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Mechanistic Study of Intramolecular Aldol Reactions of Dialdehydes

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Transition states associated with the C–C bond-formation step in proline-catalyzed intramolecular aldol reactions of 1,7-dialdehydes were studied using density functional theory methods (DFT), at the B3LYP/6-31G(d,p) level. A polarizable continuum model (PCM) was used to describe solvent effects. Two reactive channels, corresponding to the anhydrous system or to the explicit inclusion of water have been analysed. Computational data allow us to rationalize the intramolecular aldol reaction experimental outcome, validating the proposed enamine-based mechanism, as well as to suggest the importance of water in the control of the reaction stereoselectivity.

Introduction

Aldol reactions are key carbon–carbon bond-forming reactions that have tremendous synthetic utility and are often the platform of choice to examine new organocatalysts. Nature has perfected stereospecific aldol reactions using aldolase enzymes. While these enzymes have synthetic utility, they are limited by the lack of large-scale compatibility and typically do not have broad substrate recognition.[1] The most promising alternative to circumvent these limitations is organocatalysis, proline being the most-studied organocatalyst. In fact, one of the first contributions to enantioselective organocatalysis was the proline-catalyzed intramolecular aldol cyclization of triketones **1** (Scheme 1). In 1971, Hajos and Parrish at Hoffmann–La Roche[2] and Eder, Sauer and Wiechert at Schering AG[3] independently published a series of papers and patents involving this transformation. Acid-catalyzed dehydration was the last step in the synthesis of ketone **3**, an important intermediate in the total synthesis of steroids. Related cyclizations have been proven to be extremely useful in building blocks for many natural products.[1d,4] It is interesting to note that Hajos and Parrish regarded this reaction as "a simplified model of a biological system in which (*S*)-proline plays the role of an enzyme".[2]

The mechanism of this reaction has been the subject of intense discussion.[5] Today, the transition state proposed by Houk is generally accepted by the scientific community (Figure 1). This mechanism involves an enamine intermediate (Scheme 2) followed by a transition state with concerted C–C bond formation and proton transfer from the carboxylic acid group to the carbonyl acceptor (Figure 1).[6]

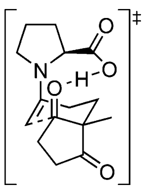
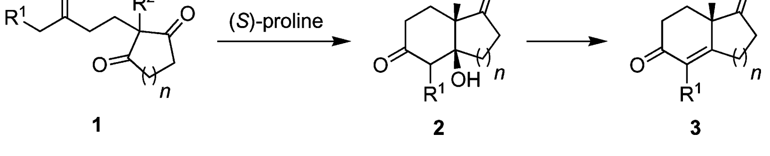


Figure 1. Houk transition state.[6f]



Scheme 1. Enantioselective intramolecular aldol cyclization.

From the point of view of the starting material, this process can formally be considered an intramolecular 6-*enolendo* cyclization, with the enamine C–C double bond being part of the newly formed carbocycle. In 2003, List de-

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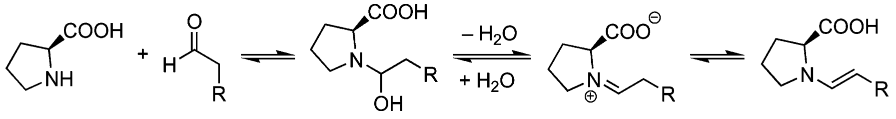
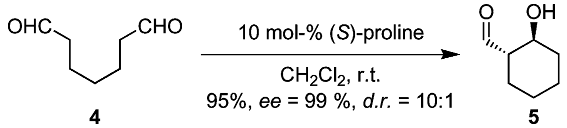


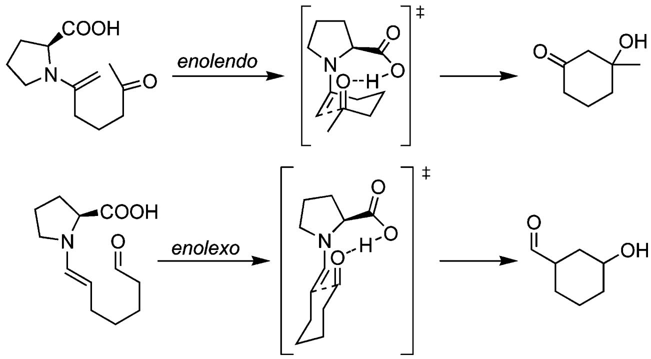
Scheme 2. Enamine formation.

scribed the first intramolecular *enolexo* aldolization in high enantioselectivity (Scheme 3).[7] This process is particularly attractive for the desymmetrization of *meso* compounds.[8] List proposed a transition-state model for 6-*enolexo* aldolizations analogous to 6-*enolendo* processes (Scheme 4).



4 **5**

Scheme 3. *enolexo* aldolization.



Scheme 4. Intramolecular aldol reactions, *enolendo* (Houk's proposal[6f]) and *enolexo* (List's proposal[7]) aldolization.

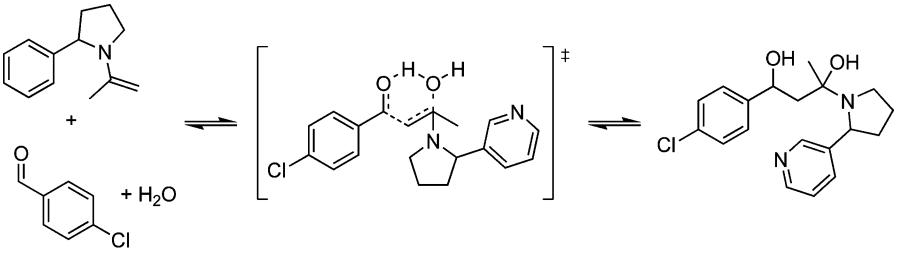
In both mechanisms, 6-*enolendo* and 6-*enolexo*, the enamine intermediate is formed by condensation of a diketone or a dialdehyde molecule with the catalyst (*S*)-proline (see general mechanism in Scheme 2). This means that even when the reaction is conducted under anhydrous conditions (the usual method) during the cyclization step, as much as 1 equiv. of water can be present. Since it is assumed that aldol reactions can be catalyzed by general-base mechanisms,[9] the presence of water can become very important in the final reaction outcome. In fact, to promote enantioselectivity by an enamine-based mechanism in the presence of water, general-base catalysis must be minimized.[10] Recent reports made evident that proline-catalyzed asymmetric aldol reactions are indeed highly sensitive towards water.[10d,11] Later, several studies of reactions in water have been published.[6e,12] Based on these results, Janda proposed a mechanism for the nornicotine-catalyzed aqueous intermolecular aldol reaction between acetone and 4-chlorobenzaldehyde, based on density functional calculations (Scheme 5).[12a] Houk had already considered a possible mechanism in which water was explicitly used as a proton donor in the TS,[6e] but Janda's proposal was the first one to consider water as an organizational factor during the carbon–carbon bond-formation step.

According to Scheme 5, during the carbon–carbon bond-formation step, the water molecule completes the ring of a six-membered transition state in which C–C bond formation, proton transfer from the water to benzaldehyde and C–O bond formation occur simultaneously.

There are several theoretical studies aiming at the rationalization of intermolecular aldol reactions of ketones[6e] or between ketones and aldehydes.[13] There are also several theoretical studies approaching the mechanism of intramolecular aldol reactions of ketones.[6c,6d,6f] Nevertheless, to the best of our knowledge, there is no theoretical study on intramolecular aldol reactions of dialdehydes, in spite of its synthetic and practical interest.[7,8b,8c,14] With this work we wish to fill this gap, presenting the first theoretical study on the intramolecular aldol reaction of dialdehydes. We analyze alternative mechanisms, with or without the explicit inclusion of water molecules in the transition state, aiming to establish a comparison with the mechanisms proposed for similar systems and to evaluate the importance of water in the reaction medium.

Results and Discussion

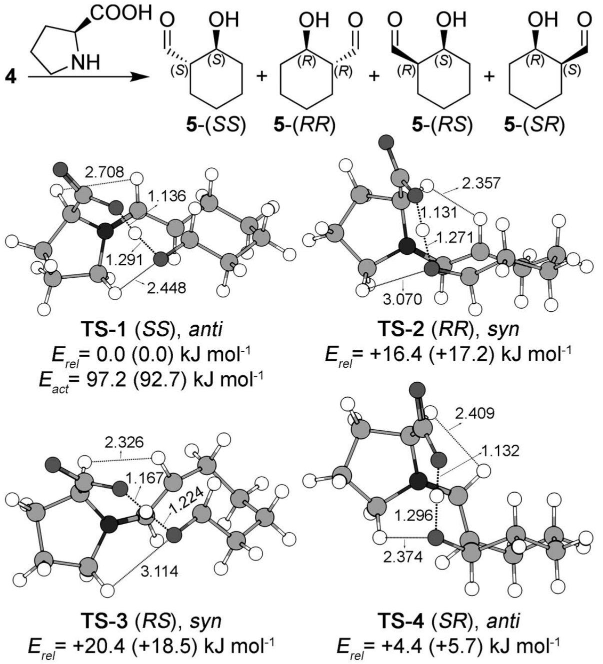
During the last decade, several computational studies have been published focusing on different aspects of proline-catalyzed aldol, Mannich, and other related reactions. Recently, List[7] proposed a mechanism for 6-*enolexo* aldolizations of dialdehydes, based on Houk's mechanism for the cyclization of diketones,[6] that involves attack of an en-



Scheme 5. Proposed mechanism for nornicotine-catalyed aqueous reaction of acetone and 4-chlorobenzaldehyde.

amine intermediate on the free carbonyl group, accompanied by proton transfer from the proline carboxylic acid moiety to the developing alkoxide (Scheme 4). In order to provide a plausible explanation for the high stereoselectivity observed experimentally in intramolecular aldol reactions of dialdehydes, we applied this model (Scheme 4) to the transition state of the intramolecular aldol reaction of dialdehyde **4**.

Regarding the structure of compound **4**, four transition states have to be considered, leading to four final diastereomers of compound **5** (Figure 2). The relative energies of the different transition states are given in Table 1, whereas Figure 2 shows the respective 3D transition structures.



TS-1 (*SS*), *anti*
E_{rel}= 0.0 (0.0) kJ mol^{-1}
E_{act}= 97.2 (92.7) kJ mol^{-1}

TS-2 (*RR*), *syn*
E_{rel}= +16.4 (+17.2) kJ mol^{-1}

TS-3 (*RS*), *syn*
E_{rel}= +20.4 (+18.5) kJ mol^{-1}

TS-4 (*SR*), *anti*
E_{rel}= +4.4 (+5.7) kJ mol^{-1}

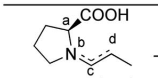
	**TS-1** (*SS*)	**TS-2** (*RR*)	**TS-3** (*RS*)	**TS-4** (*SR*)
ϕ = < abcd	160.4° (163.5°)	32.2° (32.2°)	32.6° (32.8°)	160.5° (163.3°)
μ (Debye)	7.44 (8.92)	7.52 (8.96)	8.19 (9.75)	7.22 (8.68)

Figure 2. Proposed transition states for the cyclization of **4** to **5** catalyzed by (*S*)-proline, relative gas-phase Gibbs energies, C–N–C=C dihedral angles and dipole moments. Values in parentheses include solvation in DCM.

Table 1. Relative transition-state energies, enantioselectivities and diastereoselectivities of the intramolecular aldol reaction, in the gas phase and in dichloromethane (DCM). Gibbs energy differences in parentheses, $\Delta\Delta G = \Delta G_{\mathrm{DCM}} - \Delta G_{\mathrm{GP}}$. In DCM, **TS-1** is by 4.5 kJ mol^{-1} more stable than in the gas phase.

Transition state	Gas phase			Dichloromethane			Ref.[7]	
	ΔG [kJ mol^{-1}]	*ee* (%)	*d.r.*	ΔG [kJ mol^{-1}]	*ee* (%)	*d.r.*	*ee* (%)	*d.r.*
TS-1 (*SS*)	0.0	99.7	6.0:1	0.0 (–4.5)	99.8	9.9:1	99.0 (*anti*)	10:1
TS-2 (*RR*)	16.4	(*anti*)		17.2 (–3.7)	(*anti*)			
TS-3 (*RS*)	20.4	99.7		18.5 (–6.4)	98.9			
TS-4 (*SR*)	4.4	(*anti*)		5.7 (–3.3)	(*anti*)			

Figure 2 shows transition structures for the proline-catalyzed cyclization of dialdehyde **4**, according to the model proposed by List. In all transition structures, the hydrogen bond between the carboxylic acid group and the forming alkoxide oxygen atom induces the formation of low-energy chair conformations as well as intramolecular acid catalysis. This type of interaction is characteristic of enamine-mediated aldol reactions, in which the catalyst is proline.[6e] In the gas phase, transition state **TS-1** [(*SS*) enantiomer] is the most stable and is by 16.4 kJ mol^{-1} less energetic than **TS-2** [(*RR*) enantiomer], whereas **TS-4** (*SR*) is by 16 kJ mol^{-1} more stable than its enantiomer **TS-3** (*RS*). In **TS-1** (*SS*) and **TS-4** (*SR*), the carboxylic acid group and the enamine double bond adopt an *anti* relationship with respect to the C–N axis (Figure 2), whereas in **TS-2** (*RR*) and **TS-3** (*RS*) this relationship is *syn*. These conformational differences suggest that the energy change between each pair of enantiomers is due to a combination of steric and electrostatic interactions, as discussed below. The distances of the 1–6 hydrogen–hydrogen steric contacts involving the α-hydrogen atom to the carboxyl group are 2.36 Å in **TS-2** and 2.33 Å in **TS-3** (Figure 2, *syn* conformations). In the *anti* conformations, the equivalent 1–5 hydrogen–hydrogen contacts are 2.71 Å in **TS-1** and 2.41 Å in **TS-4**. These differences lead to higher destabilization of the *syn* structures when compared with the *anti* configurations. It could be expected that the energy of the forming cyclohexane ring would depend on the relative positions of its substituents (equatorial vs. axial). Nevertheless, the analysis of the four transition structures in Figure 2, suggests that this is not a major factor, as structures **TS-1** and **TS-2** have both substituents in equatorial position, but show an energy difference of more than 16 kJ mol^{-1}. A similar conclusion can be deduced from the comparison of structures **TS-3** and **TS-4**, since they have also a large energy difference, but the substituents are in similar relative positions (one equatorial and one axial). Also, for each pair **TS-1/TS-4** or **TS-2/TS-3** the energies are similar, but they have different orientations of the substituents. Electrostatic factors contributing to the transition-state relative energies are observed as attractive interactions between the positively charged methylene group adjacent to the proline nitrogen atom (as a result of the iminium formation)[6d,15] and the negatively charged forming alkoxide group (as a result of the carbon–carbon bond formation). In structures **TS-1** and **TS-4**, the distances between these groups are 2.45 Å and 2.37 Å, respectively, whereas in structures **TS-2** and **TS-3** these distances are 3.07 Å and 3.11 Å, respectively. A direct result of this effect can be observed in the lengths of the hydrogen bonds between the carboxyl hydrogen atom and the forming alkoxide group. The distances are shorter in structures **TS-2** and **TS-3** (1.27 and 1.22 Å) than in structures **TS-1** and **TS-4** (1.29 and 1.30 Å), which indicates that the charge on the oxygen atom is more neutralized in the second pair of structures, due to its strong interaction with the methylene hydrogen atom in the proline moiety. This charge neutralization is the main driving force for the cyclization process.

According to Table 1 and Figure 2, not only the computed gas-phase enantiomeric excesses are in good agreement with the experimental values [**TS-1** vs. **TS-2** (99.7%; exp. 99%) and **TS-3** vs. **TS-4** (99.7%; exp. not available)] but also the diastereomeric excess [**TS-1** + **TS-2** vs. **TS-3** + **TS-4** (6:1; exp. 10:1)] was found to be in reasonable agreement. The diastereomer **TS-4** (*SR*) is by 4.4 kJ mol^{-1} less stable than **TS-1** (*SS*), whereas **TS-3** (*RS*) is by 4.0 kJ mol^{-1} less stable than **TS-2** (*RR*). As previously discussed, the proton–proton steric interaction seems to be the main factor responsible for this difference [$d_{\text{H-H}(\textbf{TS-1})}$ = 2.71 Å vs. $d_{\text{H-H}(\textbf{TS-4})}$ = 2.41 Å, and $d_{\text{H-H}(\textbf{TS-2})}$ = 2.36 Å vs. $d_{\text{H-H}(\textbf{TS-3})}$ = 2.33 Å] (Figure 2). Considering the four relative energies, structures **TS-1** and **TS-4** are the main ones responsible for the calculated diastereoselectivity, since the other two structures contribute less than 1% to the overall yield.

As the experimental study was performed in DCM and the transition states are ionic, it is possible that the solvent may play a key role in the reaction kinetics. PCM results in DCM are shown in Table 1 and indicate that all activation energies are indeed reduced, when compared with gas-phase values. Transition state **TS-3** (*RS*) is the most stabilized one, which directly correlates with its larger dipole moment (8.19 D) (Figure 2). Solvent effects also induce some conformational changes in the transition structures, as it can be seen in the C–N–C=C dihedral angle values (Figure 2). In spite of all these energetic and structural changes, solvent effects do not strongly affect the enantioselectivity of the reaction. **TS-1** [(*SS*) enantiomer] is still by 17.2 kJ mol^{-1} more stable than **TS-2** [(*RR*) enantiomer], and **TS-4** (*SR*) is still by 12.8 kJ mol^{-1} more stable than its enantiomer **TS-3** (*RS*). Due to these large differences, the enantioselectivity change is less than 1%. Nevertheless, the diastereoselectivity is considerably affected, increasing from 6.0:1 to 9.9:1. This result is mainly due to the lower stabilization of **TS-4** ($\Delta\Delta G$ = –3.3 kJ mol^{-1}) when compared with **TS-1** ($\Delta\Delta G$ = –4.5 kJ mol^{-1}).

As discussed in the Introduction, catalytic aldol reactions can be affected by the presence of water in the reaction medium. Usually this type of reaction is experimentally conducted under anhydrous conditions. Nevertheless, water is a side product of the enamine formation step, which can lead to water amounts in the reaction medium as large as 1 equiv., depending on the catalyst concentration. Since the reagents are more polar than the solvent, the water released during the first step can be kept connected by strong hydrogen bonds, avoiding its diffusion into the solvent. We tested several possible transition states with a water molecule explicitly included, some of them based on proposed mechanisms in the literature in which other molecules were used instead of water.[16] The majority of the structures we found were too energetic to be considered. Nevertheless, a modification of the mechanism proposed by Houk[6f] for the intramolecular aldol cyclization of triketone **1**, as described in Figure 3, gave interesting results.

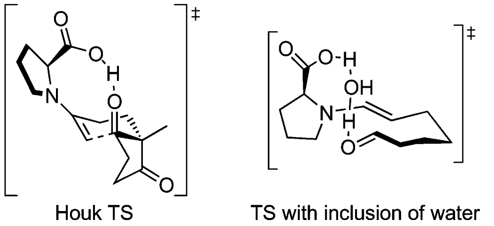
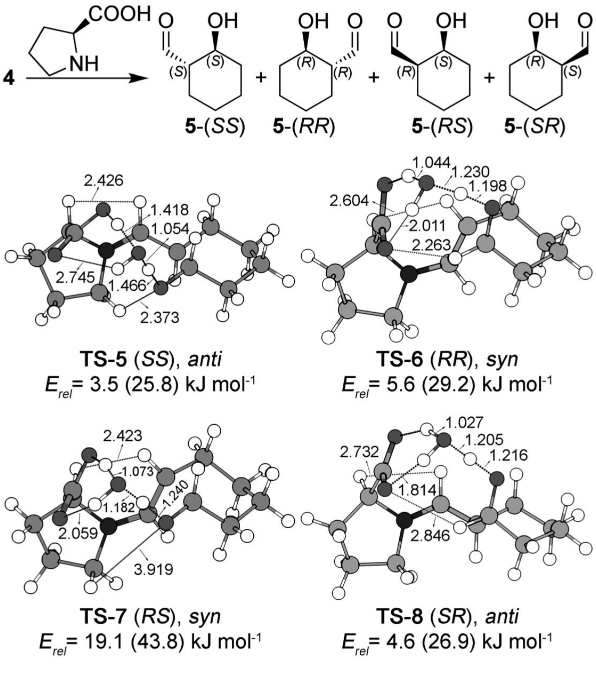

Houk TS
TS with inclusion of water

Figure 3. Mechanisms proposed for proline-catalyzed intramolecular aldol reactions.

Relative activation energies for the conversion of **4** to **5** catalyzed by (*S*)-proline, with the explicit inclusion of water, are given in Table 2, whereas Figure 4 shows the respective transition structures. All values are relative to **TS-1** (Table 1).

Table 2. Relative (to **TS-1**, Table 1) transition-state energies, enantioselectivities and diastereoselectivities of the intramolecular aldol reaction in the gas phase and in DCM, with the explicit inclusion of a water molecule.

Transition state	Gas phase			Dichloromethane			Ref.[7]	
	ΔG [kJ mol^{-1}]	*ee* (%)	*d.r.*	ΔG [kJ mol^{-1}]	*ee* (%)	*d.r.*	*ee* (%)	*d.r.*
TS-5 (*SS*)	3.5	40.8	2.3:1	25.8	59.9	1.9:1	99.0 (*anti*)	10:1
TS-6 (*RR*)	5.6	(*anti*)		29.2	(*anti*)			
TS-7 (*RS*)	19.1	99.4		43.8	99.8			
TS-8 (*SR*)	4.6	(*anti*)		26.9	(*anti*)			



TS-5 (*SS*), *anti*
E_{rel}= 3.5 (25.8) kJ mol^{-1}

TS-6 (*RR*), *syn*
E_{rel}= 5.6 (29.2) kJ mol^{-1}

TS-7 (*RS*), *syn*
E_{rel}= 19.1 (43.8) kJ mol^{-1}

TS-8 (*SR*), *anti*
E_{rel}= 4.6 (26.9) kJ mol^{-1}

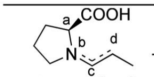
	TS-5 (*SS*)	**TS-6** (*RR*)	**TS-7** (*RS*)	**TS-8** (*SR*)
 ϕ = < abcd	163.3º (165.2º)	12.2º (13.4º)	19.7º (19.7º)	159.5º (162.4º)
$\Delta\phi$ (ϕ_{H2O}-ϕ)	+6.7º (+5.0º)	–20.0º (–18.8º)	–12.9º (–13.1º)	–1.0º (–0.9º)

Figure 4. Proposed transition states for (*S*)-proline-catalyzed cyclization of **4** to **5**, with the explicit inclusion of water. Dihedral angles (C–N–C=C) are in degrees. $\Delta\phi$, dihedral angle difference between TSs with inclusion of water and TSs without water. PCM results in DCM are in parentheses.

The gas-phase results in Table 2 show that the inclusion of water leads to strong energetic changes in structures **TS-5** (3.5 kJ mol^{-1}) and **TS-6** (5.6 kJ mol^{-1}) relative to **TS-1** (0.0 kJ mol^{-1}) and **TS-2** (16.4 kJ mol^{-1}), respectively, whereas **TS-7** (19.1 kJ mol^{-1}) and **TS-8** (4.6 kJ mol^{-1}) have almost no difference when compared with **TS-3** (20.4 kJ mol^{-1}) and **TS-4** (4.4 kJ mol^{-1}), respectively. Structure **TS-1** has the lowest calculated energy, meaning that it has the best arrangement of atoms inside the molecular structure. The newly forming ring has a chair conformation, and the carboxyl group has a proper distance to the carbonyl group, allowing for an efficient acid catalysis. The insertion of water distorts this ideal arrangement, and the result (**TS-5**) is a slight energy increase. Nevertheless, **TS-5** is very similar to **TS-1**, keeping the attractive interaction between the positively charged methylene group adjacent to the proline nitrogen atom and the negatively charged forming alkoxide group, whereas the hydrogen–hydrogen steric contact with the α-hydrogen atom to the carboxyl group in **TS-5** is now shorter than in **TS-1** ($d_{\mathrm{H-H}}$ = 2.43 Å in **TS-5** and $d_{\mathrm{H-H}}$ = 2.71 Å in **TS-1**). Structures **TS-6** to **TS-8** lose the electrostatic positive interaction between the methylene hydrogen atom and the forming alkoxide oxygen atom. The importance of this contact is clearly visible if we compare the bond length of the forming bond between the alkoxide oxygen atom and the water hydrogen atom. In **TS-5** this distance is longer than 1.4 Å, whereas in the other three structures it is around 1.2 Å. This indicates, as stated before, the strong charge stabilization due to the contact with the methylene hydrogen atom on the proline moiety. The electrostatic contact is broken in **TS-6** and **TS-8**, due to strong molecular conformational changes. In these two structures, the forming alkoxide atom is now axial and points in a direction that does not allow for the contact. At the same time, structures **TS-6** and **TS-8** have also an extra electrostatic contact between the aldehydic hydrogen atom and one of the oxygen atoms of the carboxyl group. The overall result is a slight stabilization of **TS-5** relatively to **TS-6** and **TS-8**. **TS-7** has the highest energy value. This is in part due to the shorter hydrogen–hydrogen contact with the α-hydrogen atom to the carboxyl group, when compared with **TS-6** or **TS-8**. But, more important, in **TS-7** there is no electrostatic contact between the aldehyde hydrogen atom and any of the carboxyl oxygen atoms, which renders this structure considerably more energetic than any of the other three.

Comparison of the C–N–C=C dihedral angles between the anhydrous transition structures and the structures with inserted water suggests that the values of these angles are not of major importance, meaning that the non-bonding nitrogen electrons can keep an efficient resonance with the enamine double bond, even for values as large as 30°.

The results discussed above suggest that if we consider only gas-phase values, water would be an important factor in the reaction outcome, since it strongly reduces the activation energy of the **TS-6** (*RR*) and **TS-8** (*SR*) transition states, relative to **TS-5** (*SS*), thus reducing the reaction enantioselectivity and diastereoselectivity, as shown in Table 2. Since the TSs with water are only slightly more unstable than those without water, if we weight the data from Tables 1 and 2 we obtain the values in Table 3, which indeed suggest that water should be a parameter to take into account. Nevertheless, PCM values, with DCM as solvent (Table 2), show that the inclusion of water strongly increases the activation energies of all TSs, thus suggesting that these transition structures would be of low probability and should not account for the final reaction outcome. In spite of this, considering the large number of discrepant experimental values found in the literature, we believe that water can be a possible explanation for the discrepancies, since our gas-phase study suggests that it can indeed strongly reduce the stereoselectivity of amine-catalyzed aldol reactions. As the amount of water can virtually not be controlled under the usual experimental conditions, random results can arise, as it is indeed observed.[7,8b,8c,14,17]

Table 3. Comparison of transition-state energies, enantioselectivities and diastereoselectivities of the gas-phase intramolecular aldol reaction, taking into account the participation of anhydrous and hydrated structures.

Transition state	Gas phase			Ref.[7]	
	ΔG [kJ mol^{-1}]	*ee* (%)	*d.r.*	*ee* (%)	*d.r.*
TS-1 (*SS*)	0.0		4.2:1	99.0 (*anti*)	10:1
TS-5 (*SS*)	3.5	84.6			
TS-2 (*RR*)	16.4	(*anti*)			
TS-6 (*RR*)	5.6				
TS-3 (*RS*)	20.4				
TS-7 (*RS*)	19.1	99.6			
TS-4 (*SR*)	4.4	(*anti*)			
TS-8 (*SR*)	4.6				

Conclusions

The transition state proposed by List for the intramolecular aldol reaction of 1,7-dialdehydes catalyzed by (*S*)-proline was analysed with the B3LYP/6-31G(d,p) theoretical model. The data obtained allowed the rationalization of the main factors contributing for the reaction selectivity, as being steric and electrostatic in nature. Theoretical data, in the gas phase and in DCM (PCM model) agree in good extension with List's experimental results. The explicit inclusion of a water molecule in the transition state suggests that this reagent can be of major importance for the overall reaction selectivity, and would explain the apparently random experimental data published in recent years. Nevertheless, PCM models, using DCM as solvent, suggest that transition states with the explicit inclusion of water should be of low importance, due to their relative higher energy.

Computational Methods

All calculations were performed using density functional theory (DFT)[18] methods with the Gaussian 03 software package.[19] The geometries of all stationary points were fully optimized at the B3LYP/6-31G(d,p) level, and their nature (minimum or transition state) was determined by frequency analysis. Harmonic vibrational frequencies and zero-point vibrational-energy corrections were calculated with the same model. The effect of solvent on the energies was studied by geometry optimization at the B3LYP/6-31G(d,p) level of theory. The Polarizable Continuum Model (PCM) of Tomasi et al. was used with UAKS radii[20] and the dielectric constant of dichloromethane (DCM). All bond lengths are in Å and the energies in kJ mol^{-1}. Activation energies are calculated relative to the reagents.

Supporting Information (see footnote on the first page of this article): Cartesian coordinates and computed total energies in the gas phase and in dichloromethane.

Acknowledgments

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