The Origin of Stereoselectivity in Proline-Catalyzed Intramolecular Aldol Reactions

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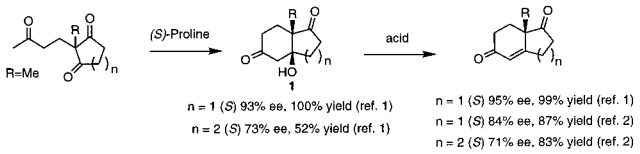
In the 1970s, Hajos and Parrish[1] and Wiechert, Eder, and Sauer,[2] discovered that proline catalyzes intramolecular aldol reactions with high enantiomeric excesses and chemical yields (Scheme 1). In the 1980s, Agami[3] found examples of asymmetric intramolecular aldol cyclizations of achiral diketones catalyzed by proline (Scheme 2). In this century, List, Lerner, and Barbas reported intermolecular aldol reactions catalyzed by proline,[4] and these studies have been extended to a variety of substrates.[5,6] Although many details about the proline-catalyzed intramolecular aldol reaction have been discovered, an explanation of the origin of stereoselectivity has been elusive.

Proline-catalyzed aldol reactions involve enamine intermediates,[3,7] and the rate-determining step of the reaction is the C−C bond forming step.[7b] Similar mechanisms are found in type-I aldolases[8] and catalytic antibodies that are type-I aldolase mimics (38C2 and 33F12).[9]

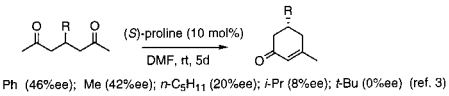
While studying the proline-catalyzed intramolecular aldol reaction, Hajos and Parrish reported the isolation of aldol intermediates such as **1** ($n = 1$, R = Me, and R = Et), and showed that stereodifferentiation occurs in the aldol step, before dehydration.[1] Agami later found that the reaction is second-order in proline and exhibits a small negative nonlinear effect.[3,10] Experiments have shown that the carboxylic acid group and pyrrolidine ring of proline are essential for effective asymmetric induction.[1,4−7a,11] Other amino acids and amino acid derivatives have also been used, but the enantioselectivities observed are generally not as impressive as with proline.[1−12]

We have explored the transition states and intermediates of these reactions. Our studies build on our previous investigation of achiral amine-catalyzed aldol reactions.[13] All ground-state and transition-state geometries were located using hybrid density functional theory (B3LYP)[14] and the 6-31G*[15] basis set as implemented in Gaussian 98.[16] Each stationary point was characterized by frequency analysis.[17] Charges were computed with the ChelpG method.[18]

Scheme 1



Scheme 2



We first studied the proline-catalyzed intramolecular aldol reactions of 4-alkylheptane-2,6-diones (**2**). Four diastereomeric aldol products can be formed (Scheme 3). We explored transition states for enamine attack on the ketone; this is likely to be the rate-determining step of the reaction, while all previous steps leading to enamine formation are reversible. Both chair and boat transition states, TS1−TS4, for forming the six-membered ring were located and analyzed. The chair transition states were always lower in energy, and only these are described here.

Two chair transition states were located for the reaction of the (*S*)-proline enamine of **2a** (R = Me) to form (*R*,*S*)- and (*S*,*R*)-ketols; these are shown in Figure 1. In both transition states the hydrogen bonding of the carboxylic acid proton to the forming alkoxide oxygen provides charge stabilization and intramolecular acid catalysis. This is a general feature of enamine-mediated aldol reactions.[13]

The lower energy of transition state (*R*,*S*)-**3** relative to transition state (*S*,*R*)-**3** appears to be due to two factors: (1) hydrogen bonding in (*R*,*S*)-**3** allows the forming iminium double bond to be almost planar; in transition state (*S*,*R*)-**3** there is considerable distortion of the forming iminium double bond away from planarity. The Newman projections of the developing iminium double bond below the figures show that the (*R*,*S*) transition state has a more nearly planar iminium than the (*S*,*R*) transition state. (2) Transition state (*R*,*S*)-**3** has more favorable electrostatic interactions between the partially positively charged forming proline iminium and the forming alkoxide. Most of the partial positive charge resides on the methylene groups adjacent to the

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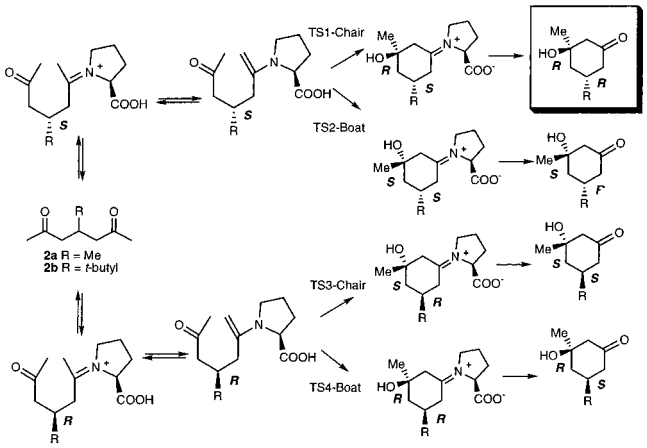
Scheme 3



nitrogen of the proline. The $^{+\delta}$NCH- -O$^{\delta-}$ distance is 2.5 Å in transition state (*R*,*S*)-**3** and 3.2 Å in transition state (*S*,*R*)-**3**, as shown in Figure 1.[19] The 1 kcal/mol preference for (*R*,*S*)-**3** is in reasonable agreement with experiment where the (*R*,*R*)-ketol (corresponding to the (*R*,*S*)-iminium intermediate) is isolated and upon dehydration forms the (*R*)-α,*β*-unsaturated cyclic ketone in 42% ee (Scheme 3).[3]

Transition states were also located for the reaction of (*S*)-proline enamine, **2b** (R = *tert*-butyl), to form ketol intermediates. The two chair transition states are now within 0.1 kcal/mol of each other, consistent with the experimental absence of enantioselectivity for this case.[3,20]

Two chair transition states for the reaction of (*S*)-proline enamine, **4**,[21] leading to the bicyclic aldol intermediates, **5a** and **5b,** were located as shown in Figure 2. For primary and secondary amine-catalyzed aldol reactions, we found that formation of *cis*-hydrindanone ketol intermediates is favored over *trans*.[13] The favorable electrostatic interactions between the carbonyl of the five-membered ring and the electron-rich enamine π bond as well as the inherent stability of *cis*-hydrindanone systems relative to *trans*[13,22] contribute to this preference.

The energy barrier to formation of (*S*,*S*)-**6** is 9.1 kcal/mol, 3.4 kcal/mol lower than the barrier to formation of (*R*,*R*)-**6**.[23] Transition state (*R*,*R*)-**6** is destabilized relative to transition state (*S*,*S*)-**6**, because intramolecular hydrogen bonding forces the iminium double bond out of planarity in (*R*,*R*)-**6**; this distortion in transition state (*R*,*R*)-**6** is much larger due to the conformational restraints imposed by the hydrindanone ring system; the Newman projections show this. The favorable electrostatic interaction of $^{+\delta}$NCH- -O$^{\delta-}$ also contributes to the lower energy of transition state (*S*,*S*)-**6**. The $^{+\delta}$NCH- -O$^{\delta-}$ distance is 2.4 Å in transition state (*S*,*S*)-**6** and 3.4 Å in transition state (*R*,*R*)-**6**. These results are in agreement with experiment where **1** has been isolated, and upon dehydration leads to the formation of the (*S*)-α,*β*-unsaturated product.[1,2,24]

Agami proposed that a second proline molecule might be involved in the intramolecular proton transfer from acid to enamine.[3,10] Alternatively, the second proline molecule could be involved in the conversion of the iminium to the reactive enamine.

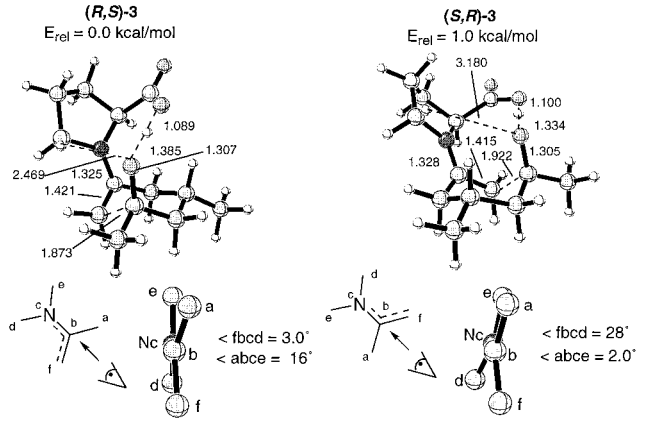


Figure 1. Transition-state geometries for cyclization of the enamine of diketone **2a**.

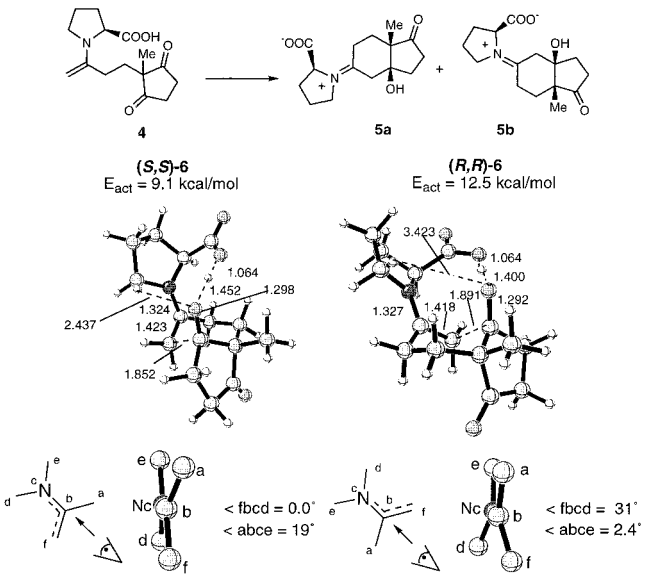


Figure 2. Transition-state geometries for cyclization of enamine **4**.

Either mechanism is consistent with the second-order dependence on proline concentration.[10]

Proline has been appropriately called a "micro-aldolase";[1,4] like the aldolase enzymes, this amino acid forms enamine intermediates. We have shown how selective hydrogen bonding and the geometry of proton transfer in the transition state determines the stereochemistry of the products.[7a] Studies of the stereoselectivities of proline-catalyzed intermolecular aldol reactions are in progress.

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Supporting Information Available: Cartesian coordinates of all reported structures as well as the total electronic and zero-point vibrational energies and authors of Gaussian (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The *tert*-butyl group of the chairlike transition state destabilizes transition-state (*R*,*S*)-**2b** due to steric interactions of the geminal hydrogen with the carboxylic acid group. The geometries for these transition states are included in Supporting Information.

(21) (*S*)-proline-enamine **4** is 5.5 kcal/mol lower in energy than (*S*)-proline-iminium in ϵ = 1 and 4.0 kcal/mol lower in energy in ϵ = 47. Single-point CPCM calculations in ϵ = 47 (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995−2001. (b) Barone, B.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404−417.

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(23) CPCM single-point energy calculations in DMSO (ϵ = 47) show that the barrier to formation of (*S*,*S*)-**6**, 3.1 kcal/mol lower in energy than the barrier to formation of (*R*,*R*)-**6**.

(24) Product **5a** is 1.76 kcal/mol lower in energy than product **5b**. Single-point CPCM calculations show that product **5a** is 1.1 kcal/mol lower in energy in DMSO (ϵ = 47).