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Isotope Effects Reveal Mechanism of Enamine Formation in L-Proline Catalyzed α-Amination of Aldehydes

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ABSTRACT: The mechanism of L-proline catalyzed aamination of 3-phenylpropionaldehyde was studied using a combination of experimental kinetic isotope effects (KIEs) and theoretical calculations. Observation of a significant carbonyl ¹³C KIE and a large primary (1°) α -deuterium KIE support rate-determining enamine formation. Theoretical predictions of KIEs exclude the widely accepted mechanism enamine formation via intramolecular deprotonation of an iminium carboxylate intermediate (7). An E2-elimination mechanism catalyzed by a bifunctional base, that directly forms an N-protonated enamine species $(12 \cdot H^+)$ from an oxazolidinone (11) intermediate, accounts for the experimental KIEs. These findings provide the first experimental picture of the transition state geometry of enamine formation and clarify the role of oxazolidinones as non-parasitic intermediates in proline catalysis.

The L-proline catalyzed α -functionalization of aldehydes via enamine catalysis has led to a number of powerful asymmetric transformations.¹ A single transition state model – the Houk-List model (H-L model) – provides a general rationale for the observed enantioselectivity in these reactions (Figure 1).² Central to this model is the anti-enamine carboxylic acid intermediate (8) that serves as both an enolate equivalent and a Brønsted acid activator of the electrophile, via proton transfer from the carboxylic acid moiety, at the stereo-determining transition state TS4 (Figure 1B). It is generally assumed that 8 forms via an intramolecular deprotonation mechanism from 7 via TS3. Oxazolidinone intermediates such as 11 and 13 are considered off-cycle parasitic species within the H-L model.³

Seebach and Eschenmoser have proposed an alternate pathway (S-E model), based on the observation of 11 and 13 by 1 H NMR.⁴ The key intermediate in the S-E pathway for enamine catalysis is not 8 but *syn*-enamine carboxylate 12. Formation of 12 occurs via an E2-elimination mechanism from 11. An electrophile-induced γ -lactonization of 12 to oxazolidinone 13 via **TS9** is the key stereo-determining event in this pathway (Figure 1B). An NMR study by Gschwind and co-workers⁵ supported a third mechanistic pathway - direct conversion of 11 to 8 (TS-Gschwind) without the intermediacy of 7. The Gschwind model combines key features of the H-L and S-E mechanisms – apparent E2-elimination from 11 (S-E proposal) results in formation of H-L intermediate 8; and TS4 (H-L proposal) is the stereo-determining event in the catalytic cycle.

The three mechanisms discussed (Figure 1A) are different with respect to the (a) mechanism of enamine formation, (b) role of the oxazolidinone intermediate 11, or (c) nature of the enantioselectivity-determining step (Figure 1C). While there is



Figure 1. (A) Mechanistic models for enamine catalysis by L-proline show the three proposed pathways for enamine formation. Inner catalytic cycle is Houk-List pathway, outer catalytic cycle is Seebach-Eschenmoser pathway and the Gschwind pathway incorporates 11 into the Houk-List pathway (B) Houk-List (TS4) and Seebach-Eschenmoser (TS9) models for the origin of enantioselectivity in the L-proline catalyzed aldol reaction (C) Distinguishing features of the three mechanistic models for enamine catalysis (D) Prototypical reaction proceeding via rate-determining enamine formation

little debate that **TS4** (H-L model) is the stereo-determining transition state,⁶ the exact mechanism of enamine formation or the role of **11** in proline catalysis is not firmly established. We report herein the results from a combined experimental and theoretical ¹³C and ²H kinetic isotope effect (KIE) study that provides the first experimental insights into the transition state geometry for enamine formation and clarifies the role of oxazolidinone intermediates in proline catalysis.

The mechanism of L-proline catalyzed α -amination of aldehydes (Figure 1D)⁷ has been investigated using experimental⁸ and computational⁹ methods. Kinetic studies by Blackmond have revealed that the reaction (a) is zero order in electrophile, (b) exhibits asymmetric amplification, and (c) is autocatalytic. Enamine formation has been implicated as the ratedetermining step in the catalytic cycle. This reaction was therefore chosen for determination of ¹³C and ²H KIEs as a direct probe of the mechanism for enamine formation in catalysis by proline.

Experimental KIEs. Experimental ¹³C KIEs for 1a were determined from analysis of starting material using NMR methodology at natural abundance.¹⁰ Two separate reactions of 1a and 2a were taken to 84±2 % and 77±2 % conversion of 1a. Unreacted 1a was re-isolated from the reaction mixture and the ¹³C isotopic composition compared to samples of unreacted 1a, not subjected to reaction conditions.¹¹ From the changes in relative isotopic composition and the fractional conversion, ¹³C KIEs were determined. Additionally, α deuterium KIEs $(k_{\rm H,2}/k_{\rm D,2})$ were measured, from two independent reactions of a 4:1 mixture of $\alpha - H_2$ -1a: $\alpha - D_2$ -1a, taken to 48±2 % and 47±2 % conversion of α -H₂-1a, using ²H NMR analysis (of NaBD₄ reduced reaction mixtures) to accurately determine the enhancement of deuterium content in unreacted starting material.¹¹ Experimentally measured ¹³C and ²H KIEs, from the four independent experiments are shown in Figure 2.



Figure 2. Experimental KIEs for L-proline catalyzed reaction of 1a with 2a. Two sets of ¹³C KIEs and two sets of ²H KIEs represent independent experiments with six measurements per experiment. Numbers in parentheses show the uncertainty in the last digit of each measurement.

Qualitative interpretation of experimental KIEs. Observation of a significant carbonyl (C1) ¹³C KIE and a large primary (1°) α -deuterium KIE ($k_{\text{H-2}}/k_{\text{D-2}}$) is indicative of a ratedetermining step involving α -deprotonation concomitant with bonding changes at C1. The small, yet non-unity KIE on the α -carbon (C2) suggests that C2 is not completely rehybridized during the proton transfer event. The experimental KIEs are qualitatively consistent with a mechanism involving rate-determining E2-elimination; however, a quantitative interpretation is deferred until all possible transition structures in the various models (Figure 1A) are ruled out by a comparison of predicted KIEs to experimental values. **Theoretical studies.** To aid in this quantitative interpretation of experimental KIEs, transition structures for each step in Figure 1A were computed using the B3LYP-GD3 method^{12,13} employing a 6-31+G** basis set and a PCM solvent model¹⁴ for acetonitrile. This method adequately describes energetics and predicts KIEs in other proline-catalyzed reactions.¹⁵ The ¹³C and ²H KIEs were computed from the scaled vibrational frequencies of the respective transition structures using the program ISOEFF98.^{16,17} A Wigner tunneling correction was applied to all predicted KIEs.¹⁸

Table 1. Comparison of experimental and predicted KIEs for all transition structures in Figure 1 not involved in enamine formation.

Predicted KIEs	C1	C2	C3	$\frac{k_{1-\alpha-H2}}{k_{1-\alpha-D2}}$
TS1	1.025	1.001	1.005	0.8
TS2	1.024	0.994	1.000	0.8
TS4	1.004	1.018	1.001	1.0
TS5	1.027	0.985	1.000	0.6
TS6	1.020	0.988	0.999	0.6
TS7	1.026	1.002	1.000	0.9
TS9·H⁺	1.028	1.006	1.003	0.9
TS10	1.028	0.990	1.000	0.6
Experimental	1.019 (4) 1.020 (3)	1.006 (2) 1.006 (3)	0.999 (2) 1.000 (2)	2.3 (5) 2.6 (5)

KIEs for steps not involved in enamine formation. A comparison of experimental and predicted KIEs for all transition structures in Figure 1A, excluding those involved in enamine formation (**TS3**, **TS8** and **TS-Gschwind**), are shown in Table 1.¹⁹ A key observation is the poor match between *all* experimental and predicted KIEs for **TS4** (H-L TS). This confirms Blackmond's finding^{7c} that TS4 is not rate-determining. Predicted ¹³C KIEs at C1 for the remaining transition structures (Table 1) are reasonably close to the experimental C1 KIE. However, the corresponding predicted α -²H KIEs for these transition structures are inverse – an unsurprising observation considering the α -carbon is either uninvolved or completely rehybridized in all these structures. Thus, the experimental 1° α -deuterium KIE excludes all structures in Table 1 as the ratedetermining step in catalysis.



Figure 3. Lowest energy transition structures for enamine formation via deprotonation of 7 and comparison of experimental and predicted KIEs¹⁹

Transition structures and KIEs for enamine formation. The next step is to explore all possible transition structures for enamine formation and compare the KIE predictions for each structure to experiment. Intramolecular deprotonation of the α -proton of 7 by the carboxylate moiety (**TS3**) is the proposed

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59 60 mechanism of enamine formation in the H-L pathway. This mechanism, along with a water-assisted conversion of 7 to 8 (**TS3-wat**), has previously been studied computationally Figure 3).⁶ While the predicted normal α -²H KIEs for **TS3** and **TS3-wat** are in crude agreement with experiment, the near unity predicted ¹³C KIE on C1 is clearly inconsistent with experiment (Figure 3). *This result strongly rules against the widely accepted notion that iminium carboxylate 7 is a direct precursor to key enamine intermediate 8.*



Figure 4. More O'Ferrall–Jencks plot summarizing possible elimination pathways for the conversion of **11** to **12**. The lower left-hand corner of the plot corresponds to zwitterionic intermediate **7**, which facilitates an E1-elimination pathway.

Direct conversion of 11 to 12 (TS8_{Seebach}) or 11 to 8 (TS-Gschwind) occurs via an elimination mechanism involving α deprotonation and C-O bond scission (Figure 4).²⁰ Seebach has proposed that an E2-elimination pathway⁴ - represented by the diagonal in the More O'Ferrall-Jencks plot for this transformation (Figure 4) - could be initiated by a number of bases including another molecule of 4, 11, or even the product 3a (autocatalysis). We tried modeling TS8_{Seebach} (or TS-Gschwind) using these and other bases but all attempts to locate an E2-elimination transition structure resulted in geometries with the C-O bond completely cleaved as the base deprotonated the a-proton. This corresponds to the second step in a stepwise E1-elimination mechanism proceeding via the zwitterionic intermediate 7 – unsurprising, considering α– deprotonation is more likely to occur from 7 than the less acidic 11. The magnitude of the predicted α -deuterium KIE for TS8_{Seebach} depends on the extent of deprotonation, which is a function of the base employed for the particular calculation. However, near-complete C-O bond cleavage in all these structures leads to close-to-unity values for the predicted C1 KIE an observation that is in clear disagreement with the $\sim 2\%$ experimental measurement.²¹

The conversion of **11** to **12** favors a stepwise E1-elimination mechanism over a concerted E2-pathway due to stabilization of the carbocation intermediate by the lone pair of electrons on the pyrrolidine nitrogen in C-O bond cleavage. However, the experimental KIEs point toward a concerted pathway. Disengaging the nitrogen lone pair from the reaction coordinate for the elimination, by H-bonding or protonation, destabilizes the bottom left corner of Figure 4 and shifts $TS8_{Seebach}$ towards an E2-type transition structure. Based on this reasoning, an alternate mechanism for direct formation of an enamine intermediate from 11 is proposed (Figure 5). In this new transition structure **TS8'**, a bifunctional acid-base molecule protonates the pyrrolidine nitrogen while simultaneously deprotonating the α -proton of 11. The initial product from **TS8'** is *N*-protonated *syn* or *anti* enamine carboxylate 12•H⁺ which can re-enter the H-L pathway after a proton transfer to form **8** (Figure 5).



Figure 5. Transition structure (**TS8'a**) for an E2-elimination mechanism consistent with experimental KIEs – most hydrogens have been removed for clarity. Key bond-breaking/making (black) and H-bonding (red) distances (Å) shown along with predicted KIEs.

Several bifunctional bases²² were employed to model **TS8**' and the best match of experimental and predicted KIEs was obtained when soluble product-proline H-bonded complex 15 was employed as the bifunctional base to effect the direct conversion of *exo*-11 to *syn*-12•H⁺. The key features of the resulting transition state geometry **TS8'a**, along with a comparison of experimental and predicted KIEs, are shown in Figure 5. Considering the complete mismatch between experimental and theoretical KIEs for every transition structure modeled thus far (TS1-10), the predicted values for TS8'a provide the best simultaneous match to all three key experimental measurements -C1, C2, and α -deuterium KIEs. Finally, the calculated E+zpe and free energy barriers for TS8'a are 14.1 and 28.0 kcal/mol, respectively - values consistent with the facility of the reaction.²³ These results strongly support E2-elimination from 11 as the most likely mechanism of enamine formation in proline catalysis. We recognize that the α -deuterium KIEs for TS8'a are predicted high in comparison to experimental values.¹⁵ Uncertainty regarding the exact identity of the base that catalyzes TS8' possibly accounts for this discrepancy. This inconsistency could also arise from the known failure of calculations based on conventional transition state theory (TST) in accurately describing structures with concomitant heavy and light atom motion.²⁴ A variational transition state theory²⁵ (VTST) treatment, for example, may give predictions that are closer to experiment but the broad mechanistic picture that emerges from such advanced calculations is expected to be identical to the conclusions presented herein.

Our proposal, that 15 is likely the bifunctional base that catalyzes the rate-determining step (TS8'), is consistent with (a) Seebach's proposal⁴ that base catalysis is the chemical origin of autocatalysis observed in this reaction, i.e. product formation accelerates the reaction by increasing the concentration of base that catalyzes the rate-determining step, and (b) Blackmond's observation that the autocatalytic nature of this reaction is a result of 'a catalytic cycle involving only soluble proline complexes or soluble proline adducts.^{8a} After the original submission of this manuscript, we were made aware of a new NMR study by Gschwind and co-workers probing the mechanism of enamine formation in the proline catalyzed selfaldol reaction of 3-methylbutanal in DMSO. This new study rescinds their original proposal (Ref. 5, TS-Gschwind) and supports the Houk-List pathway (TS3) as the most likely mechanism of enamine formation.²⁶ This is in direct conflict with our results (vide supra) and led us to further question the conclusions presented in this manuscript.

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We questioned whether our experimental KIEs resulted from multiple steps in the catalytic cycle being partially rate determining - for example, a weighted average of the predicted KIEs of TS2 and TS3 could potentially account for our experimental KIEs. In order to probe this possibility experimentally, we determined the C1 KIEs using $\alpha - D_2$ -1a as the aldehyde. If TS3 was indeed partially rate determining, it is expected that α -deuteriums would increase the barrier to TS3 and make it 'more rate-determining'. This would result in a C1 KIE value closer to the predicted value for TS3 - 1.002 (Figure 3). We conducted duplicate ¹³C KIE experiments using α - D_2 -1a and found the C1 KIE to be 1.024(4) and 1.021(4) virtually identical to our measurements using 1a.¹¹ This result confirms that our experimental KIEs originate from a single rate-determining step and reaffirms that TS3 is not involved in the mechanism of enamine formation in our system. The discrepancy between our study and Ref. 26 is most likely attributable to the choice of electrophile (2a versus 3methylbutanal) and/or solvent (acetonitrile versus DMSO) for the respective reactions.

In conclusion, this work resolves the mechanism of enamine formation in the proline catalyzed α -amination of aldehydes. Our data supports a mechanism involving direct conversion of oxazolidinone 11 to *N*-protonated enamine 12•H⁺ via an E2elimination initiated by a bifunctional base. Rapid proton transfer from 12•H⁺ presumably forms 8 followed by re-entry into the Houk-List pathway. These results confirm the role of oxazolidinone 11 as a key *non-parasitic* intermediate in the Houk-List catalytic cycle while invoking base catalysis as the possible origin of autocatalysis observed in this reaction.

ASSOCIATED CONTENT

Supporting Information. Complete experimental and computational details, and NMR data are included in the Supporting Information. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

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- (21) See Supporting Information for detailed discussion
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