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Clarification of the Role of Water in Proline-Mediated Aldol Reactions

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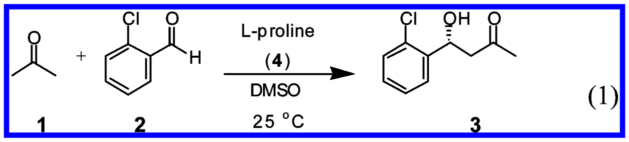
The report by List, Lerner, and Barbas[1] in 2000 of an intermolecular direct aldol reaction catalyzed by proline became an unexpected watershed for the field of organocatalysis.[2−4] Pihko and co-workers[4b,c] were the first to observe significantly higher yields with addition of water to intermolecular aldol reactions, even allowing employment of stoichiometric substrate ratios in some cases. This finding has great potential to widen the scope of proline catalysis, which to date has not achieved practical levels of efficiency. Pihko suggested that in the absence of water the formation of oxazolidinones deactivates proline, concluding that water accelerates the reaction. As pointed out recently,[5] however, rate acceleration by water is counter-intuitive in the generally accepted enamine mechanism. Seebach, Eschenmoser, and co-workers[6] have recently provided an alternative view of the role of oxazolidinones within the aldol reaction network.

In this report, kinetic and spectroscopic studies provide a coherent mechanistic rationalization of the role of water in the aldol reaction shown in eq 1. Our work highlights the importance of deconvoluting the intrinsic kinetic effect of water within the catalytic cycle from its effects off the cycle.



(1)

The methodology of reaction progress kinetic analysis[7] was employed using the "same excess" experimental protocol to establish conditions of steady state in active catalyst concentration *within the cycle* (see Supporting Information). Under these conditions, the observed global rate reflects the intrinsic kinetics of the catalytic cycle deconvoluted from any influence from spectator species. Figure 1 shows that in the case of the reaction in eq 1, the role of water within the catalytic cycle is to *suppress*, rather than to accelerate, reaction rate. In agreement with Pihko, product ee was unaffected by water in this concentration range.[4b,8] We also confirmed Pihko's observation that addition of water allows the reaction to proceed in quantitative yield for both stoichiometric and excess ketone conditions. The trend in Figure 1 is consistent with the generally accepted enamine mechanism shown in Scheme 1 for a case where the rate-determining step succeeds enamine formation but precedes product hydrolysis, as supported by an observed positive dependence on the aldehyde concentration (see Supporting Information).

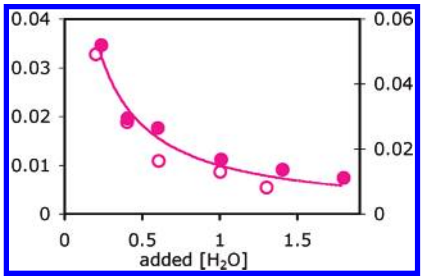


Figure 1. Pseudo-first-order rate constant for the aldol reaction of eq 1 as a function of added water. Open circles, left axis: stoichiometric conditions; filled circles, right axis: 1.75 M excess **1**. Final conversion is 88−99% and product ee is 64−69% ee.

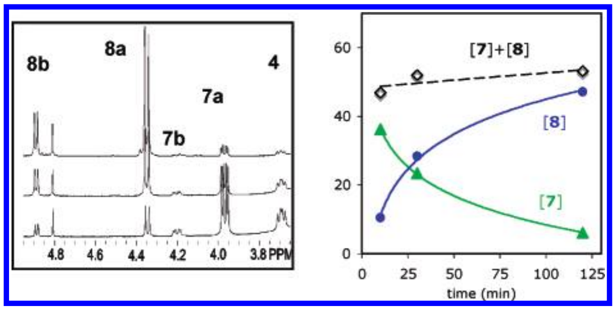
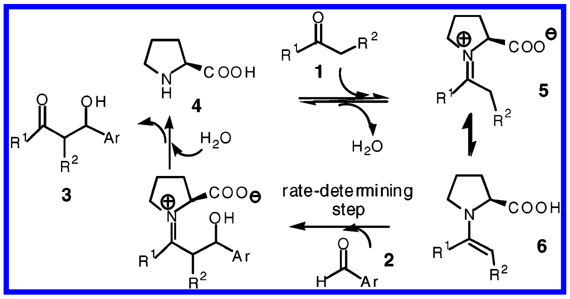


Figure 2. Temporal change in species **7** and **8** in the interaction between **2** and **4** at 25 °C in DMSO-d_6. Left: ^{1}H NMR spectra, bottom to top: 10, 30, 120 min. Right: [**7**], green triangles; [**8**], blue circles; [**7**] + [**8**], open black diamonds.

Scheme 1. Proposed Catalytic Cycle for Aldol Reaction of Eq 1



^{1}H NMR spectroscopic monitoring of the reaction of eq 1 in the absence of water showed a species **7** forming within the first few minutes of the reaction, which then decreased over time while a second species **8** increased. Further experiments revealed that **7** and **8** may be attributed to species formed between aldehyde **2** and proline **4.** The concentration of **7** was roughly equal to that of solution proline after 10 min. The concentration of **7** decreased to one-third of this value concomitant with increasing [**8**] that ultimately equaled that of the initial solution proline concentration (Figure 2).

The ^{1}H NMR shifts for species **7**, representing a doublet of doublets, are in good agreement with Seebach's characterization of the oxazolidinone derived from proline and pivaldehyde.[9] Species **7** is therefore tentatively assigned as the two diastereomers of the proline oxazolidinone of **2** (**7a**/**7b** = 6:1). Although we were unable to isolate species **7**, we were able to obtain **8**, identified by spectroscopic analysis (^{1}H, COSY, NOESY, ^{13}C NMR, HMQC, and HMBC; see Supporting Information) as the two diastereomers present in a 2.5:1 ratio of **8a**/**8b** from our data and in analogy with

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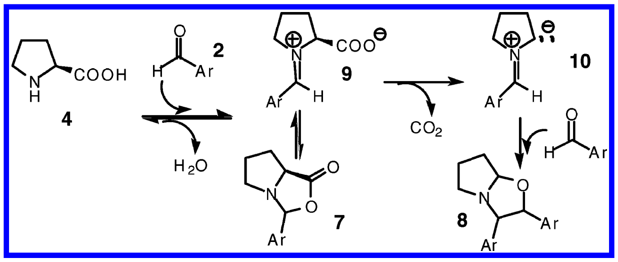
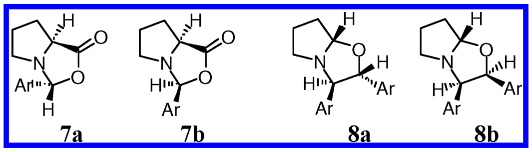
Scheme 2. Reactions of Aromatic Aldehydes with Proline



Orsini.[10] When the mixing of **2** and **4** was carried out in the presence of 0.6 M water in DMSO, the solution concentration of proline remained fairly constant over time while formation of both **7** and **8** was suppressed by more than 75%.



These results agree with previous studies suggesting that irreversible deactivation of proline in the presence of aromatic aldehydes and in the absence of added water occurs as shown in Scheme 2. Oxazolidinones are reversibly formed as has previously been shown for electron-rich aldehydes. In the case of electron-deficient aromatic aldehydes such as **2** or *p*-nitrobenzaldehyde, the iminium species **9** may undergo decarboxylation to form the azomethine ylide **10** which may then react with a further aldehyde molecule to form the stable 1-oxapyrrolizidine **8**.[10−12] The first report of intermolecular aldol reactions mediated by proline alluded to such deactivation, although experimental observations were not reported in that work.[1]

Oxazolidinone formation serves as a parasitic off-cycle equilibrium for nonaromatic aldehydes that do not undergo the further reactions shown in Scheme 2.[4b,c] Addition of water has implications for the catalytic cycle shown in Scheme 1 for both irreversible and reversible off-cycle reactions. Addition of water suppresses formation of both on- and off-cycle iminium ions **5** and **9** by Le Chatelier's principle, concomitantly suppressing on-cycle species **6** and off-cycle species **7**, **8**, and **10**.

Thus two conflicting roles are delineated for water: increasing water *increases* the total catalyst concentration within the cycle due to suppression of spectator species, and water *decreases* the relative concentration of key intermediates in the cycle by shifting the equilibrium from **5** back toward proline **4**. The net effect of added water on the globally observed rate will depend on the relative concentrations of iminium ions **5** and **9**, which may be different for different aldehydes and can be a complicated function of substrate concentrations and the various rate and equilibrium constants for the steps shown in Schemes 1 and 2. The mechanistic point revealed by our kinetic studies is that for substrate combinations of acetone and aromatic aldehydes, the intrinsic rate *per active catalyst species within the cycle* is suppressed, not accelerated, by added water.

In the absence of water, irreversible deactivation due to formation of **8** from one molecule of **4** and two molecules of **2** causes the reaction rate and maximum achieveable yield to be lower than that expected for the given initial concentrations of **2** and **4**. By contrast, reversibly formed oxazolidinones such as those formed from aliphatic aldehydes may be converted back through aldehyde to product at late stages in the reaction.[4b] Such a case may ultimately provide high yields but will still exhibit less than optimal efficiency by siphoning off proline **4** as a spectator oxazolidinone for a significant part of the reaction.

Oxazolidinone formation from proline **4** and acetone **1**, which is less favored for the ketone than for the aldehyde, is also observed under reaction conditions in the absence of water (see Supporting Information). We have been unable to observe enamine formation from acetone, although a recent ESI-MS study claims evidence for this species.[13] Our studies cannot directly address the question[6] of the role of oxazolidinones as active intermediates in the aldol catalytic reaction network, but the proposed rate acceleration by H_2O via activation of the electrophile does not appear to operate in our case.[6,14]

Addition of water to the proline-mediated aldol reaction is shown to suppress the intrinsic kinetic rate for the reaction of aromatic aldehydes, where the rate-limiting step succeeds enamine formation but precedes product hydrolysis. This work clarifies and highlights the complex and often opposing roles that water may play both on and off the catalytic cycle. Deconvoluting these effects will allow observations of the role of additives such as water to serve as mechanistic probes and will aid in obtaining true mechanistic understanding in these reactions. A full kinetic and mechanistic study of the proline-mediated aldol reaction will be reported separately.

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Note added After ASAP Publication. Reference numbering was corrected in paragraphs 6 and 10 on November 26, 2007.

Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
(2) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.
(3) (a) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. (b) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16. (c) Clemente, F. R.; Houk, K. N. *Angew. Chem., Int. Ed.* **2004**, *116*, 5890.
(4) (a) Hartikka, A.; Arvidsson, P. M. *Tetrahedron: Asymmetry* **2004**, *15*, 1831. (b) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, *11*, 1891. (c) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg A.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317. (d) Mathew, S. P.; Klussmann, M.; Iwamura, H.; Wells, D. H., Jr.; Armstrong, A.; Blackmond, D. G. *Chem. Commun.* **2006**, *41*, 4291.
(5) (a) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798. (b) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100.
(6) Seebach, D.; Beck, A. K.; Badine, D. M.; Limbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R.; Prikoszovich, W.; Linder, B. *Helv. Chim. Acta* **2007**, *90*, 425.
(7) (a) Mathew, J. S.; Klussmann, M.; Iwamura, H.; Valera, F.; Futran, A.; Emanuelsson, E. A. C.; Blackmond, D. G. *J. Org. Chem.* **2006**, *71*, 4711. (b) Blackmond, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302.
(8) Two out of 30 reactions reported in ref 4b showed an increase in ee with addition of water at <500 mol%, in both cases the non-H_2O cases exhibited ≤10 % conversion in ≥6 days. A significant influence of water on ee or de in less sluggish, clean reactions has not been clearly shown.
(9) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.
(10) Orsini, F.; Pelizzoni, F.; Forte, M.; Destro, R.; Gariboldi, P. *Tetrahedron* **1988**, *44*, 519.
(11) (a) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055. (b) Dambruoso, P.; Massi, A.; Dondoni, A. *Org. Lett.* **2005**, *9*, 4657.
(12) Grigg, R. E.; Sarker, M. A. B. *Tetrahedron* **2006**, 10332.
(13) Marquez, C.; Metzger, J. O. *Chem. Commun.* **2006**, 1539.
(14) As suggested in ref 6, a mechanism may be envisioned where the rate of electrophile addition to enamine could be assisted by H_2O even when this step is rate-limiting. Scheme 1 does not account for this possibility, and it is not consistent with our results for aromatic aldehydes.

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