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Kinetic Rationalization of Nonlinear Effects in Asymmetric Catalysis Based on Phase Behavior**

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The rapidly expanding field of organocatalysis has received considerable attention[1–4] since the earliest reports of the proline-mediated intramolecular aldol reaction.[5,6] Observation of a weak negative nonlinear effect in this reaction led Kagan and co-workers to include this example in their earliest reports on developing mathematical models for nonlinear effects of catalyst enantiomeric excess (*ee*) on product enantioselectivity in asymmetric catalysis.[7] The two-proline mechanism that was offered to explain the nonlinear effect has since been discounted, however, by experimental studies[8–10] that revealed linearity between proline and product enantiomeric excess values in both inter- and intramolecular aldol reactions, supported by theoretical studies.[10] The prevailing model for proline-catalyzed aldol and related reactions involves the reaction of one proline molecule with a donor molecule to form an enamine, followed by attack on an electrophile;[11,12] nonlinear effects would appear to be incompatible with this model. Nevertheless, the original observation of a nonlinear effect remains unreconciled, and instances of nonlinear behavior in proline-mediated reactions have persisted.[13–16]

Our reports in 2004 of nonlinear effects in proline-mediated α-aminoxylation[14] and α-amination[15] reactions rekindled interest in exploring such behavior in amino acid catalysis. We recently showed that these effects are not related to the catalytic reaction mechanism, as we had previously suggested, but instead to the ternary phase behavior of proline in solvent.[17] This finding was extended to include other amino acids and has implications for the evolution of biological homochirality. However, the nonlinear

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trends originally reported by Kagan and co-workers[7] remain unexplainable by the equilibrium model developed in that work.

We report here how the concept of a "kinetic conglomerate" phase can rationalize the findings of Kagan and co-workers[7] in a manner that remains compatible with the currently accepted one-proline reaction mechanism and reconciles reports of both linearity and nonlinearity in this system. Implications of this behavior for the interpretation of nonlinear effects in general are shown to extend beyond amino acid catalysis and are demonstrated for the particular case of a tetraaryl-1,3-dioxolane-4,5-dimethanol (taddol) ligand system.

Although the solid–solution phase behavior of racemic and enantiopure compounds was studied more than a century ago[18] and is well understood,[19] scalemic mixtures of amino acids have received less attention. Of the twenty proteinogenic amino acids, only threonine and asparagine crystallize as "conglomerates" or separate enantiomeric solid phases. All of the others, including proline, cocrystallize in a 1:1 ratio of the enantiomers, known as a "racemic compound".[19] For a scalemic system at equilibrium, the solution composition at the eutectic point is fixed and is necessarily 0 % *ee* for amino acids that form conglomerates; for racemic compounds, however, the eutectic *ee* can have a value anywhere between 0–100 % *ee* and is not known a priori. We reported the first measurements of eutectic *ee* values for proteinogenic amino acids that form racemic compounds.[17] Most recently, we have developed a model to predict the eutectic *ee* of a chiral substance based on simple solubility concepts.[20]

In these earlier studies, we reported that the eutectic for proline in dimethyl sulfoxide (DMSO) at 25 °C is approximately 50 % *ee*. Under solid–solution equilibrium, this eutectic value dictates the enantiomeric excess of the solution for all values of scalemic proline *ee* employed, which in turn dictates the product *ee* that may be achieved in solution-phase reactions catalyzed by scalemic proline. This fact rationalized our unusual observation of a constant product *ee* value in aldol reactions over a wide range of total proline *ee* values, manifested as a positive nonlinear effect at overall proline *ee* values below the eutectic *ee*, and as a negative nonlinear effect at proline *ee* values above the eutectic *ee*. However, it is clear that such an equilibrium model cannot explain the fact that negative nonlinear effects were reported by Kagan and co-workers at *all* proline *ee* values.[7]

We turned instead to consideration of the phase behavior of proline under the non-equilibrium conditions that ensue during catalyst dissolution. In studies of nonlinear behavior where, typically, the desired proportions of the two pure enantiomers are physically mixed with the other components of the reaction mixture, it might be expected that the enatiomeric excess of the solution would initially represent a linear combination of the two separate enantiomers as the catalyst begins to dissolve, ultimately to establish either equilibrium solid–solution phase behavior or a homogeneous system. Figure 1 shows that in fact the solution *ee* value for scalemic proline is close to zero immediately following addition of the enantiomers in any proportion. The solution *ee* value rises from near zero over time to stabilize at the value of its eutectic composition under solid–solution equilibrium, regardless of whether the initial proportions of the enantiomers is lower or higher than the eutectic value. We also found that the addition of water results in a faster equilibration. Interestingly, the solution concentration of proline for the cases shown in Figure 1 is *higher* during this transient initial period—in fact, exceeding its equilibrium concentration by as much as 40 %—and decreases over time concomitant with the rise in solution *ee* (see Supporting Information).

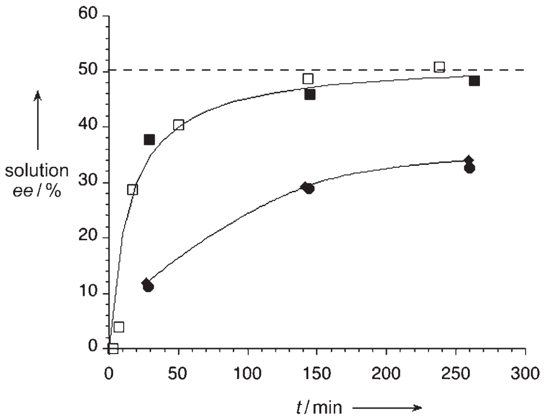


Figure 1. Solution *ee* values as a function of time for physical mixtures of pure D- and pure L-proline in DMSO at 25 °C at different overall proline *ee* values. Total proline concentration: 12 mg mL^{-1}, unless noted otherwise. Filled squares (■): 20 % *ee*; open squares (□): 19 % *ee*, 40 mg mL^{-1}; filled circles (●): 40 % *ee*; filled diamonds (◆): 60 % *ee*. The dashed line represents the eutectic *ee* value for proline in DMSO.

These unexpected observations may be rationalized by considering that the solid L- and solid D-proline mixture is more similar to a conglomerate than to a racemic compound when first mixed in solvent at the outset of the experiment; thus it exhibits the phase behavior known for this type of solid before equilibrating to the true racemic compound that proline forms at equilibrium.[21] The low solution *ee* value at the outset is observed because the D and L crystals are separately in equilibrium with the solution phase as in a conglomerate, which exhibits 0 % *ee* at the eutectic. The anomalously high proline solution concentration observed during the transient period occurs because conglomerates exhibit a higher solubility at the eutectic relative to the enantiopure phase than do racemic compounds.[19,20] These considerations indicate that solid–solution equilibration of the pure enantiomers as shown in Equations (1) and (2) is rapid and occurs before a significant fraction of the solid DL racemate has formed [Eq. (3)].[22]

$$\text{L(solid)} \rightleftharpoons \text{L(liquid)} \tag{1}$$

$$\text{D(solid)} \rightleftharpoons \text{D(liquid)} \tag{2}$$

$$\text{L(liquid)} + \text{D(liquid)} \rightleftharpoons \text{DL(solid)} \tag{3}$$

Ultimately, at equilibrium, the scalemic system will consist of a solution phase at its eutectic composition and two separate solid phases, the racemic DL(solid) and the enantiopure solid of the enantiomer in excess (L in this case). The minor enantiomer (D in this case) will no longer retain its own enantiopure solid phase—and the process in Equation (2) will no longer occur—at equilibrium. Thus, we propose that our observations may be attributed to the transition between a transient "kinetic conglomerate" phase and the true racemic compound that proline forms at equilibrium.

The concept of a kinetic conglomerate phase may have a significant impact in studies of nonlinear effects in asymmetric catalysis. The data in Figure 1 suggest that if proline dissolution occurs simultaneously with turnover in an asymmetric reaction, the product *ee* may be lower than expected based on total proline *ee*. This suggestion is confirmed in Figure 2, which shows product *ee* versus proline *ee* for the aldol reaction shown in Scheme 1 initiated by adding a mixture of separate solid D- and L-proline to a solution containing solvent and reactants, instead of premixing the proline in solvent prior to addition of the substrate.[23] These results provide the first explanation of the origin of the negative nonlinear effect observed by Kagan and co-workers[7] in intramolecular aldol reactions.[24] The sensitivity of the solution *ee* to factors such as mixing times and water content help to rationalize observed differences in reactions carried out under seemingly identical conditions.

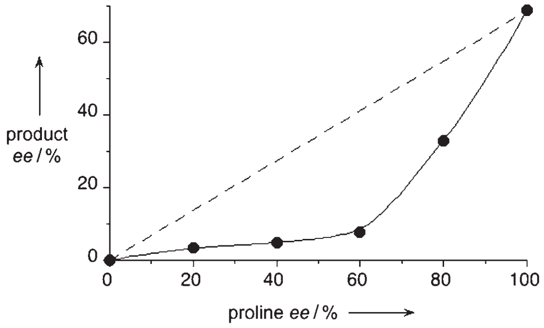
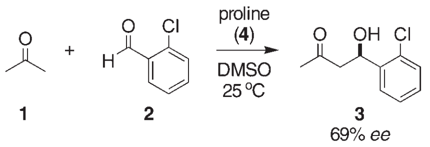


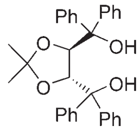
Figure 2. Product *ee* values versus overall proline *ee* for the aldol reaction of Scheme 1 carried out in DMSO at 25 °C using 40 mg proline per mL of DMSO. Reaction time: 30–45 min; conversion was greater than 98 % in all cases. The dashed line represents the expected linear relationship.



Scheme 1. Proline-mediated aldol reaction.

The implications of the phase behavior reported here are not limited to amino acid catalyst systems but have significance in general for understanding nonlinear effects in other asymmetric catalyst systems. Probing of nonlinear effects has become a common tool in mechanistic studies in all areas of asymmetric catalysis. The observation of nonlinear behavior is in many cases assumed to be diagnostic of the presence of more than one chiral ligand in the transition state, and explanations such as Kagan's ML_n models are typically invoked.[7,25] However, such interpretations could be misleading if the observed nonlinearity is due to physical phase behavior as we have described. Our work shows that temporal evolution of catalyst *ee* in solution may occur in any case where full solubility of chiral catalysts, ligands, or auxiliaries has not been established either prior to reaction or prior to formation of the active catalyst, even in instances where homogeneous conditions are ultimately achieved.

The quantitative phase behavior of most commonly employed chiral ligands remains virtually unexplored, although nonlinear effects have been reported in a number of cases that may be related to factors influenced by solid–solution phase behavior, such as the concentration and preparation of the catalyst as well as reaction protocols.[25–30] This work shows that both the sign and the magnitude of the observed nonlinear effect may depend on the kinetics of catalyst dissolution. As an example, we studied both the equilibrium phase behavior and the dissolution kinetics of taddol derivative **5**; nonlinear behavior has been reported in a variety of asymmetric reactions using this class of compounds.[25–27] We found that **5** forms a true racemic compound exhibiting an extremely high eutectic *ee* value of over 99 % *ee* under solid–solution equilibrium.[20] Figure 3 reveals that taddol exhibits the behavior of a kinetic conglomerate phase as it dissolves; for a 40 % *ee* taddol mixture, solution *ee* values spanning the entire range from nearly racemic to nearly enantiopure are obtained over time.



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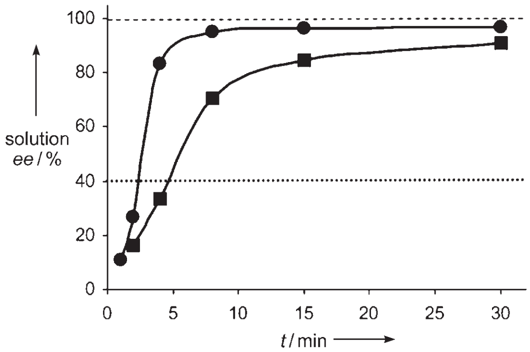

Figure 3. Solution *ee* values versus time for dissolution of taddol **5** in hexane (1.76 wt %) at 21 °C (●) and 0 °C (■). Overall *ee* for taddol: 40 % (•••••); eutectic *ee* for taddol: 99 % (-----).

This result suggests that a wide range of possibilities for both positive and negative nonlinear effects on product *ee* may result in asymmetric reactions using **5** in cases where dissolution occurs concomitant with reaction or with preparation of active catalyst species. Indeed, the experimental protocol in many taddol-mediated reactions involves initiation by mixing catalyst and reaction components at temperatures as low as −78 °C; the time dependence of solution *ee* values may be expected to be more significant at lower temperature. The reaction often proceeds non-isothermally as the vial is allowed to warm to ambient temperature. Such conditions may be conducive to simultaneous catalyst dissolution and catalytic turnover, giving the potential for nonlinear effects due to transient phase behavior.

In summary, this report demonstrates that reactions using enantioimpure catalysts must be probed carefully in order to elucidate the origin of an observed nonlinear effect. Most importantly, nonlinear effects of a true chemical origin such as that described by Kagan's ML_n models must be distinguished from those caused by physical phase behavior. Nonlinear effects observed in mixed-phase systems must be further characterized according to whether the effects originate from equilibrium or kinetic behavior. These concepts apply not only to the amino acid systems we originally studied but also to other asymmetric catalysts and ligands that are used to prepare asymmetric catalysts. Further studies are underway to identify and quantify nonlinear effects in asymmetric catalysis that may be traced to physical phase behavior.

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