A Coherent Mechanistic Rationale for Additive Effects and Autoinductive Behaviour in Proline-Mediated Reactions

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Abstract: Differences in the kinetic behaviour of aldol reactions compared to aminoxylation and amination reactions are rationalized by consideration of the rate-determining step in each case. Both autoinductive behaviour and the rate-enhancing effect of additives are attributed to an effect on the enamine formation step.

Keywords: amino acid catalysis; autoinduction; kinetics; organocatalysis; reaction mechanisms

Proline catalysis, elegantly revived by List, Lerner and Barbas in 2000,[1] has demonstrated efficient and enantioselective carbon-carbon and carbon-heteroatom bond-forming reactions, including those shown in [Eq. (1)], and has inspired the development of many other catalysts for a myriad of selective transformations.[2] Computational studies[3] have suggested a mechanistic analogy to reactions of aldolase enzymes.[4] Our recent work provided the first kinetic support for the enamine mechanism in aldol reactions and clarified the role of water on and off the catalytic cycle.[5,6]

A number of intriguing experimental observations have yet to be rationalized for these reactions. One unusual feature is a striking temporal increase in reaction rate that is observed in the α-aminoxylation[7,8] [Eq. (1a)] and α-amination of aldehydes[9,10] [Eq. (1b)], but is not observed in aldol reactions [Eq. (1c)]. In addition, additives including acids and bases have been observed to influence reactions employing proline as well as other pyrrolidine-based catalysts.[11,12] Here we present kinetic results that offer a coherent mechanistic rationalization for both the role of additives and the autoinductive behaviour in pro-line-mediated reactions. These findings suggest an important role for detailed kinetic analysis in understanding and improving catalyst efficiency.
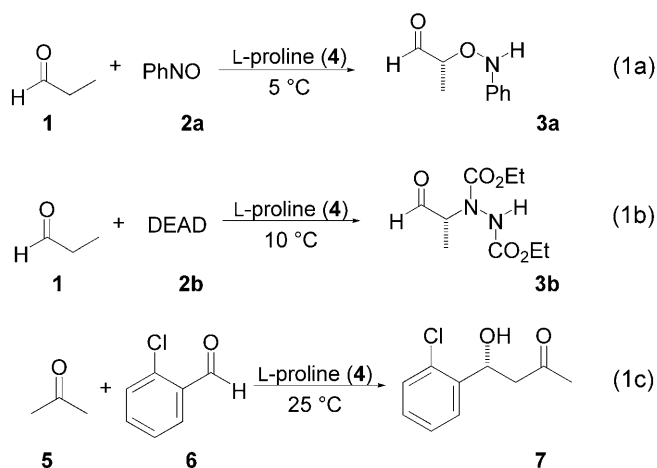
The autoinductive behaviour observed in the reactions of Eqs. (1a) and (1b) suggests that the product plays a role in accelerating rate, as is confirmed in Figure 1 for addition of product **3b** to the α-amination reaction of Eq. (1b). The figure also shows that addition of aldol product **7** to the aldol reaction of Eq. (1c) has no influence on the rate of this reaction.

The two reactions exhibit distinctly different kinetic profiles, with the aldol reaction characterized by well-behaved positive order kinetics while the reactions of Eqs. (1) and (1b) show the sigmoidal conversion profile characteristic of an autoinductive process. Product *ee* is unaffected by added product in either reaction. The reactions of Eqs. (1a) and (1b) do not proceed in the presence of product and absence of proline, confirming that the reactions are product-accelerated, or autoinductive, but not truly autocatalytic.[14] Careful studies, including those using fully soluble proline de-
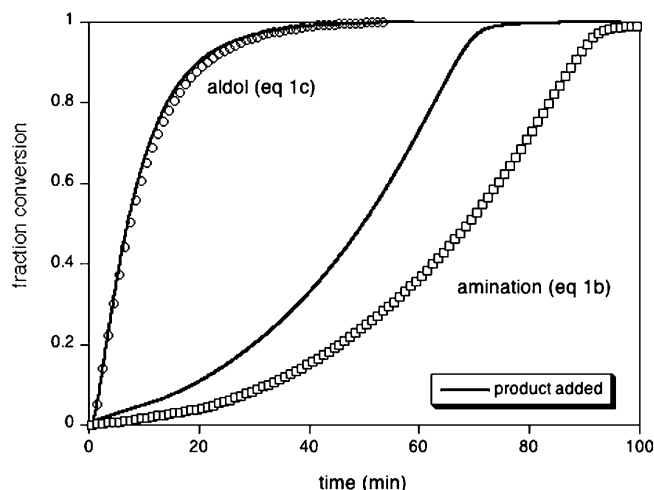
Figure 1. Effect of the addition of amination reaction product **3b** (0.2 equiv.) or aldol product **7** (1.1 equiv.) to the reactions of Eq. (1b) or (1c), respectively. Open symbols: reaction without added product; solid lines: reaction with added product.

rivatives, showed that the effect could not be attributed to increasing solubilization of proline as the reaction proceeds.[13]

Interestingly, however, our further studies show that the source of the rate enhancement in the reactions of Eqs. (1a) and (1b) is not limited to the product specific to that reaction: Figure 2 shows that reaction rate in the fully homogeneous[15] α-aminoxylation reaction of Eq. (1a) is also strongly enhanced by addition of *aldol product* **7**. A gradual shift away from the autoinductive kinetic profile was observed as the concentration of added **7** was increased (Figure 2a).

A similar influence on rate and rate profile was observed with additives ([**add**]) such as CH_3OH and CH_3COOH, where rate appears to saturate as [**add**] reaches higher concentrations (Figure 3).[16,17] By contrast, the aldol reaction of Eq. (1c) showed neither rate enhancement nor a change in the kinetic profile for reactions with any of these additives (see Supporting Information).

These results show that rate in reactions of Eqs. (1a) and (1b) is proportional to the concentration of the rate-enhancing species, be it the reaction's own product or an additive. In the case of the reaction product, the autoinductive profile observed may thus be attributed to the reaction progress: the temporal enhancement in rate results from the increasing reaction product concentration over time. In the case where a species such as CH_3OH or CH_3COOH is added at a fixed concentration, this rate-enhancing effect of the reaction's own product competes with a similar effect of the additive. At higher additive concentrations, the influence of the additive begins to dominate, resulting in a shift away from the autoin-
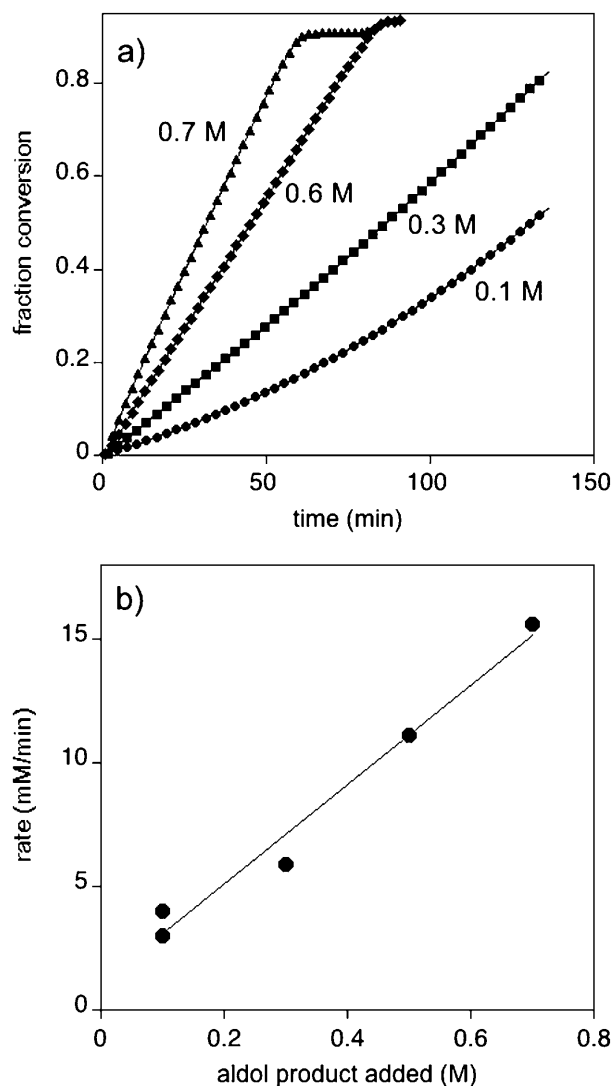

Figure 2. Fraction conversion *vs.* time for the aminoxylation reaction of Eq. (1a) with 2 M **1**, 0.5 M **2**, 0.04 M **4** and added aldol product **7** in $CHCl_3$ under homogeneous conditions.[15] **a)** Conversion *vs.* time for added [**7**] as noted. **b)** Initial rate constant *vs.* added [**7**]. Product *ee* 97–98%.

ductive kinetic profile. This suggests that a single mechanistic rationalization may explain both the autoinductive profile and the rate-enhancing effect of additives for the reactions of Eqs. (1a) and (1b). Since these reactions are thought to proceed by a pathway similar to that of the aldol reaction of Eq. (1c), such a rationale should also be able to account for the lack of effect of additives on rate in the aldol reaction.

The generally accepted mechanism for the reactions of Eq. (1) involves nucleophilic attack of proline on the carbonyl compound to form an enamine, followed by its attack on an electrophile **E**, and finally hydrolysis to form the product. The intrinsic kinetic dependences of substrate concentrations for the reactions of Eq. (1) may be compared in the context of this mech-
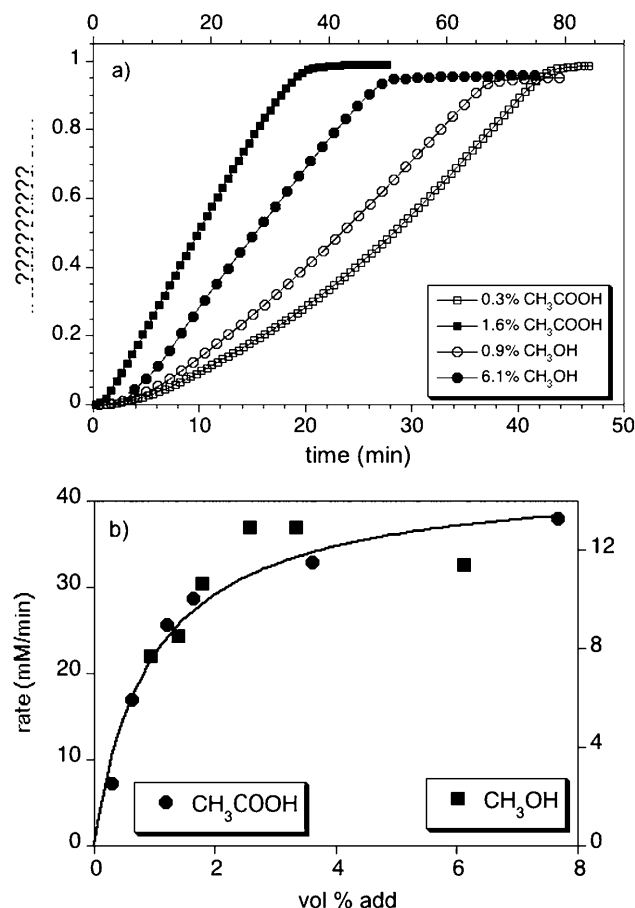
Figure 3. CH_3OH or CH_3COOH added to the aminoxylation reaction of Eq. (1a); 2 M **1**, 0.5 M **2a**, 0.04 M **4** and CH_3OH or CH_3COOH as [**add**] in $CHCl_3$ under homogeneous conditions.[15] **a)** Conversion *vs.* time (upper time axis for CH_3OH). **b)** Rate *vs.* [**add**]; *left axis:* CH_3COOH; *right axis:* CH_3OH. Product *ee* 96–98% in all cases; conversion is quantitative in all cases.

anism. We have shown that the aldol reaction of Eq. (1c) exhibits a positive rate dependence on the concentrations of both substrates acetone **5** and aldehyde **6** and a negative order in [H_2O], implicating rate-determining attack of enamine **9** on electrophile **6** for the intermolecular aldol reaction, with the further suggestion that the enamine formation steps are in pre-equilibrium (saturation kinetics in [**9**]).[5,6] The reactions of Eqs. (1a) and (1b), by contrast, exhibit zero order kinetics in concentration of the highly active electrophiles **2a** and **2b** and first order dependence on the concentration of the carbonyl substrate **1**,[13] dependences that hold in the presence of additives such as CH_3OH and CH_3COOH. Thus for reactions of Eqs. (1a) and (1b), enamine formation between aldehyde **1** and proline **4** is proposed as rate-determining. This is further supported in our current work by observation of a large primary isotope effect in reactions employing deuterium labelled propionaldehyde

1, where k_H/k_D is found to be *ca.* 6.0 (see Supporting Information).

These combined observations allow a comprehensive explanation of the role of reaction products and additives in all of the proline-mediated reactions of Eqs. (1a)–(1c) based on simple considerations of the rate-determining step in relation to the step affected by additives, as summarized in Scheme 1. If the role
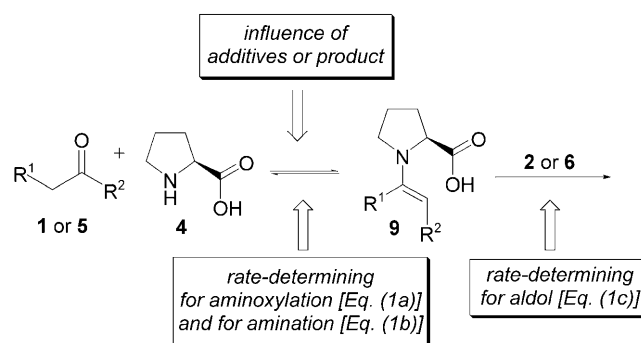
Scheme 1. Influence of additives and rate-determining steps for reactions of Eqs. (1a) and (1b) compared to (1c).

of the additive (or product) is to enhance the rate of enamine formation, then this will be manifested as a rate increase in reactions where this step is rate-determining [reactions of Eqs. (1a) and (1b)] but will not affect rate in a case where this step is in pre-equilibrium [reaction of Eq. (1c)]. This conclusion is general regardless of the identity of the rate-enhancing species or the specific nature of the rate-enhancing interaction.

The concept shown in Scheme 1 is supported by a recent computational study revealing that enamine formation between dimethylamine and acetone is accelerated by methanol as a cocatalyst.[18] Scheme 1 is also in accordance with Seebach and Eschenmoser's[19] interpretation of the rate enhancement we reported in the reactions of Eqs. (1a) and (1b), which they suggest may be attributed to acceleration of the transformation of an oxazolidinone to an enamine as the rate-determining step. In the proposal of Scheme 1, identical kinetic consequences result from the accelerated formation of the enamine regardless of the pathway this process takes.

Seebach and Eschenmoser have also argued for a prominent role for base catalysis in these proline-mediated transformations. Based on our earlier studies[9] implicating both substrate and product oxazolidinones as competent species in stoichiometric transformations of Eq. (1b), they suggest that the basic functionality of the reaction products formed during the catalytic cycle of reactions of Eqs. (1a) and (1b) could serve as the rate-enhancing species. They propose a cycle in which the enamine exists as a deprotonated

species and suggest that the proposed role of the carboxyl proton in an intramolecular Brønsted acid activation of the electrophile might instead be fulfilled by other species in the system, citing the promoting role of H_2O that has been suggested in other work.[11] However, our previous studies of the aldol reaction argue against this proposal. First, we showed clearly that the intrinsic kinetic effect of water is in fact to suppress, not to promote, the rate of the catalytic reaction;[6] second, our reported deuterium isotope effect of $k_H/k_D \approx 2$ in the aldol reaction of Eq. (1c) supports a role for the carboxyl proton in the rate-determining enamine attack on the aldehyde **6**. Further experimental studies to investigate the role of added base in the reactions of Eq. (1) are underway.

McQuade has studied the behaviour of amine-thiourea additives in the reaction of Eq. (1a), attributing an observed rate enhancement to specific bifunctional interactions with oxazolidinone intermediates that promote their transformation to enamines, while proposing a separate rationale for product-enhanced rate.[12] These authors cited the lack of observed rate enhancement due to the additive in the same reaction using a proline-tetrazole catalyst that cannot form oxazolidinones as support for a key role of these species. Direct observation of species within an operating catalytic cycle has not been reported for these reactions[20] and kinetic analysis alone cannot reveal the structure of the species involved or specific features of the interaction. However, our results indicate that rate enhancement due to additives is a more general phenomenon; it may occur in cases where such bifunctional interaction is not possible (CH_3OH and CH_3COOH, Figure 2 and Figure 3) and is lacking in some cases where oxazolidinone formation is possible [aldol reaction, Eq. (1c)]. Furthermore, the kinetic profiles reported in Ref.[12] for the reaction of Eq. (1a) with proline-tetrazole resemble those where the rate-determining step is enamine attack on electrophile **2a** rather than formation of the enamine. The proposal of Scheme 1 simplifies the mechanistic picture and, in addition, obviates the need to develop separate explanations for autoinductive and additive behaviour, such as the "inner" and "outer" cycles proposed by McQuade.[12]

In summary, a difference in the rate-determining step for proline-mediated aldol and aminoxylation reactions rationalizes why autoinductive behaviour is observed in the latter but not the former, and also explains the rate-enhancing effect of additives including alcohols and acids.[21] Interactions between catalytic and additive or product species may result in rate enhancement, but only when such interactions influence steps of kinetic consequence in the catalytic cycle. The differences observed between the reactions of Eqs. (1a)–(1c), even while they follow the same basic mechanistic framework, suggest that an understanding of the specific mechanistic constraints of each transformation will help in designing productivity-enhancing improvements. Detailed kinetic analysis of the catalytic cycle under operating conditions has been shown to be a useful tool for providing mechanistic information in these reactions. Further studies aimed at understanding the nature of the interactions between components in the catalytic cycle are underway.

Experimental Section

Reactions were carried out in an Omnical Insight reaction calorimeter, which allows continuous monitoring of the instantaneous enthalpy balance around the vessel. Further details are available in the Supporting Information.

Acknowledgements

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[15] We confirmed again that the observed rate enhancement cannot be attributed to increased proline solubilization over the course of the reaction by employing the following experimental protocol in all reactions reported here. A mixture of proline **4** and the additive **add** (either aldol product **7**, CH$_3$OH, or CH$_3$COOH), was stirred in CHCl$_3$ and the solution filtered at reaction temperature to remove any remaining solid proline. The filtrate containing only solution phase **4** and **add** was used as the base reaction in the series of aminoxylation reactions shown in Figure 2 and Figure 3 in which increasing amounts of **add** were included. This excludes the possibility of that proline solution concentration could increase over time due to dissolution of the solid.

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