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Probing the Active Catalyst in Product-Accelerated Proline-Mediated Reactions

Hiroshi Iwamura, David H. Wells, Jr., Suju P. Mathew, Martin Klussmann, Alan Armstrong, and Donna G. Blackmond*

Department of Chemistry, Imperial College, London SW7 2AZ, United Kingdom

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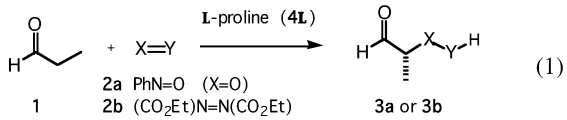
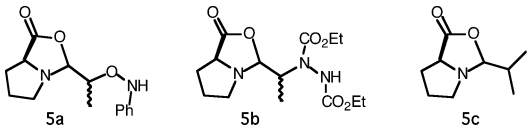
The α-amination[1] and the α-aminoxylation[2] of aldehydes are two recent additions to the rapidly expanding list of proline-based reactions introduced with the discovery of the Hajos−Parrish−Eder−Wiechert−Sauer reaction[3] and elegantly revived by List et al.[4] with the intermolecular aldol reaction. We recently showed that both of the reactions in eq 1 exhibit the unusual characteristics of a rising reaction rate and a positive nonlinear effect, distinguishing them mechanistically from proline-mediated reactions that do not exhibit these features.[5] As a mechanistic model, we invoked an autoinductive reaction resulting in selective formation of a proline−product species within the catalytic cycle.



(1)

For the α-aminoxylation reaction, we initially suggested that a species such as the enamine isomer of **5a** acts as an improved catalyst via enhanced nucleophilicity of the product N−H group.[5a] Although the oxazolidinone **5b** was isolated and shown to be significantly more active when employed instead of proline in the reactions of eq 1, an analogous explanation seemed to be less likely in this case.[5b] Therefore, the nature of the active species in the autoinductive reactions of eq 1 remains an important question.



We report here results suggesting that these reactions proceed via product displacement by aldehyde from a hydrogen-bonded product−proline adduct, affording a catalytic cycle that circumvents free proline but retains other features central to the generally accepted enamine mechanism for proline catalysis.[6]

A key question is whether the low solubility of proline in organic solvents complicates kinetic analyses by including a solid−liquid transport step in the overall observed rate process. Figure 1 compares reaction progress profiles in CH_2Cl_2 for the largely insoluble L-proline (**4L**) with soluble oxazolidinones **5b** and **5c** as catalysts in the α-amination of eq 1 (X = Y as **2b**), obtained from reaction calorimetry (Omnical SuperCRC and Omnical Insight) as previously described.[5] The reaction is significantly faster with the soluble catalysts than with **4L**; remarkably however, oxazolidinone **5c**, derived from isobutyraldehyde, is equally efficient as **5b**, which is derived from the reaction product. It is also important to note that an accelerating rate is observed in reactions employing the soluble oxazolidinones as well as in that using **4L**, indicating that this feature cannot be attributed simply to the dissolution of solid proline. This point is highlighted in the inset of Figure 1, which

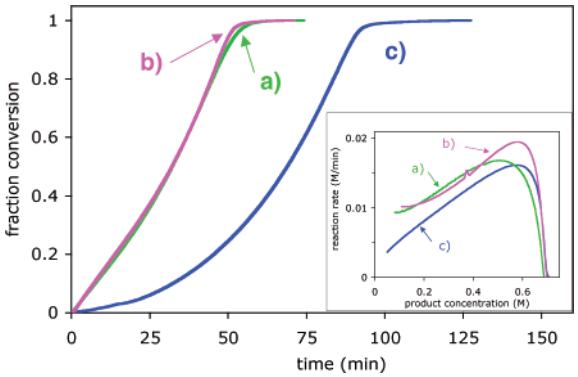


Figure 1. Fraction conversion versus time for the reaction of eq 1 with 2 M propionaldehyde and 0.7 M **2b** in CH_2Cl_2 at 278 K with catalyst (a) 10 mol % **5b**, (b) 10 mol % **5c**, and (c) 20 mol % **4L**. Inset: reaction rate versus product concentration for the reactions shown in the main figure.

replots these data as reaction rate versus product concentration. Strikingly, the curves for the three reactions exhibit similar slopes (slope = Δrate/Δ[product]). In an autoinductive reaction where catalyst concentration increases as the reaction proceeds, reaction rate at any point is proportional to instantaneous catalyst concentration. This demonstrates that the increasing catalyst concentration within the catalytic cycle is not simply a temporal phenomenon (the reaction in Figure 1c required twice as long as those of Figures 1a and 1b) but instead is directly linked to the instantaneous *product concentration* for both the soluble oxazolidinones **5b** and **5c** as well as the insoluble **4L**.

Given that an initially saturated reaction mixture has a solution proline concentration of less than ca. 0.005 M in nonpolar, aprotic solvents (see Supporting Information), this autoinductive phenomenon cannot be rationalized simply by an increase in the level of free proline in solution but instead implicates a cycle that precludes the presence of free proline.

NMR studies of the interaction of the oxazolidinone **5b** or **5c** with propionaldehyde reveal facile exchange giving a mixture of the original oxazolidinone and its aldehyde as well as propionaldehyde and its oxazolidinone (see Supporting Information). Direct exchange could suggest a reaction pathway circumventing free proline but fails to explain why aldol reactions do not exhibit rising rates.

DFT calculations using B3LYP/6-31G(d) (see Supporting Information)[7] lend clues to the possible nature of species within the catalytic cycle and highlight features that distinguish the reactions of eq 1 from other proline-mediated transformations. As product **3a** or **3b** begins to separate from proline at the end of the reaction, a series of hydrogen-bonding interactions can take place.[8] For the reactions of eq 1, we found that the initial energy minimum[9] involves three-point hydrogen bonding between product and proline to form species **4L**·**3a** or **4L**·**3b** (the former is shown in Figure 2a

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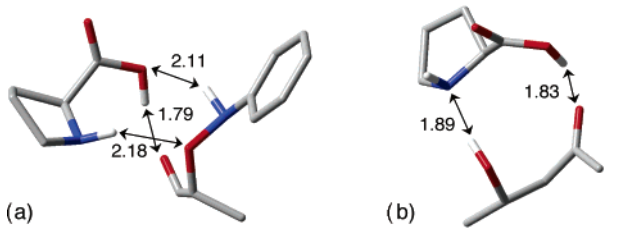
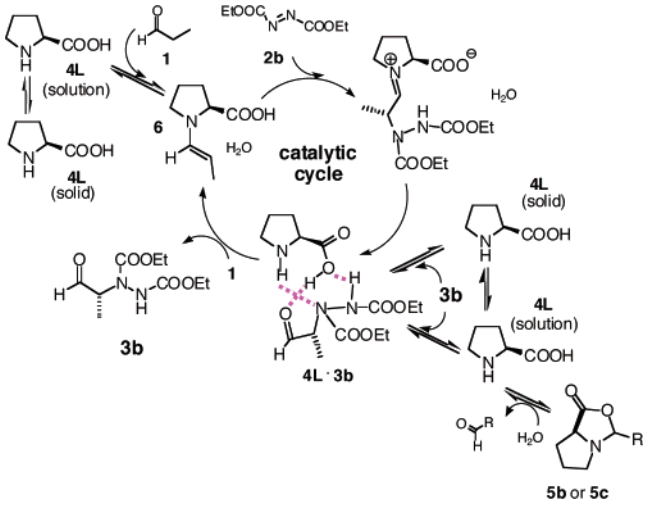


Figure 2. Calculated structures for hydrogen-bonded product−proline adducts (a) **4L·3a** in the aminoxylation reaction of eq 1 with X = Y as **2a**, and (b) **4L** hydrogen bonded to the product of the aldol reaction between acetone and acetaldehyde. Distances are given in angstroms.

Scheme 1. Proposed Autoinductive Reaction Mechanism for the Reaction in eq 1 with X = Y as **2b**[a]



[a] Hydrogen-bonding interactions in species **4L·3b** shown in dotted magenta lines.

and the latter in Scheme 1). Hydrogen bonding between the product N−H and the carboxylic O tethers the carboxylic group; this positions the proline N such that its lone pair is accessible for attack on an incoming aldehyde substrate, which in turn can be activated by a developing interaction with the carboxylic proton. By contrast, hydrogen bonding between aldol products and proline forms two-point adducts, such as that shown in Figure 2b, effectively shielding the proline nitrogen and necessitating product dissociation prior to association with incoming aldehyde. That proline can be solvated by aldol reaction products as well as by the products of the reactions in eq 1 is borne out by the fact that reaction solutions become clear as aldol product is formed. However, such aldol reactions exhibit positive-order kinetics and no product acceleration.[10] The structures in Figure 2 help to suggest why a product-assisted catalytic cycle is more likely in the α-aminoxylation and α-amination reactions than in aldol reactions, in accordance with our kinetic observations.

Scheme 1 outlines a proposed new catalytic cycle that rationalizes the role of the reaction product in increasing the concentration of active catalyst species (and therefore rate) in the reactions of eq 1, employing either proline or oxazolidinone **5b** or **5c** as precatalysts. Initial reaction between solution proline and substrates **1** and **2a** or **2b** forms the hydrogen-bonded product **4L·3a** or **4L·3b**. Proline species, whether initially present as solid proline, solution proline, or in the form of oxazolidinone **5b** or **5c**, are channeled into a catalytic cycle where all active species are highly soluble. Product concentration acts as a driving force to increase the concentration of active proline adducts or complexes within this cycle. Aldehyde displacement of the hydrogen-bonded reaction product from **4L·3a** or **4L·3b** affords enamine **6**, suggesting a transition state similar to that previously proposed via experimental work by List et al.[4,6] and in theoretical studies by Houk[11] for aldol and related reactions.

The importance of hydrogen bonding in organocatalytic reactions has recently been highlighted.[12] Significant distinctions in the reactions of eq 1 include our observations that product, rather than substrate, is involved in a three-point, rather than double, hydrogen-bonding interaction, and that this interaction results in product acceleration rather than inhibition.

A catalytic cycle involving only soluble proline complexes or adducts is proposed for the reactions in eq 1 based on kinetic observations and molecular modeling studies. This reaction pathway circumventing free proline and incorporating hydrogen-bonded reaction product helps to rationalize the observations of accelerating reaction rate in both the α-aminoxylation and α-amination reactions. Detailed kinetic and molecular modeling studies will be reported in due course.

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Supporting Information Available: Details of kinetic data manipulations, NMR experiments, DFT calculations, and solubility measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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