 of the Supporting Information, have barriers less than 25 kJ mol^{-1} the introduction of additional steps in the reaction mechanism does not seem as likely considering the low barrier for proton transfer from the methyl group cis to the α-carbon.

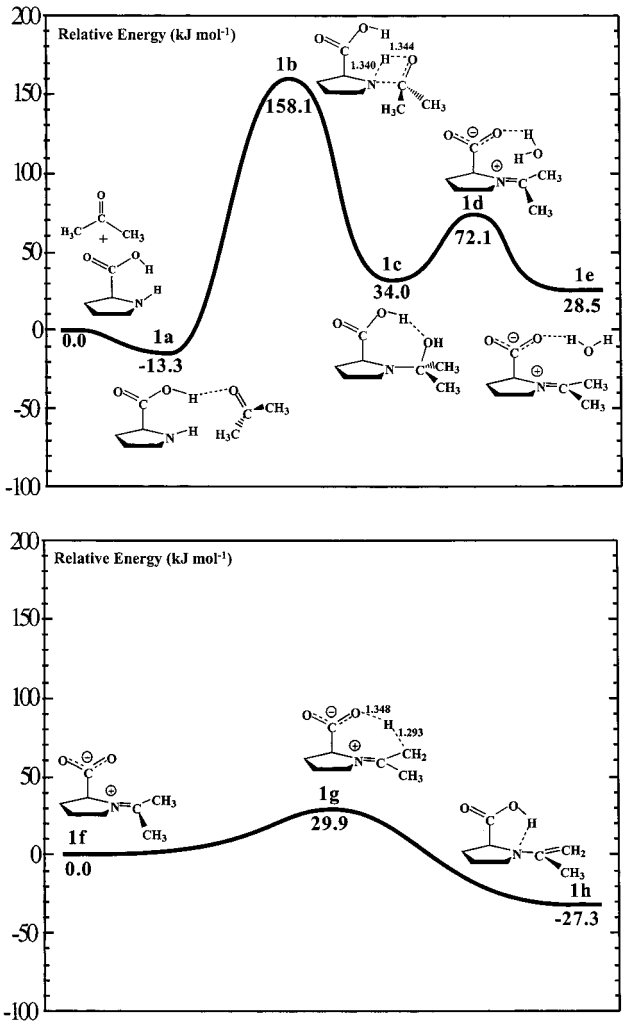


Figure 1. Schematic energy profile of the **(a)** reaction of acetone with proline yielding the imine complex, and **(b)** imine-enamine tautomerism.

The addition of acetaldehyde to enamine **1h**, which proceeds along a reaction pathway lower in energy than for the acetaldehyde addition to enamine **1h′**, is summarized in Figure 2a. Initially, acetaldehyde interacts with the enamine moiety via an O···HO hydrogen bond (2.012 Å) to form the hydrogen-bonded complex **2a** lying 21.2 kJ mol^{-1} lower in energy. As the carbonyl carbon of acetaldehyde forms a C−C bond to the terminal carbon of the alkene segment of the enamine, the proton of the carboxylic acid of proline is transferred to the carbonyl oxygen of acetaldehyde via TS **2b** with a barrier of 36.1 kJ

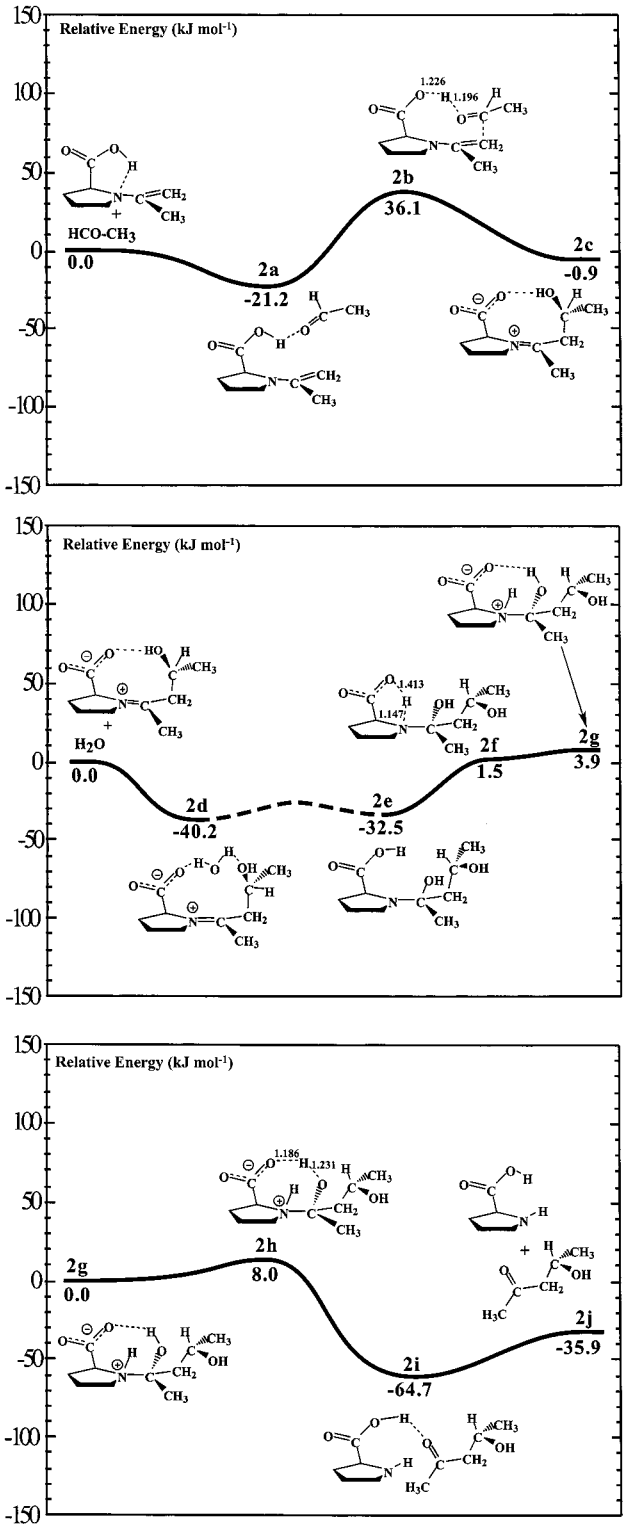


Figure 2. Schematic energy profile of the **(a)** addition of acetaldehyde to the enamine complex, **(b)** addition of water across the C═N bond of the enamine complex, and **(c)** formation of the aldol product and its subsequent release from proline.

mol^{-1}. Complete proton transfer to the attached acetaldehyde yields the zwitterionic imine complex **2c**, lying 0.9 kJ mol^{-1} lower in energy than the nonreacted enamine and acetaldehyde.

The introduction of a water molecule and its addition across the C═N bond of the substituted imine complex is illustrated in Figure 2b. The addition of H_2O to the substituted imine proline, complex **2c**, yields the doubly hydrogen-bonded complex **2d** lying 40.2 kJ mol^{-1} lower in energy. As the water

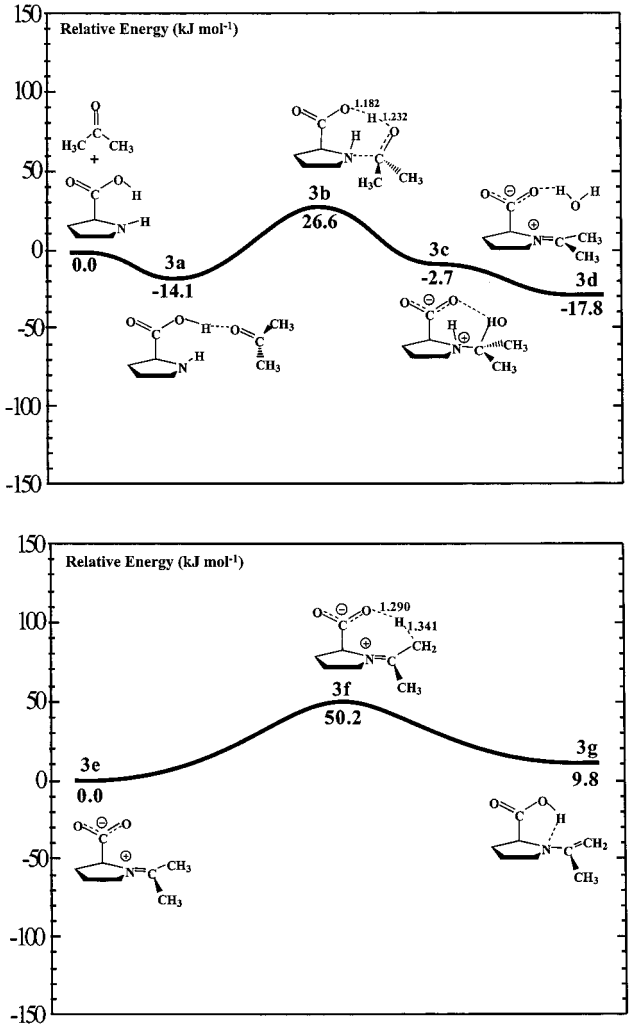


Figure 3. Schematic energy profile illustrating the effect of DMSO on the **(a)** reaction of acetone with proline yielding the imine complex, and **(b)** imine-enamine tautomerism.

molecule breaks apart and adds to the carbon of the C═N bond in the imine, complex **2e** is generated lying 7.7 kJ mol^{-1} higher in energy (32.5 kJ mol^{-1}). We were unable to locate a transition structure connecting complexes **2d** and **2e**. However, it is anticipated that should such a structure exist, it would possess a very small barrier. Proton transfer from the carboxylic acid moiety in complex **2e** to the N in proline proceeds via TS **2f**, with a barrier of 31.0 kJ mol^{-1}. Complete proton-transfer yields the zwitterionic complex **2g**, lying 2.4 kJ mol^{-1} higher in energy than TS **2f**. The final stage in the reaction, summarized in Figure 2c, involves the formation of the aldol product and its subsequent release from proline. As the hydroxyl proton in complex **2g** is transferred to the carboxylic anion of proline, the formal C−N bond between the aldol product and proline elongates, forming the hydrogen-bonded complex **2i** lying 64.7 kJ mol^{-1} lower in energy. The conversion from complex **2g** to **2i** proceeds via TS **2h** with a barrier of 8.0 kJ mol^{-1}. As the O···HO hydrogen bond of 1.796 Å between the aldol product and proline in complex **2i** breaks, the products are formed lying 28.8 kJ mol^{-1} higher in energy than the hydrogen-bonded complex **2i**.

Previously,[11] it has been suggested that enamine and C−C bond formation are rate limiting with catalysts that utilize an analogous mechanism to that proposed for class I aldolases. However, the theoretical calculations on the proposed mechanism of Scheme 1 illustrate that the formation of the enamine (**1h**) from the imine (**1f**) requires a mere 29.9 kJ mol^{-1} of

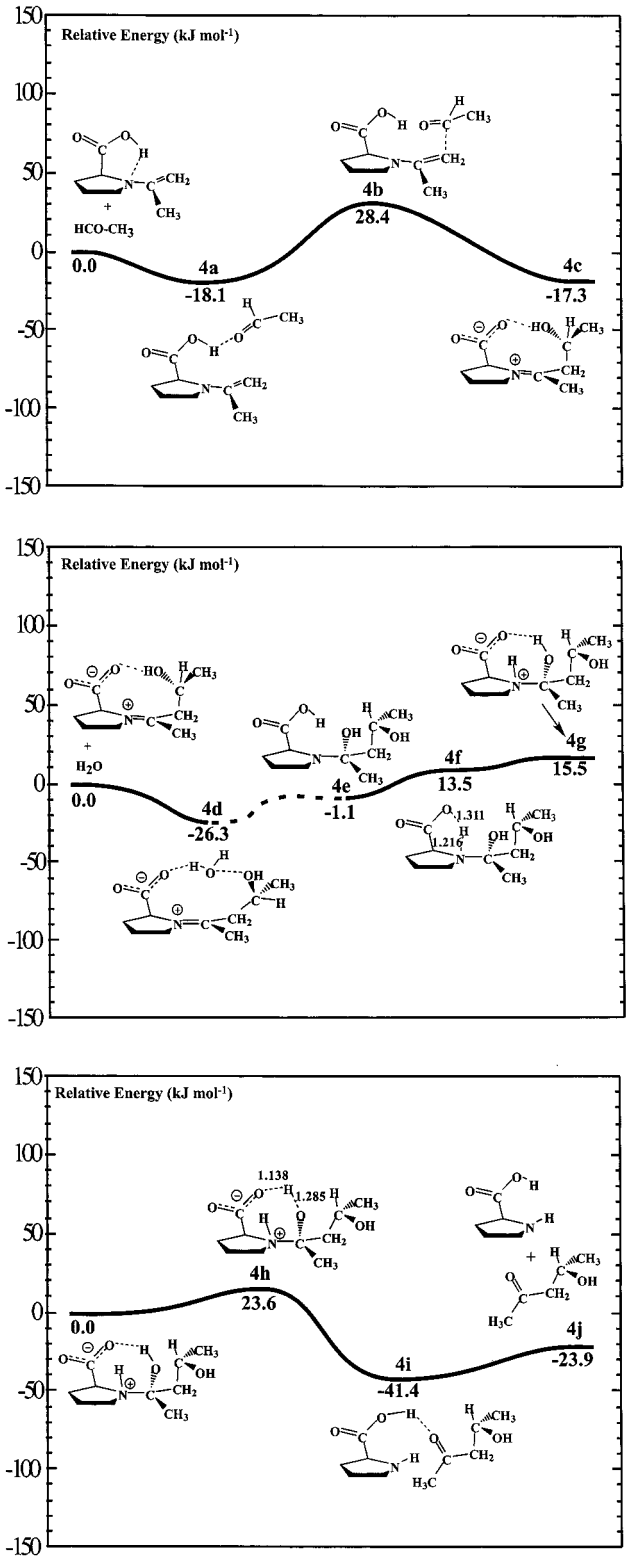


Figure 4. Schematic energy profile illustrating the effect of DMSO on the **(a)** addition of acetaldehyde to the enamine, **(b)** addition of water across the C═N bond of the enamine complex, and **(c)** formation and release of the aldol product from proline.

energy. Similarly, the formation of the C−C bond in Figure 2a, which involves the addition of acetaldehyde to the enamine (complex **2a** to **2c**), requires only 57.2 kJ mol^{-1} of energy. Thus, neither of these two steps are rate limiting in the catalysis. However, as seen in Figure 1a, a significant barrier of 158.1 kJ mol^{-1} exists for the addition of acetone to proline, a key step in the proposed mechanism.

As the original study was performed in DMSO, a moderately ionizing solvent, it is possible that the solvent may play a key role stabilizing zwitterionic structures and lowering key barriers in the reaction. The initial interaction between acetone and proline, in DMSO, is summarized in Figure 3a. Initially, acetone interacts with proline via an O···HO hydrogen bond (1.713 Å) forming complex **3a** lying 14.1 kJ mol^{-1} lower in energy than the reactants. In the presence of DMSO, the proton of the carboxylic acid moiety of proline, rather than the proton from the N of proline as observed in Figure 1a, is transferred to the carbonyl oxygen of acetone. This alternate mechanism, which also involves the formation of a formal C−N bond between the two moieties in TS **3b**, lying 26.6 kJ mol^{-1} higher in energy, has a barrier 130.7 kJ mol^{-1} smaller than that observed in the nonsolvated surface. Complete proton-transfer yields the zwitterionic structure **3c**, lying 2.7 kJ mol^{-1} lower in energy than the reactants. Removal of a water molecule yields the imine complex **3d** lying 17.8 kJ mol^{-1} lower in energy than the isolated proline and acetone. Conversion of the isolated imine molecule (**3e**) to the enamine molecule (**3g**), Figure 3b, proceeds via TS **3f** with a barrier of 50.2 kJ mol^{-1}, 20.3 kJ mol^{-1} higher in energy than that observed in the nonsolvated surface.

The addition of acetaldehyde to the enamine, Figure 4a, generates complex **4a** lying 18.1 kJ mol^{-1} lower in energy than the isolated enamine molecule. The formation of a formal C−C bond between the enamine and acetaldehyde in the zwitterionic complex **4c** proceeds via TS **4b** with a barrier of 46.5 kJ mol^{-1}, a decrease of 10.8 kJ mol^{-1} relative to the nonsolvated addition reaction. The final two segments of the mechanism, involving the addition of H_2O across the C═N bond of the imine and subsequent formation of the aldol product, are summarized in Figures 4b and 4c, respectively. These portions of the mechanism are thermodynamically endergonic and not greatly affected by inclusion of solvent. On the nonsolvated surface, the addition of H_2O across the C═N bond of the imine and subsequent proton rearrangement, complex **2d** to complex **2g** (Figure 2b) requires 44.1 kJ mol^{-1} of energy. The analogous conversion (complex **4d** to complex **4g**) on the DMSO surface (Figure 4b) requires 41.8 kJ mol^{-1} of energy. Both the solvated and nonsolvated surfaces conclude with the release of the aldol product and the regeneration of the unsubstituted proline.

Conclusions

The direct aldol reaction between acetone and acetaldehyde, in which the amino acid proline functions as the catalyst during the enamine mechanism, was investigated using density functional theory. Previous studies of antibodies utilizing the analogous mechanism indicate that enamine formation and/or C−C bond breaking/forming is rate limiting. The aforementioned processes require 29.9 and 57.2 kJ mol^{-1} of energy, respectively; not enough to inhibit the reaction. However, the calculations indicate that the initial complexation between proline and acetone requires substantial energy (171.4 kJ mol^{-1}) and would inhibit further progression of the reaction.

As the enamine mechanism involves the formation of charged species, the effect of solvent was examined using the Onsager model. In the presence of DMSO, the barrier for the initial complexation between proline and acetone is reduced to 40.7 kJ mol^{-1} while the enamine and C−C bond formation steps require 50.2 and 46.5 kJ mol^{-1}, respectively. Thus, solvent plays a critical role in the direct aldol reaction by stabilizing ionic charges and providing an alternate, lower energy, pathway by which the reaction may proceed.

Thus, the DFT calculations confirm that proline efficiently catalyzes the direct aldol reaction using the enamine mechanism

characteristic of nature's class I aldolase enzymes. The aldol reaction between acetone and acetaldehyde, in which proline acts as an enzyme mimic, is a simple example illustrating the potential of small organic molecules to act as chiral catalysts in asymmetric synthesis and the complementary nature of theoretical calculations.

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Supporting Information Available: Archive entries of the B3LYP/6-31G(d,p) optimized structures on the nonsolvated and solvated surfaces (Table S1 and S2, respectively), total energies of all molecules on the nonsolvated and solvated surfaces (Tables S3 and S4, respectively) and schematic energy profiles illustrating the two possible reaction pathways for the imine-enamine tautomerism (Figure S1) and enamine conversion by C−N bond rotation (Figure S2). This material is available free of charge via the Internet at http://pubs.acs.org.

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