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Kinetic and mechanistic studies of proline-mediated direct intermolecular aldol reactions

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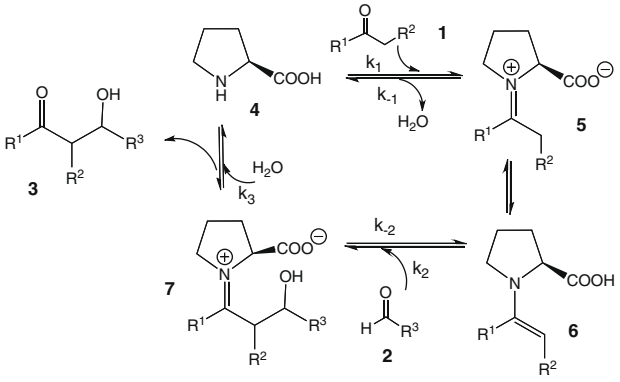
ABSTRACT

Reaction progress kinetic analysis of the proline-mediated intermolecular aldol reaction shows that the rate depends on the concentrations of both the donor ketone**1** and the electrophilic aldehyde **2**, implying that enamine formation cannot be rate-determining. The observed kinetics and deuterium isotope effects are consistent with formation of the product iminium species as the rate-determining step.

Organocatalytic reactions might be thought of as the 'first' catalysis, dating back to the Strecker reaction of 1850[1] and being implicated in even more ancient prebiotic processes.[2] Modern research in this field was galvanized by the report by List, Lerner, and Barbas in 2000[3] of an intermolecular direct aldol reaction catalyzed by proline. Since then, an intensive and ongoing activity has progressed in the development of new catalysts and the discovery of new organocatalytic transformations.[4] In analogy with reactions catalyzed by Class I aldolase enzymes,[5] the enamine-based mechanism shown in Scheme 1 is now generally accepted for many proline-mediated transformations.

While theoretical studies have added to our understanding of these systems,[6] experimental kinetic and mechanistic studies have been slower to follow.[7–9] Here we report detailed investigations of a proline-mediated intermolecular direct aldol reaction between ketone **1** (acetone, $R^1 = -CH_3$; $R^2 = -H$) and aldehyde **2** (R^3 = *m*-Cl-benzene). Our results support the proposal that the rate-determining step involves addition of the aldehyde **2** to enamine **6**. This represents the first comprehensive kinetic study of an important organocatalytic system and may contribute both to our general mechanistic understanding of organocatalysis and to the development of new catalysts and new transformations.

Experimental kinetic studies were carried out by in situ monitoring of reaction progress with reaction calorimetry for the reaction between acetone 1 and *m*-Cl-benzaldehyde 2 carried out at 25 °C in DMSO or DMF. Correlation between the measured heat flow and the reaction progress has been established by comparison with HPLC sampling and FTIR spectroscopic monitoring, and catalyst stability was confirmed under all conditions using the 'same excess' protocol, as previously described.[8e,10] The absolute solution catalyst concentration of proline was quantitatively established by ^{1}H NMR spectroscopy.



Scheme 1. Proposed mechanism for the proline-mediated intermolecular aldol reaction.

Our previous studies found a negative order dependence on added water and positive order dependences on both ketone and aldehyde substrates.[8e] The overall rate expression for the reaction may be written in power-law form (Eq. 1).

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$$\text{rate} = k \cdot [\mathbf{1}]^m \cdot [\mathbf{2}]^n \cdot [\mathbf{4}] \cdot [H_2O]^{-0.7} \quad (1)$$

Power law expressions for multi-step reactions do not necessarily imply the molecularity of any single elementary step. However, consideration of the magnitude of the exponents in a rate law like Eq. 1 can prove helpful in constructing a viable reaction pathway, as we discuss below.

Our previous work established the magnitude of the negative order in $[H_2O]$,[11] and our present task is to determine the magnitude of reaction orders m and n. In a classical kinetic approach, this would require two sets of experiments: one series is carried out with the concentration of [**1**] held constant at a high value while the dependence on [**2**] is probed, and then a second series reverses the procedure to find the order in [**1**]. By contrast, reaction progress kinetic analysis involves the design a mathematically rigorous set of experiments that allow extraction of the reaction order in both [**1**] and [**2**] from a small number of reactions (two or three) instead of two complete series of reactions, obviating the requirement to hold one concentration constant while probing the dependence of the other. Two important feature of this analysis are that (i) the kinetic behavior of a reaction may be rapidly and quantitatively investigated from significantly fewer experiments, and (ii) the reactions are carried out under synthetically relevant conditions rather than using the highly distorted concentration ratios required in a classical kinetic analysis.

The set of experiments for reaction progress kinetic analysis is designed to vary a parameter called the 'excess', [e], defined as the difference (in units of molarity) between the initial starting concentrations of the two substrates: $[\mathbf{1}]_0 - [\mathbf{2}]_0$. Excess [e] can be a small number or a large number, it can be positive, negative, or zero. Table 1 gives the initial concentrations of substrates **1** and **2** and the value of excess for each of three kinetic runs in this study. Reaction progress kinetic analysis methodology has demonstrated that two runs of 'different excess' provide a mathematically unique solution for m and n in Eq. 1.[10b] Adding a third run helps to improve accuracy and validate the model.

Reaction results for these three runs are plotted as conversion versus time in Figure 1. The curves appear as well-behaved positive order kinetic profiles, suggesting positive order dependence on both substrates.

Table 1
Experimental conditions for reaction progress kinetic analysis of the proline-catalyzed reaction of acetone **1** with aldehyde **2** at 25 °C in DMSO using 0.014 M proline and 0.4 M added H_2O. Product ee = 69%.

Run	$[\mathbf{1}]_0$ (M)	$[\mathbf{2}]_0$ (M)	Excess [e] (M)
a	2.75	0.5	2.25
b	2.00	0.5	1.50
c	1.24	0.5	0.74

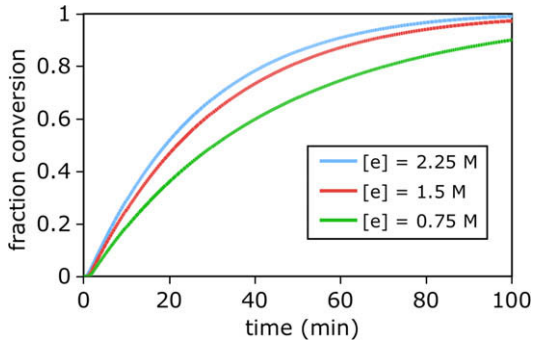


Figure 1. Kinetic profiles for the proline-mediated intermolecular aldol reaction carried out under conditions shown in Table 1.

When the data are plotted as in Figure 1, however, it is difficult to extract quantitative information about the magnitude of the reaction orders m and n from these kinetic profiles. In order to do this, we rearrange the rate Eq. 1 as shown in Eq. 2, where the (constant) proline and water concentrations have been grouped together into the constant k'.

$$\frac{\text{rate}}{[\mathbf{1}]^m} = k' \cdot [\mathbf{2}]^n \quad (2)$$

This is an equation for a straight line $y = mx$, with the slope $m = k'$, where y equals the left side of the equation and x equals to the function $[\mathbf{2}]^n$. If we find values of m and n that correctly describe our data, then re-plotting the data from Figure 1[12] with these functions as our y- and x-axes should obtain a straight line for each reaction run, and the three profiles should overlay on the same plot. The values for the orders m and n may be easily obtained by a trial and error procedure seeking straight lines and overlay. Figure 2 shows the re-plot of these data following Eq. 2 with $m = 0.58$ and $n = 0.9$.

The power-law rate expression obtained from reaction progress kinetic analysis as described above represents an empirical approximation describing the molecular-level behavior of the system. Consideration of the magnitude of the power-law exponents in this expression helps to extract valuable clues about the reaction mechanism. The observed nearly first-order dependence on [**2**] suggests that **2** is involved in the rate-determining step. The smaller fractional dependence in [**1**] suggests saturation kinetics in [**1**], meaning that a catalyst species associated with **1** is involved in the rate-limiting step. The negative order in $[H_2O]$ suggests an inhibiting effect of water on a key catalytic species. With these points in mind, we now turn back to the proposed multi-step mechanism of Scheme 1 to rationalize these observations.

The full steady-state rate expression for the catalytic network of Scheme 1 is given by Eq. 3:

$$\text{rate} = \frac{k_1 k_2 k_3 [\mathbf{1}][\mathbf{2}][H_2O][\mathbf{4}]_{total}}{[H_2O](k_{-1}k_{-2} + k_{-1}k_3[H_2O] + k_2k_3[\mathbf{2}]) + k_1k_{-2}[\mathbf{1}] + k_1k_3[\mathbf{1}][H_2O] + k_1k_2[\mathbf{1}][\mathbf{2}])} \quad (3)$$

Clearly, the intrinsic kinetic role of both substrates as well as water can be complex. This reaction rate law may be simplified by assuming limiting cases in which the rate-determining step and the catalyst resting state differ. If enamine **6** formation is rate-determining, the rate is given by Eq. 4:

$$\text{rate} = k_1[\mathbf{1}][\mathbf{4}] \quad (4)$$

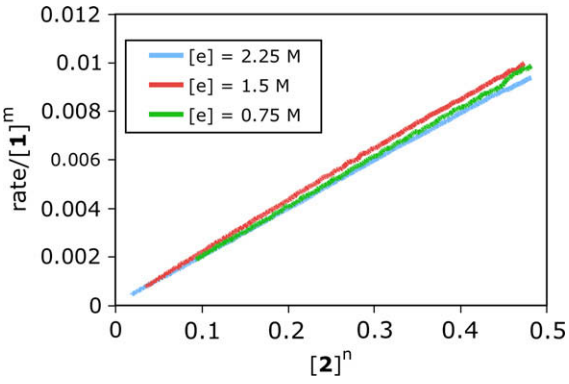


Figure 2. Kinetic profiles from Figure 1 replotted according to Eq. 2, with $m = 0.58$ and $n = 0.9$. The straight lines and the overlay of the three traces indicate that appropriate values have been chosen for m and n.

If product iminium hydrolysis is rate-determining, the rate is given by Eq. 5:

$$\text{rate} = k_3[\mathbf{7}][H_2O] \quad (5)$$

Neither of these expressions correctly describes the observed non-integer positive order in [**1**], the nearly first-order behavior in [**2**], or the suppression in rate by water.

If aldehyde addition to the enamine is rate-limiting, the steady-state rate may be described by Eq. 6:

$$\text{rate} = k_2[\mathbf{6}][\mathbf{2}] \quad (6)$$

The nearly first-order dependence of rate on [**2**] is consistent with Eq 6. When the steady-state approximation is used to derive an expression for enamine concentration [**6**] in terms of measurable species, Eq. 7 is obtained.

$$\text{rate} = \frac{k_1 k_2[\mathbf{1}][\mathbf{2}][\mathbf{4}]_{\text{total}}}{k_{-1}[H_2O] + k_1[\mathbf{1}] + k_2[\mathbf{2}]} \quad (7)$$

The form of Eq. 7 approximates that of the power-law expression of Eq. 1 over the concentration ranges studied. Eq. 7 may be analyzed in the context of the mechanism proposed in Scheme 1. Increasing the amount of added [H_2O] drives the equilibrium position for enamine **6** back towards proline **4**, resulting in a decrease in concentration of a key intermediate in the step involving addition of aldehyde **2**, which we have ascertained is rate-determining. For both [**1**] and [**2**], the first-order dependence in the numerator of the rate expression in Eq. 7 is tempered by a term in the denominator containing that concentration, with the order in [**1**] more strongly affected than that in [**2**]. This suggests that $k_1[\mathbf{1}] > k_2[\mathbf{2}]$, which is in accordance with the fact that k_2 appears in the rate-determining step.

Further mechanistic clues may be obtained from studies of deuterium isotope effects by carrying out reactions using acetone-d_6. FTIR spectroscopy and ^{1}H NMR spectroscopy revealed rapid exchange between acetone and water protons, and acetone and product –OH protons in the presence of proline and no exchange in the absence of proline. Figure 3 shows that reaction rate is linearly proportional to the fraction of deuterium, confirmed at two different overall initial concentrations of acetone, for a normal isotope effect of $k_H/k_D \approx 2$ with **1**-d_6 compared to fully protiated **1**. These results suggest a fast exchange involving acetone protons in the presence of proline yielding an average deuterium concentration in all exchangeable hydrogens (proline, acetone, water, aldol product) that is proportional to the amount of deuterium initially present in the acetone.

The isotope effect is complex to interpret. Linearity between the observed rate and the fraction of deuterium implicates the transfer of one proton in the transition state. However, $k_H/k_D \approx 2$ is smaller

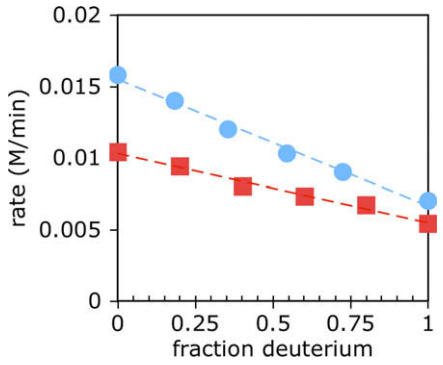
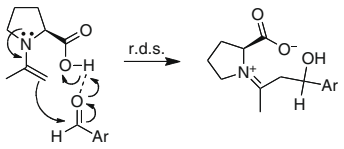


Figure 3. Kinetic isotope effect on rate for the intermolecular aldol reaction carried out at constant overall [**1**] with varying fractions of [**1**-d_6]. Initial overall acetone concentration $[\mathbf{1}]_0$ is: 2.75 M (filled blue circles); 1.25 M (filled red squares.



Scheme 2. Proposed mechanism of the rate-limiting step in the proline-mediated aldol reaction, showing opposite contributions to the overall deuterium isotope effect.

than expected for a primary isotope effect. Indeed, an inverse isotope effect would be expected if attack of the enamine on the aldehyde carbonyl is rate-determining as suggested by the kinetic data, since a change from sp^2 to sp^3 character occurs in this step.[13] Thus the lack of an inverse isotope effect provides evidence for previous mechanistic suggestions that nucleophilic addition of the enamine to the aldehyde carbonyl may be aided by protonation of the carbonyl oxygen by the carboxyl proton of the amino acid, a process that would exhibit a normal isotope effect. The overall effect of the processes shown in Scheme 2 is thus a balance between normal and inverse isotope effects. This was supported by quantum chemical calculations. Rate coefficients calculated using density functional theory (B3LYP/6-31G(d) in a CPCM solvent of DMSO) for the step in which the enamine **6**-aldehyde complex forms a tetrahedral intermediate as in Scheme 2 gave a k_H/k_D value of 1.97, in good agreement with our experimental value of ca. 2 (1.93–2.26).

The fact that addition of water has an intrinsic inhibitory effect on reaction rate demonstrates conclusively that water does not aid in this step, as has been suggested for nornicotine-catalyzed aldol reactions carried out in water.[14] That catalyst system lacks the carboxyl proton of the proline system. Perhaps the rate of a water-mediated enamine addition to aldehyde in the proline system is not competitive with that mediated by the proximate carboxyl proton acting as an intramolecular Bronsted acid co-catalyst.

Recent experimental and theoretical studies of the intramolecular aldol reaction catalyzed by proline suggested that enamine formation is rate-limiting in that case,[15] in contrast to our results for the intermolecular reaction. Attack of the enamine on the aldehyde may be accelerated by an apparent concentration effect in the intramolecular case.

Experimental and computational studies help to support a proposal for the mechanistic pathway of Scheme 1 for the proline-mediated intermolecular aldol reaction. These results clearly show that neither enamine formation nor product iminium hydrolysis is rate-limiting. Isotope effects support a role for the carboxyl group in the rate-determining step, which is suggested to be aldehyde addition to the enamine. Reaction progress kinetic analysis is demonstrated to play an important role in rapid and comprehensive mechanistic analysis. Further studies are underway to compare these mechanistic findings to those in other proline-mediated reactions.

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