Quantum Mechanical Predictions of the Stereoselectivities of Proline-Catalyzed Asymmetric Intermolecular Aldol Reactions

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Abstract: Quantum mechanical calculations were employed to predict the ratio of four stereoisomeric products expected from two complex reactions involving the aldol reactions of cyclohexanone with benzaldehyde or with isobutyraldehyde catalyzed by (S)-proline. Experimental tests of these predictions provide an assessment of the state-of-the-art in quantum mechanical prediction of products of complex organic reactions in solution.

I. Introduction

Although Dirac once noted that the Schrödinger equation "leads to equations much too complicated to be soluble,"[1] quantum mechanics has had an enormous impact on chemistry. Although computers and algorithms bring us closer to accurate approximations to exact solutions, quantitative predictions are rare. We report quantum mechanical predictions of stereoselectivities of a synthetically useful reaction: the ratios of four possible stereoisomeric aldol products of the reactions of cyclohexanone and two aldehydes, catalyzed by proline, were predicted using quantum mechanical hybrid density functional theory,[2] and then the experimentally determined product yields were compared to theoretical predictions. These results provide an assessment of the current state of computational methods for the prediction of the products of complicated organic processes.
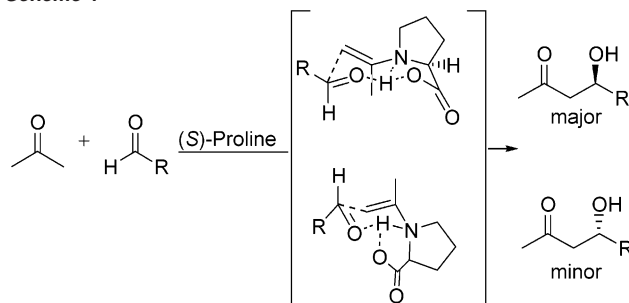
Proline has long been known as an effective asymmetric catalyst for the intramolecular aldol reaction.[3] Recently, it was discovered that this amino acid could also catalyze intermolecular aldol reactions between ketones and aldehydes.[4-9] These reactions proceed through an enamine-mediated mechanism[10-12] and provide a prototype for the burgeoning area of organocatalysis.[13,14]

Scheme 1

R = Ph: 62% yield, 60% ee; R = 4-$O_2NC_6H_5$: 68% yield, 76% ee; R = *i*-Pr: 97% yield, 96% ee; R = *tert*-butyl: 81% yield, >99% ee.

The stereoselectivities of intermolecular proline-catalyzed direct aldol reactions of acetone with a variety of aldehydes have been rationalized with a Zimmerman−Traxler six-membered ring chair-like model[15] (shown at the top of Scheme 1).[4,5,8,9] The minor product could arise from a switch to an axial R, or via the alternative Zimmerman−Traxler transition state shown at the bottom of Scheme 1.

Aldol reactions of cyclohexanone enamines with aldehydes can produce four stereoisomers that are syn- and anti-diastereomeric pairs of enantiomers (Scheme 2). Because the aldehyde and enamine may adopt three staggered arrangements about the forming bond, and because the cyclohexene of the enamine can adopt two-half-chair conformations, there are 24 reasonable transition states for this reaction.

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Scheme 2. Possible Products from Cyclohexanone Enamine Reactions with Aldehydes
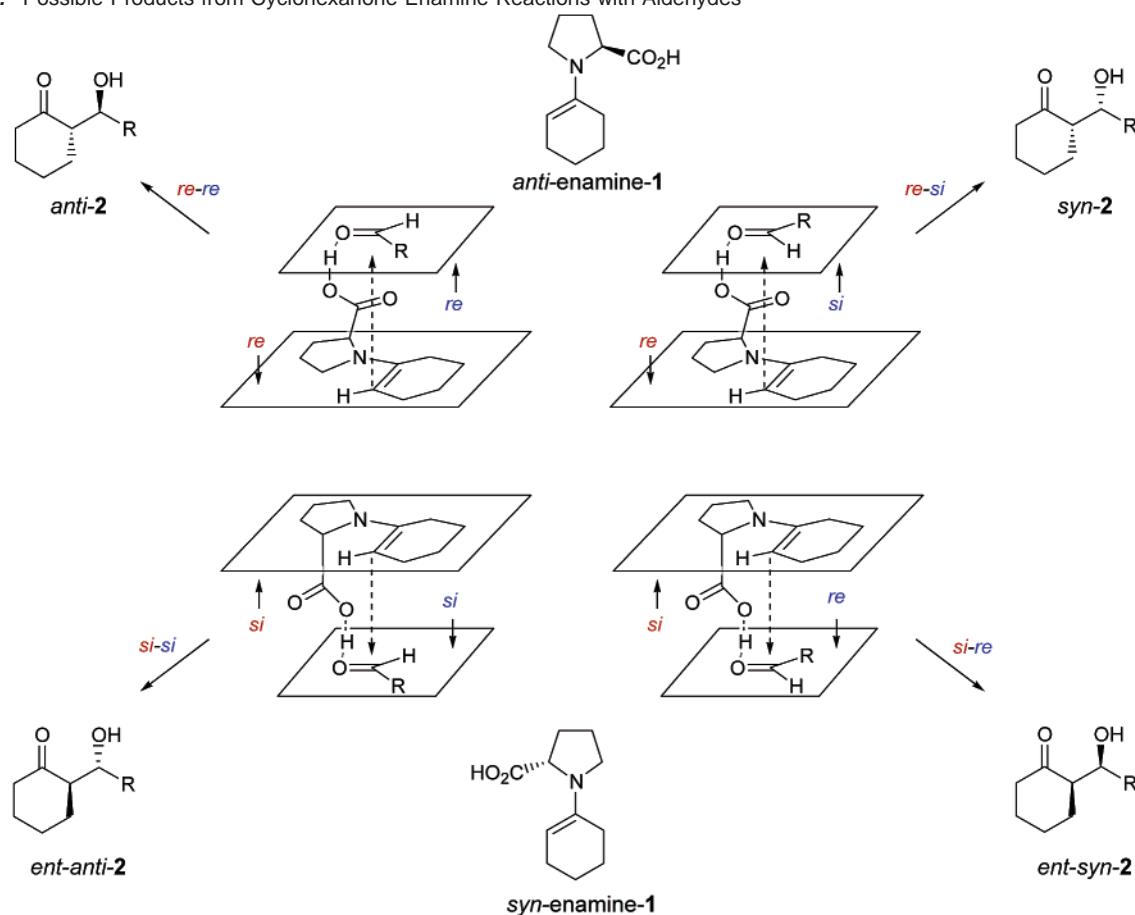
Previous theoretical studies show that proton transfer from the amine or carboxylic acid group of proline to the forming alkoxide is essential for charge stabilization and to facilitate C—C bond formation in the transition state.[16,17] The carboxylic acid can be syn or can be anti and hydrogen bond to the enamine nitrogen in the starting enamine, but becomes strongly associated with the developing alkoxide in the transition state for the aldol reaction. Consequently, only transition states that involve hydrogen bonding between the carboxylate and the aldehyde were considered here. In addition, only transition states involving the carbonyl group of the aldehyde with dihedral angles of $\pm 60°$ relative to the C=C bond of the enamine can involve intramolecular acid catalysis, so all other rotamers were excluded from consideration (Scheme 3).

Transition states of simple systems with a dihedral angle $-60°$ were found to be 5–10 kcal/mol higher in energy than those with $+60°$ in simple models, and so the higher energy conformers are excluded as well (Figure 1). This leaves eight possible transition states for four possible stereoisomeric products in each reaction.

II. Computational Methods

Stationary points (reactant and transition state geometries) were optimized and characterized by frequency analysis using hybrid density functional theory (B3LYP)[18] and the 6-31G*[19]

Scheme 3. Various Rotamers Involving the Carbonyl Group of the Aldehyde with Dihedral Angles of $\pm 60°$ and 180° Relative to the C=C Bond of the Enamine. Only Those Transition States with Dihedral Angles of $\pm 60°$ Can Involve Intramolecular Acid Catalysis
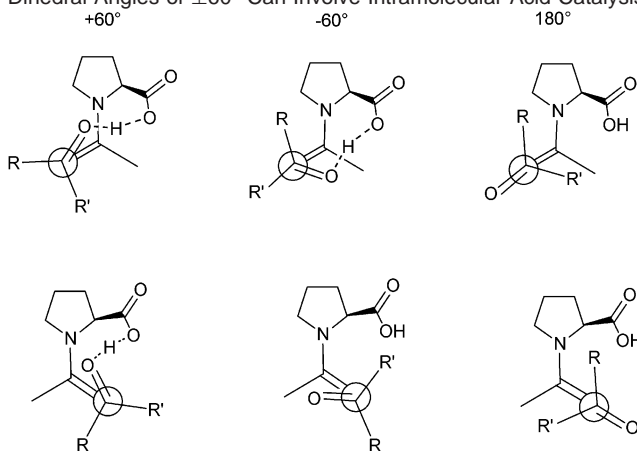
basis set as implemented in Gaussian 98.[20] Enthalpies, ΔH_{298}, and free energies, ΔG_{298}, were computed for the gas phase, and the solvation energies, $\Delta G_{298(\epsilon=47)}$, for reactants and for transition states were computed using a polarizable continuum model with a permittivity of 47, the value for DMSO, the solvent used in the experiments. These calculations involve the solvation model CPCM[21] as implemented in Gaussian 98.

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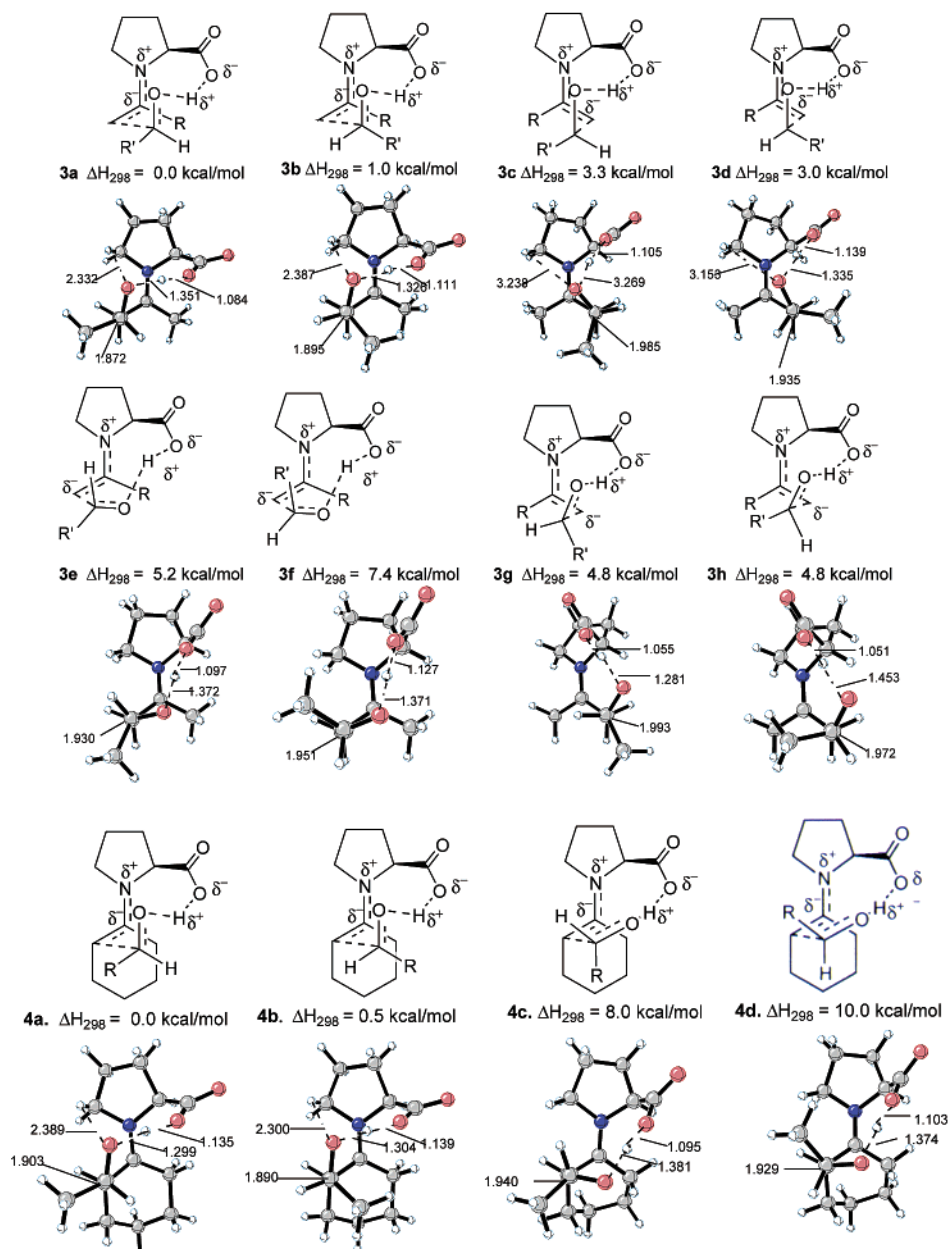
Figure 1. Relative energies of transition states for the reaction of the proline-enamine of acetone (**3a**–**3h**, R = CH$_3$, R′ = CH$_3$) and cyclohexanone (**4a**–**4d**, R = CH$_3$) with acetaldehyde. After optimization, intramolecular hydrogen bonding changes the ideal arrangement for staggering substituents (±60° and 180°) to more eclipsed arrangements (∼±5°–80°). This change is most dramatic in transition states **3e**–**3h**. Newman projections along the forming C–C bond are shown.

III. Results and Discussion

The lowest energy transition states leading to the four products from the reactions of the proline enamine of cyclohexanone with benzaldehyde and isobutyraldehyde are shown in Figure 2.[22] The transition states involving the re attack on the anti-enamine (**TS 5a,b** and **TS 6a,b**) are lower in energy

than the transition states for si attack on the syn-enamine (**TS 5c,d** and **TS 6c,d**) as shown in Figure 2. Transition states for reaction of the anti-enamine with aldehydes have the NCC–CO atoms in a half-chair conformation (**5a**, **5b** R = Ph; **6a**, **6b** R = *i*-Pr). The H of the carboxylic acid group of proline is being transferred to the forming alkoxide. Favorable hydrogen bonding interaction between the partial positive hydrogens of the carbon adjacent to the proline nitrogen to the forming alkoxide ($^{\delta+}$NCH–O$^{\delta-}$ distances: 2.36–2.47 Å) contribute to further electrostatic stabilization of **TS 5a,b** and **TS 6a,b**.[23]

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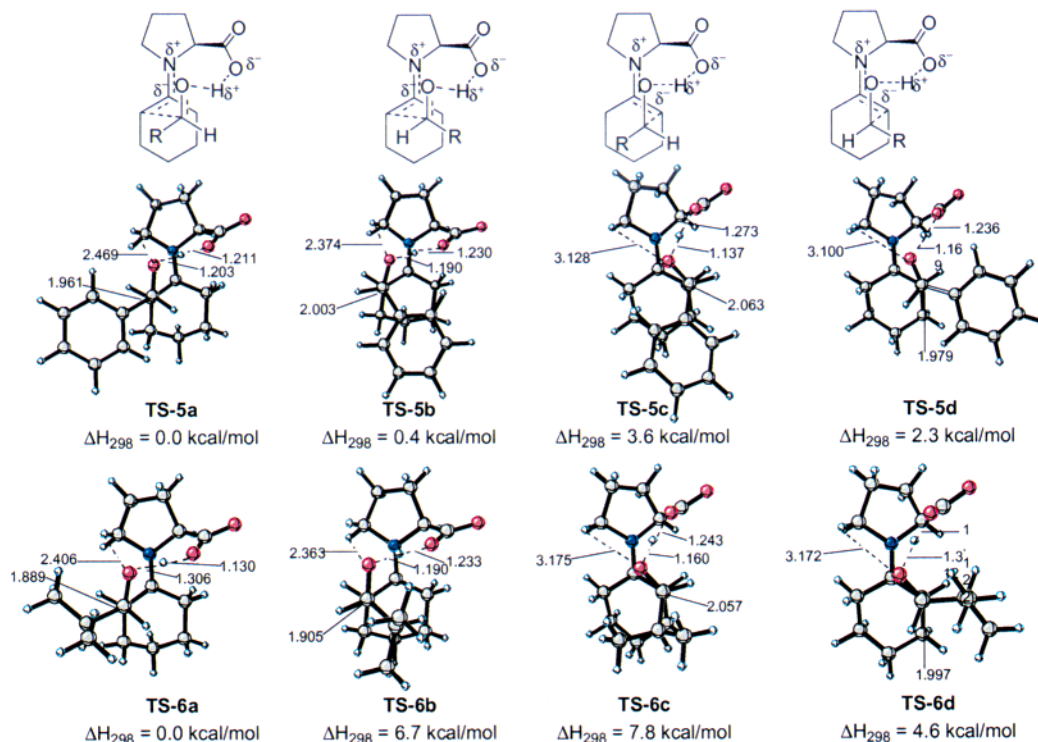
Figure 2. Transition state geometries for the reaction of syn- and anti-enamine with benzaldehyde (**5a−5d**) and isobutyraldehyde (**6a−6d**). Newman projections along the forming C−C bond are shown.

Transition state **5b** is slightly destabilized due to additional interactions of the pseudoaxial phenyl ring of the aldehyde with the cyclohexane enamine, whereas transition state **6b** is highly destabilized. The phenyl group can easily adopt a relatively sterically unhindered arrangement in **5b**, whereas **6b** suffers from the large steric repulsion involving the isopropyl tertiary hydrogen. Transition states involving the *syn*-enamine force the substituents at the forming C−C bond to be nearly eclipsed, and the $^{\delta+}$NCH−O$^{\delta-}$ distances (3.12−3.18 Å) are longer and therefore the electrostatic stabilization of these transition states is diminished. The computed transition state geometries reveal that the carboxylic acid proton and enamine nitrogen (N−H distance ~2.5 Å) are not arranged to form an ideal Zimmerman-Traxler six-membered ring as shown in Scheme 1.

To gauge the inaccuracies involved in our prediction of product ratios, the average absolute errors in calculations for known proline-catalyzed aldol reactions were determined. For three reactions studied earlier, the calculated gas-phase enthalpies of activation have the smallest error (standard deviation ± 0.4 kcal/mol) when compared with the experimental enantio-selectivities as shown in Table 1.[24] Table 2 gives the predicted product ratios.[25] From ΔH_{298} values, the proline-catalyzed reaction of cyclohexanone with benzaldehyde should give syn-**2** and anti-**2** products involving attack on the enamine in comparable amounts (between 50:50 and 80:20). The reaction

(23) These types of favorable CH−O bonds have been observed in other systems. Cannizzaro, C. E.; Houk, K. N. *J. Am. Chem. Soc.* **2002**, *124*, 7163−7169.
(24) Absolute average errors were computed for the three intermolecular aldol reactions in Table 1) by averaging the absolute differences between $\Delta G_{298expt}$ and either $\Delta H_{298theory}$, $\Delta G_{298theory}$, or $\Delta G_{298(\epsilon=47)}$.
(25) Product ratios for the experiments (%ee) were determined by HPLC (see the Supporting Information). Product ratios for the predictions were determined by converting calculated gas-phase enthalpies of activation $\Delta H_{298} \pm 0.4$ kcal/mol to %ee using absolute rate theory: $\ln(k_1/k_2) = -\Delta\Delta G/RT$.

Table 1. Comparison of Computed Energies versus Known Experimental Results

	Experiment	Theory
	%ee; ΔG_{298}	ΔH_{298}; ΔG_{298}; $\Delta G_{298(\epsilon=47)}$*
ref. 4		
	60; 0.82	1.4; 1.9; 2.3
	96; 2.3	1.7; 2.0; 1.5
ref. 9		
	57; 0.75	0.6; 0.7; 0.7

^{a} Reaction carried out at 323K; %ee extrapolated for 298K.
*Calculated by CPCM solvation model ($\Delta G_{298(\epsilon=47)}$)

Average Absolute Errors in Energy (kcal/mol)
$\Delta H_{298} = \pm 0.44$
$\Delta G_{298} = \pm 0.48$
$\Delta G_{298(\epsilon=47)} = \pm 0.78$

^{a} Reaction carried out at 323 K; %ee extrapolated for 298 K. *Calculated by CPCM solvation model ($\Delta G_{298(\epsilon=47)}$).

of cyclohexanone with isobutyraldehyde is predicted to be substantially more stereoselective.

The experiments were conducted using standard conditions (20 vol % cyclohexanone/DMSO, 30 mol % of (S)-proline). The experiments were conducted in triplicate, and control experiments show that anti and syn isomers do not equilibrate under reaction conditions. In the reaction of cyclohexanone with benzaldehyde, anti-**2** and syn-**2** were formed in equal amounts in 85 ± 5% ee and 76 ± 5% ee, respectively. Absolute and relative configurations of the products were assigned based on literature optical rotation values and ^{1}H NMR data and product ratios were determined by HPLC. In the reaction of cyclohexanone with isobutyraldehyde, a single diastereomer, anti-**2**, was formed in 97 ± 3% ee. In this case, absolute and relative

Table 2. Predicted and Experimental Product Ratios for the Reaction of Cyclohexanone with Benzaldehyde and Isobutyraldehyde

	R = Ph		R = i-Pr	
	Predicted	**Experiment**	**Predicted**	**Experiment**
anti-2	50-80% ($\Delta H_{298} = 0.0$)	45-47% $\Delta G_{exp} = 0.0$	$\geq$99% ($\Delta H_{298} = 0.0$)	97-100% $\Delta G_{exp} = 0.0$
syn-2	20-50% ($\Delta H_{298} = 0.4 \pm 0.4$)	43-45% $\Delta G_{exp} = 0.03 \pm 0.05$	<1% ($\Delta H_{298} = 6.7 \pm 0.4$)	<1% $\Delta G_{exp} > 4.1 \pm 0.03$
ent-syn-2	<1% ($\Delta H_{298} = 3.6 \pm 0.4$)	5-7% $\Delta G_{exp} = 1.2 \pm 0.05$	<1% ($\Delta H_{298} = 7.8 \pm 0.4$)	<1% $\Delta G_{exp} > 4.1 \pm 0.03$
ent-anti-2	1-4% ($\Delta H_{298} = 2.3 \pm 0.4$)	3-5% $\Delta G_{exp} = 1.4 \pm 0.05$	<1% ($\Delta H_{298} = 4.6 \pm 0.4$)	0-3% $\Delta G_{exp} = 2.5 \pm 0.03$

configurations were determined based on the X-ray structure of the corresponding tosylhydrazone.

The predictions are compared with experimental results in Table 2. There is excellent agreement between the quantum mechanical prediction and the experimental results for these synthetically useful reactions. The only difference between theory and experiment involves the unexpected formation of 5−7% of ent-syn-**2**. This may be due to a background pathway of different or lower selectivity that uses an alternative reaction mechanism such as general acid or base-catalyzed aldolization.

Quantum mechanical calculations can successfully predict the product ratios of a synthetically useful reaction with a complex stereochemical outcome. With the increasing speed and efficiency of computers, quantum mechanical calculations of this type will soon become a common predictive tool.

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

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