Catalysis of the Hajos–Parrish–Eder–Sauer–Wiechert Reaction by *cis*- and *trans*-4,5-Methanoprolines: Sensitivity of Proline Catalysis to Pyrrolidine Ring Conformation

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Received: May 3, 2004; Accepted: July 26, 2004

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Methanoprolines are found to be catalysts for the Hajos–Parrish–Eder–Sauer–Wiechert reaction.[1] *cis*-4,5-Methanoproline exhibits catalytic ability similar to proline (86% yield, *93% ee*), whereas the *trans*-4,5-methanoproline is less selective (67% yield, *83% ee*) and shows less acceleration. The reaction was also studied with hybrid density functional theory (B3LYP). The nearly planar *cis*-4,5-methanoproline amine better reflects the planar iminium of the transition states than the pyramidalized *trans*-4,5-methanoproline. This difference in conformation is responsible for the observed higher enantioselectivity and enhanced catalytic behavior of the *cis*-4,5-methanoproline.

Keywords: aldol; asymmetric catalysis; cyclization; hybrid density functional theory; organic catalysis; proline

Proline has received attention as an efficient and general organic catalyst for several powerful asymmetric transformations such as the aldol,[2] Mannich,[3] Michael,[4] reactions and, most recently, the asymmetric α-carbonyl oxidations.[5] However, despite the success of proline, few useful catalytic proline derivatives have been reported in literature. Theoretical studies of the aldol[6] and the Mannich[7] reactions at UCLA led to the identification of iminium planarity[8] as a key component in proline catalysis. Interestingly, at Montreal the synthesis[9] of 3,4-methanoprolines and their use as conformationally rigid planar proline replacements in enzyme inhibitors has been accomplished.[10] We have now joined forces to explore the use of *cis*- and *trans*-4,5-methanoproline as catalysts for the Hajos–Parrish–Eder–Sauer–Wiechert reaction (Scheme 1) experimentally and computationally.[11]

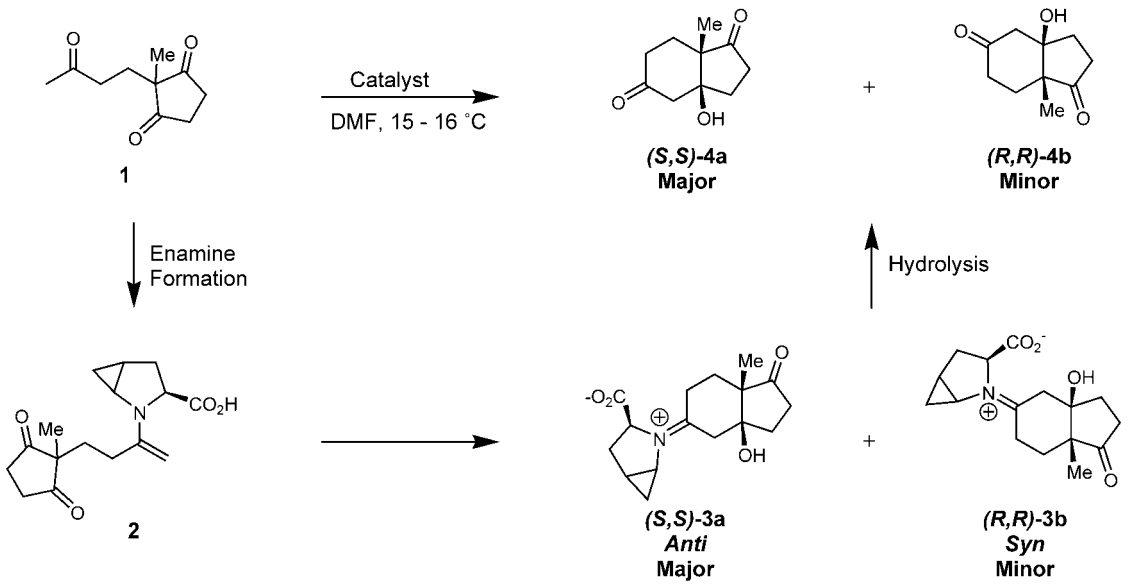
cis-4,5-Methanoproline (entry 2, Table 1) exhibits catalytic and enantioselective behavior much akin to proline (*93%* and *95% ee*, respectively), whereas the *trans*-4,5-methanoproline (entry 3, Table 1) was found to be slower and less enantioselective (*83% ee*) than either proline or the *cis* derivative.

Transition structures for the Hajos–Parrish–Eder–Sauer–Wiechert reaction catalyzed by proline, *cis*- and *trans*-4,5-methanoproline are shown in Figure 1. Transition states in which the enamine is *anti* to the carboxylic acid are more favorable than the corresponding *syn* enamine transition states. The activation energies of cyclizations for proline and *cis*-4,5-methanoproline are 10.5 kcal/mol and 10.7 kcal/mol, respectively. The *trans*-4,5-methanoproline-catalyzed reaction has a higher activation energy of 12.4 kcal/mol, approximately a 25-fold decrease in rate. The *anti-syn* transition state energy differences for proline and the *cis*-4,5-methano derivative are nearly identical at 2.2 kcal/mol and 2.1 kcal/mol, respectively, while *trans*-4,5-methanoproline has a substantially lower difference of 1.3 kcal/mol.

Our calculated results are compared with experiment in Table 2. There is an excellent agreement between the experimental free energy difference and the calculated gas phase enthalpy differences (MAD = 0.1 kcal/mol).

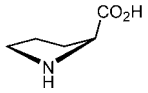
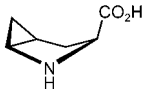
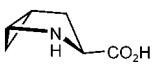
Bicyclo[3.1.0]hexanes are known to favor the boat conformation over the chair due to the torsional interactions involving the cyclopropane ring.[12] We have calculated the lowest energy conformations of the *cis*- and *trans*-methanoproline enamines, and our results show the *trans*-methanoproline enamine to be the expected boat (ω_σ[13] = −13°) with a significantly pyramidalized amine (χ_N[14] = 46°). The *cis*-methanoproline is also the expected boat; however, the steric repulsion of the carboxylic acid group *cis* to the cyclopropane ring results

 DOI: 10.1002/adsc.200404127



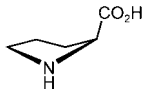
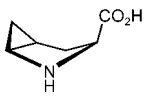
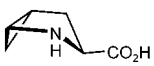
Scheme 1. Mechanism of proline derivative-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert reaction.

Table 1. Proline derivative-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert reaction.

Entry	Catalyst	% mol cat.	Time [h]	Yield [%] *(% ee)*
1		3%	48	98% *(95%)*
2		3%	140	86%[a] *(93%)*
3		3%	125	67%[b] *(83%)*

[a] 14% starting material recovered.
[b] 28% starting material recovered. Reaction never goes to completion.

Table 2. Comparison of experimentally observed and calculated enantioselectivity of methanoproline derivative catalyzed Hajos–Parrish–Eder–Sauer–Wiechert reaction.

Entry	Catalyst	Experiment ($\Delta G^{\ddagger}$)	Calculated ($\Delta H^{\ddagger}$)
1		2.1	2.2
2		1.9	2.1
3		1.4	1.3

in a rather planar *cis*-methanoproline enamine ($\omega_\sigma = 8°$), with a relatively planar amine ($\chi_N = -10°$).

The *anti-syn* selectivity is dictated by this conformational bias of the respective methanoproline derivatives. The origin of enantioselectivity of proline-catalyzed reactions arises from the different degrees to which each diastereomeric transition state satisfies iminium planarity and stabilizes the forming alkoxide.[15] The *anti* transition structures have a planar iminium (*cis*-methanoproline TS **6a**: $\chi_N = -3°$ and *trans*-methanoproline TS **7a**: $\chi_N = 0°$), while the *syn* transition structures have a pyramidalized iminium (*cis*-methanoproline TS **6b** $\chi_N = 13°$ and *trans*-methanoproline TS **7b**: $\chi_N = 12°$). In the *cis*-methanoproline case, the planar enamine ($\chi_N = -10°$) allows for a facile transition to the *anti*, planar iminium transition structure, whereas the realization

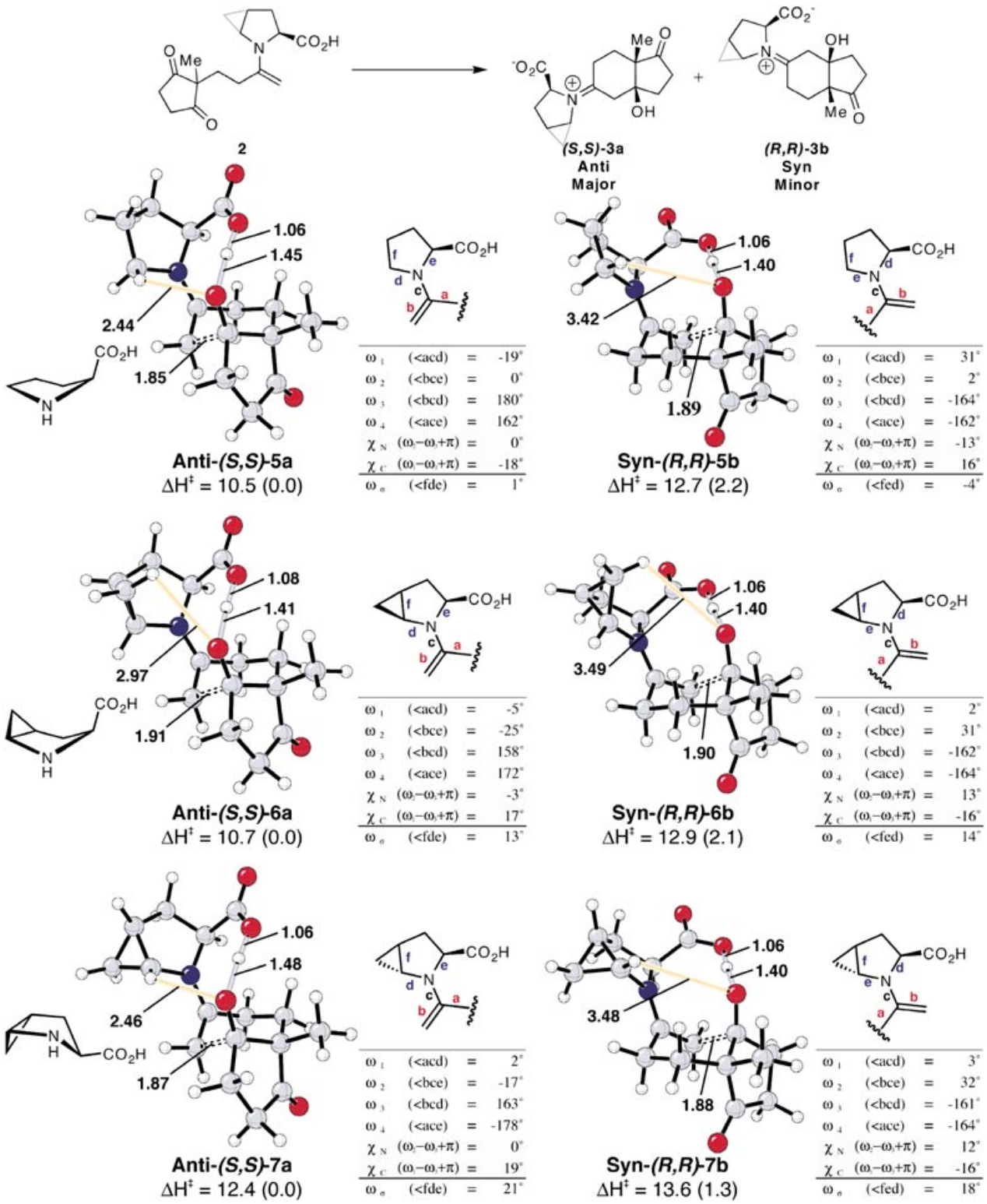


Figure 1. *anti* and *syn* transition structures for proline, *cis*- and *trans*-4,5-methanoproline catalyzed cyclization of enamine **2** (Hajos–Parrish–Eder–Sauer–Wiechert reaction). Shown on the tables are dihedral angles relevant to the measure of iminium planarity.

of the pyramidalized *syn* transition structure would require heavy geometric distortion. This is in contrast to the *trans*-methanoproline, where the naturally pyramidalized enamine ($\chi_N = -46°$) requires less geometric

distortion to reach the *syn*, pyramidalized iminium transition states, than the planar *anti*. Despite this conformational bias, *trans*-methanoproline is still *anti*-selective not only due to the stability gained by the more planar iminium of the *anti* transition structure, but because of the accentuated $NCH^{\delta+}-O^{\delta-}$ interactions of the cyclopropyl protons.

The observed catalytic ability of the two derivatives can also be explained by the conformational biases. Given the enamine-mediated mechanism of the Hajos–Parrish–Eder–Sauer–Wiechert reaction,[16] it stands to reason that the activation barrier to distort the enamines from their lowest energy conformations to reflect the partial iminium (ideal $\chi_N = 0°$) of the transition states is higher for the non-planar *trans*-methanoproline ($\chi_N = 46°$) and lower for the planar *cis*-methanoproline ($\chi_N = -10°$). The energy required for the *trans* stereoisomer to achieve the necessary planar iminium arrangement in the aldol transition state is responsible for its poorer catalytic ability. It is of interest to note that despite this planar conformational preference of *cis*-methanoproline, it is still slightly slower than the parent proline catalyst by a factor of ~ 3. We attribute the most probable cause to the retardation of the hydrolysis of the product iminium by the above unusual conformational biases.

We have demonstrated the use of unique conformational preferences imparted by the fused cyclopropanes to identify a new catalytic proline derivative for the Hajos–Parrish–Eder–Sauer–Wiechert reaction. Analogous studies of methanoproline-catalyzed intermolecular aldol reactions are in progress.

Experimental Section

Typical Procedure

4 mg each of *(S)*-proline, *cis*-4,5-methanoproline, and *trans*-4,5-methanoproline, were mixed respectively with 0.5 mL of DMF and stirred at 15–16 °C for 15 min. A solution of triketone (0.182 gm) in 1 mL of DMF was added and stirred for 140 h at 15–16 °C in a reaction tube, immersed in a water bath and protected from light. DMF was removed under reduced pressure and the residual dark oil was chromatographed using 1:1 EtOAc:hexanes. The product was dehydrated using 1 N H_2SO_4 in DMF at 95 °C for 5–6 h. The solvent was removed under reduced pressure, dissolved in EtOAc, washed with saturated sodium bicarbonate and dried over sodium sulfate. The solution was passed through a silica gel bed, and the solvent was removed under reduced pressure. The enantiomeric excess was determined using chiral phase HPLC [Chiralpak AS-RH. 72% H_2O (0.1% TFA)/28% CH_3CN; t_r *(S)* = 9 min and t_r *(R)* = 14 min].

Acknowledgements

We are grateful to the National Institute of General Medical Sciences, National Institutes of Health for financial support of this research. We thank the National Computational Science Alliance, the National Science Foundation, and UCLA Academic Technology Services for computer resources. The Montreal group acknowledges financial support from the Natural Science and Engineering Council of Canada, and X-ray crystallographic analyses by Michel Simard and Francine Bélanger-Gariépy.

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[11] a) The stationary points (reactants and transition structures) were optimized and characterized by frequency analysis using hybrid density functional theory (B3LYP) and the 6–31G(d) basis set as implemented in Gaussian 98. Enthalpies, ΔH_{298}, and free energies, ΔG_{298}, were computed at the same level of theory for the gas phase. The electronic energies were taken from a single point at the B3LYP/6–311+G(2df, p) level of theory. Stereoselectivities were predicted using transition state theory; b) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr.; R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, *Gaussian 98, Revision A.9*, Gaussian, Inc.; Pittsburgh PA, **1998**.

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[13] The dihedral ω_σ reflects the boat or chair conformation of the methanoprolines. Positive angles reflect an axial orientation of the carboxylic acid group whereas negative angles reflect equatorial carboxylic acid groups. It then follows that *cis*-methanoprolines prefer positive ω_σ, and *trans*-methanoprolines prefer negative ω_σ.

[14] The choice and definition of these dihedral angles have been adapted from K. L. Brown, L. Damm, J. D. Dunitz, A. Eschenmoser, R. Hobi, C. Kratky, *Helv. Chim. Acta* **1978**, *61*, 104; χ_N and χ_C reflect the deviation from planarity of the iminium nitrogen and the carbon atoms.

[15] a) Electrostatic stabilizations are provided by the donation of the acidic proton as well as the $^{\delta+}$NCH–O$^{\delta-}$ electrostatic interactions, as described in reference for the Hajos–Parrish–Eder–Sauer–Wiechert reaction; b) the relative magnitudes and chemical significances of $^{\delta+}$NCH–O$^{\delta-}$ electrostatic interactions are discussed in: S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 11273.

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