Published in final edited form as:
J Am Chem Soc. 2009 February 11; 131(5): 1632–1633. doi:10.1021/ja806672y.

Rate Limiting Step Precedes C–C Bond Formation in the Archetypical Proline-Catalyzed Intramolecular Aldol Reaction

Hui Zhu[†], **Fernando R. Clemente**[‡], **K. N. Houk**[‡], and **Matthew P. Meyer**[*,†]
University of California, Merced, School of Natural Sciences, P.O. Box 2039, Merced, California 95344

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

The burgeoning field of organocatalysis has given rise to numerous successful examples of chirality transfer from proline or proline derivatives.[1] The versatility of proline as a catalyst has led some to call it “the simplest enzyme”.[2] This moniker is apt, since proline is capable of transferring chirality as either an iminium electrophile[3] or as an enamine nucleophile, a role often assumed by lysine in enzymes. One of the most successful examples of proline catalysis is the intramolecular aldol reaction reported independently by two research groups over 30 years ago (Scheme 1).[4]

Despite intensive mechanistic study of the Hajos–Parrish–Eder–Sauer–Wiechert reaction by numerous groups, important questions still remain, such as the following: (1) Do measured isotope effects corroborate computational results[5] which indicate partial rate limitation by enamine formation and C–C bond formation? (2) Are the product- and rate-determining steps identical? Kinetic isotope effect (KIE) studies are acutely sensitive to the structural composition of the transition state. The currently accepted mechanism for proline-catalyzed aldol reactions is soundly based upon numerous empirical[6,7] and computational[5,8–11] data. The mechanism is currently thought to proceed through partially rate-limiting enamine and C–C bond formation, with product-determining C–C bond formation via intramolecular general acid catalysis by the carboxylic acid group on proline. Compelling comparisons between experimentally determined product distributions and computational predictions in closely related reactions are supportive of a general paradigm in which C–C bond formation is product-determining.[10]

Based on the preceding mechanistic model, we sought to answer the questions posited above. In fact, the current system appeared to be an ideal means to extend the concept of KIEs at enantiotopic groups[12] to $^{12}C/^{13}C$ competition. We performed four replicates of traditional ^{13}C KIEs experiments and four independent replicates of ^{13}C KIEs measured by observing fractionation in desymmetrized starting material. Two noteworthy observations can be made from these measurements (Figure 1). First, the only significant KIE resides upon the acyclic carbonyl. Second, KIEs measured upon desymmetrized reisolated starting material yield no statistically significant differences between prochiral carbonyls. If isotopic fractionation was controlled by either enamine formation or C–C bond formation, a sizable

[*] mmeyer@ucmerced.edu .
[†]University of California, Merced.
[‡]University of California, Los Angeles.

Supporting Information Available: Detailed experimental procedures, tables of integrations from quantitative NMR measurements, and Cartesian coordinates for all computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

isotope effect would be anticipated at the methyl position adjacent to the nucleophilic carbonyl. Likewise, if C–C bond formation or any step subsequent to C–C bond formation was responsible for the observed effects, the pro-*S* and pro-*R* carbonyls would likely display significantly disparate KIEs. The measurements in Figure 1 unequivocally implicate a reaction step previous to enamine formation as the rate-limiting step. There are two principal steps prior to enamine formation that might reasonably be expected to yield the measured values: carbinolamine formation or subsequent loss of water to yield the iminium intermediate. Classic studies of iminium formation in aqueous solutions by Cordes and Jencks implicate carbinolamine formation as rate-limiting under acidic conditions and formation of the iminium ion as the rate-limiting step under basic conditions.[13] However, it is difficult to predict a correspondence between the activity of the prolyl carboxylic acid proton in a dimethylformamide solution to the activity of a hydronium ion aqueous solution with any degree of reliability.

The KIEs shown in Figure 1A were measured using the technique developed and widely applied by Singleton, whereby KIEs are computed from isotope fractionation in reisolated starting material (**1**) in reactions taken to high conversion.[14] Four reactions were taken to 80.7, 91.3, 86.8, and 93.4% conversion. The triketone reactant (**1**) was isolated after aqueous workup using flash chromatography. Relative ^{13}C enrichment was measured using quantitative ^{13}C NMR compared against a standard sample of the triketone. The KIEs shown in Figure 1B were obtained using a new method that consists of desymmetrizing the reisolated starting material previous to quantitative ^{13}C NMR analysis. The standard sample is also desymmetrized prior to analysis. In principle, any quantitative reaction that makes the prochiral groups inequivalent with high selectivity can be used. Because this technique is most useful for studying highly stereoselective reactions, the reaction being studied is often the best choice for desymmetrizing the reactant. After desymmetrization, relative ^{13}C enrichment is measured in **2** derived from quantitative conversion of reisolated **1** and a sample of **2** obtained from a quantitative conversion of stock reactant. To collect the data in Figure 1B, four reactions were taken to 91.0, 90.4, 92.7, and 80.1% conversion, and the reisolated **1** was desymmetrized as described above. NMR assignments were performed using a combination of TOCSY and HMQC spectra. In these experiments, the proline-catalyzed intramolecular aldol cyclization of **1** proceeded with 93.0% ee or a ratio of 96.5% (*S*,*S*)-enantiomer (**2**) to 3.5% (*R*,*R*)-enantiomer (ent-**2**). Because the reaction pathways that lead to these two enantiomers are likely to proceed through similar transition structures, it is unlikely that the small systematic error induced by the presence of the minor enantiomer has a significant effect upon the results.

The entire reaction pathway for the archetypical proline-catalyzed intramolecular aldol addition has been computed previously (Scheme 2).[5] The transition structures for carbinolamine formation (**TS1**) and iminium formation (**TS2**) were optimized along with the structure for the triketone reactant using the B3LYP[15] functional with the 6–31+G(d,p) basis set[16] in the current study. Subsequent force constant calculations were performed, frequencies were computed for isotopologues of interest, and the resulting frequencies were used as input into the Bigeleisen equation.[17] The Bell infinite parabola correction was used to account for tunneling.[18] As a point of comparison, we also computed the ^{13}C KIEs expected to arise from the previously suggested[5] rate-limiting C–C bond formation (**TS3**) using the same functional and basis set as above. The results of these calculations are shown in Figure 2. The three transition structures of interest were also optimized [B3LYP/6–31+G(d,p)] using a polarizable continuum model (IEFPCM) for the solvent.[19]

It is obvious that **TS3** does not contribute significantly to the observed KIEs. The complete absence of statistically relevant KIEs in the electrophilic cyclic carbonyl position and the α-methyl group precludes rate-determining C–C bond formation. Likewise, a significant value

at the nucleophilic acyclic carbonyl position is at variance with **TS3**. Discerning between **TS1** and **TS2** as transition structures for the rate-determining step using computed KIEs is problematic. KIEs computed from gas phase structures strongly implicate **TS2**; however, it is difficult to justify such a model, given the presence of substantial localized charges in the intermediates and transition structures. To mitigate the potential inaccuracies associated with gas phase calculations, the transition structures were optimized with an IEFPCM model for the solvent. However, KIEs computed from these structures yield essentially identical values at the acyclic carbonyl for both **TS1** and **TS2**. Imperfect agreement between experiment and theory is understandable, given that the rate-determining step likely involves proton transfer, significant changes in charge distribution, and solvent reorganization. Energeti-cally, both gas-phase and IEFPCM calculations find **TS2** lower in energy than **TS1** by ~3 kcal/mol (see Supporting Information).

We have presented data that implicate a reaction step previous to C–C bond formation in the Hajos–Parrish–Eder–Sauer–Wiechert reaction. This finding represents a substantial change in our understanding of proline-catalyzed aldol reactions. Kinetics and isotope effect experiments are currently underway to determine whether this is a general feature of proline-catalyzed intramolecular aldol reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

M.P.M. thanks the University of California for funding and Michael Colvin at UCM for the use of his Linux cluster. K.N.H. and F.R.C. acknowledge financial support from NIH-NIHGMS Grant GM-36700.

References

(1). Reviews: (a) Jarvo ER, Miller SJ. Tetrahedron 2002;58:2481.. (b) List B. Tetrahedron 2002;58:5573.. (c) Dalko PI, Moisan L. Angew. Chem., Int. Ed 2004;43:5138.. (d) Notz W, Tanaka F, Barbas CF III. Acc. Chem. Res 2004;37:580. [PubMed: 15311957] . (e) List B. Acc. Chem. Res 2004;37:548. [PubMed: 15311954] . (f) Seayad J, List B. Org. Biomol. Chem 2005;3:719. [PubMed: 15731852] . (g) Mukherjee S, Yang JW, Hoffman S, List B. Chem. Rev 2007;107:5471. [PubMed: 18072803]

(2). Movassaghi M, Jacobsen EN. Science 2002;298:1904. [PubMed: 12471240]

(3). A possible example: Hannessian S, Pham V. Org. Lett 2000;2:2975. [PubMed: 10986086]

(4). (a) Eder U, Sauer G, Wiechert R. Angew. Chem., Int. Ed 1971;10:496. (b) Hajos ZG, Parrish DR. J. Org. Chem 1974;39:1615.

(5). Clemente FR, Houk KN. Angew. Chem 2004;116:5890.

(6). Hoang L, Bahmanyar S, Houk KN, List B. J. Am. Chem. Soc 2003;125:16. [PubMed: 12515489]

(7). List B, Hoang L, Martin HJ. Proc. Natl. Acad. Sci. U.S.A 2004;101:5839. [PubMed: 15073330]

(8). Bahmanyar S, Houk KN. J. Am. Chem. Soc 2001;123:11273. [PubMed: 11697970]

(9). Bahmanyar S, Houk KN. J. Am. Chem. Soc 2001;123:12911. [PubMed: 11749554]

(10). Bahmanyar S, Houk KN, Martin HJ, List B. J. Am. Chem. Soc 2003;125:2475. [PubMed: 12603135]

(11). Allemann C, Gordillo R, Clemente FR, Cheong PH-Y, Houk KN. Acc. Chem. Res 2004;37:558. [PubMed: 15311955]

(12). West JD, Stafford SE, Meyer MP. J. Am. Chem. Soc 2008;130:7816. [PubMed: 18517199]

(13). Cordes EH, Jencks WP. J. Am. Chem. Soc 1963;85:2843–2848.

(14). Thomas AA, Singleton DA. J. Am. Chem. Soc 1995;117:9357.

(15). (a) Becke AD. J. Chem. Phys 1993;98:1372. (b) Lee C, Yang W, Parr RG. Phys. Rev. B 1988;37:785.

(16). (a) Ditchfield R, Hehre WJ, Pople JA. J. Chem. Phys 1971;54:724. (b) Hehre WJ, Ditchfield R, Pople JA. J. Chem. Phys 1972;56:2257. (c) Hariharan PC, Pople JA. Theor. Chim. Acta 1973;28:213.

(17). Bigeleisen J, Wolfsberg M. Adv. Chem. Phys 1958;1:15.

(18). Bell, RP. The Tunnel Effect in Chemistry. Chapman and Hall; New York: 1980.

(19). Tomasi J, Mennucci B, Cammi R. Chem. Rev 2005;105:2999. [PubMed: 16092826]

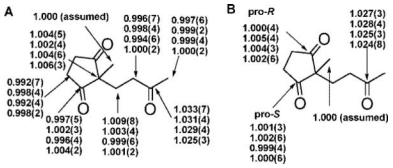


Figure 1.

^{13}C KIEs obtained by measuring isotopic fractionation in the (A) reisolated reactant and (B) reisolated reactant after desymmetrization. Errors in the last digit are in parentheses.

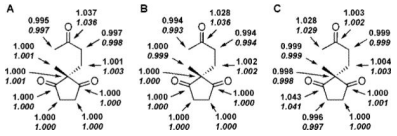
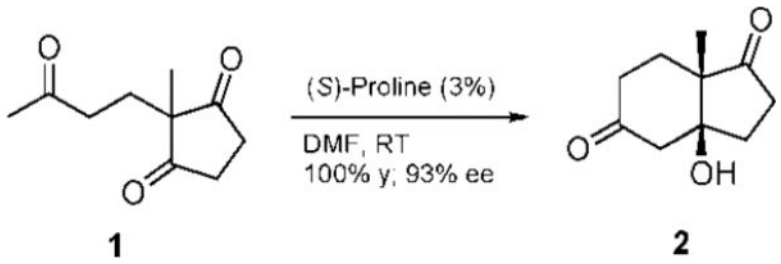


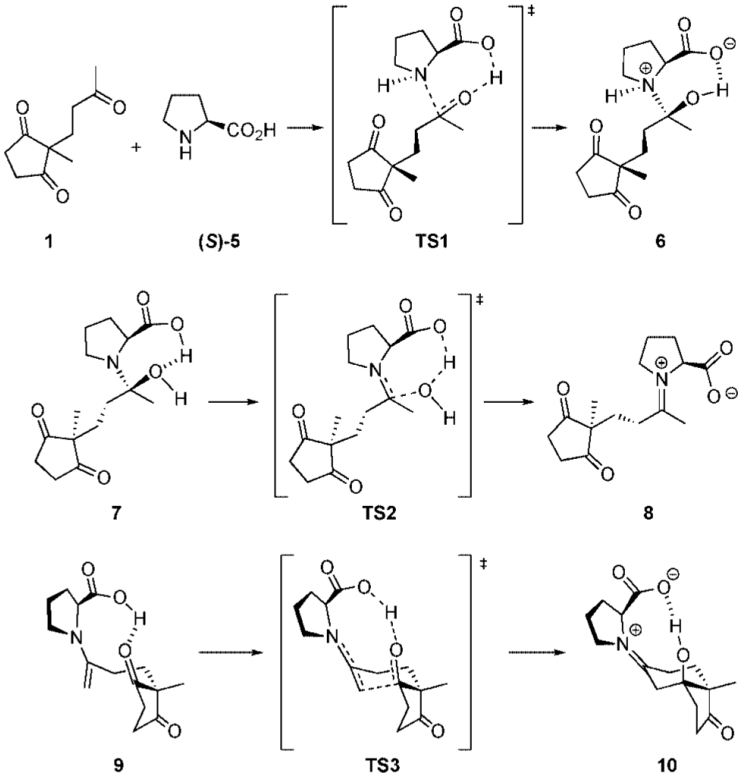
Figure 2.

^{13}C KIEs computed from force constant calculations upon the triketone reactant and **A**. **TS1**, **B**. **TS2**, and **C**. **TS3**. Isotope effects computed using the IEFPCM model for solvent are in italics.



1 2

Scheme 1.



Scheme 2.