Enantioenriched Proline

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The Crystallization Behavior of Proline and Its Role in Asymmetric Organocatalysis**

*Richard M. Kellogg**

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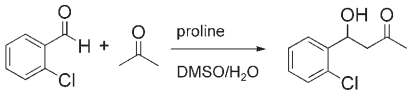
Proline is a remarkably effective soluble catalyst for enantioselective aldol and Mannich reactions, aminoxylations, and other reactions.[1] Interest remains intense with regards to how and why proline and structurally related systems function,[2] and new applications are reported regularly.[3] Four papers recently appeared that give remarkable insight into the behavior of enantiomerically enriched proline and other amino acids under heterogeneous conditions. These may provide an explanation for the nonlinear effects sometimes observed.[4] The immediate implications for asymmetric catalysis are appreciable, and the findings could have a bearing on other aspects of enantioenrichment, including the origin of homochirality in nature.

The story begins chronologically with a report by Blackmond and co-workers.[5] In DMSO with a small amount of water, the L-proline-catalyzed aldol reaction of acetone with 2-chlorobenzaldehyde carried out under *heterogeneous* conditions (L-proline is poorly soluble in DMSO/H_2O) using L-proline with 20–80% *ee* afforded product with a fairly constant enantiomeric excess of around 35% (Scheme 1).

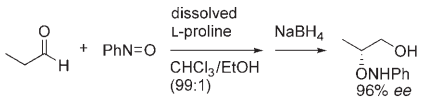
There was no nonlinear effect in solution despite the nonlinearity of the solid-state composition. The aldol reaction occurs, as far known, only in solution. On using enantiopure proline in solution, the enantiomeric excess of the aldol product was around 70% *ee*. That the *ee* value of the product obtained is only half of the maximum value for a large range of enantiomeric compositions of the solid state was shown to be the result of the fact that the *eutectic composition* (see below) for proline lies at 50% *ee*, as determined from the solubility behavior of a saturated solution of proline in equilibrium with racemic and enantiopure crystalline phases.



Scheme 1. L-proline-catalyzed aldol reaction of acetone with 2-chlorobenzaldehyde.[5] DMSO = dimethyl sulfoxide.

These observations bear on a subsequent and independent report by Hayashi et al.,[6] who studied the behavior of enantioenriched solid proline under heterogeneous conditions in $CHCl_3$ as solvent. Neither racemic nor enantiopure proline dissolves well in pure, dry $CHCl_3$. However, enantiopure proline becomes more soluble if a small amount of ethanol is added. The racemate has a solubility of only approximately 4.3×10^{-4} mol L^{-1} in $CHCl_3$/EtOH (99:1), whereas the pure enantiomers are over 100 times more soluble (5.4×10^{-2} mol L^{-1}). Hayashi et al. prepared a solid sample of proline of 1–10% *ee* by mixing well-ground enantiopure materials. For the case of proline with 1% *ee*, after equilibrium had been reached in the presence of solvent ($CHCl_3$), a saturated solution with 97–99% *ee* of proline was obtained! Solutions of proline with 85–99% *ee* were obtained from an initial solid of 10% *ee*. The solid that was recovered after equilibrium had been reached consisted of crystals of racemic proline (see below) rather than crystals of the pure enantiomers used to make the original solid. Over time, as equilibrium is reached, enough enantiopure proline eventually dissolves to allow the less-soluble racemate to crystallize out. A highly enantioenriched solution remains behind. The low solubility of the racemate is rationalized on the basis of the more closely packed crystal structure (almost identical to that already published[7]) compared to that of enantiopure proline. (This, however, is not the end of the story (see below).)

The enantioenriched solution was filtered to remove the solid and used to carry out aminoxylation reactions (Scheme 2). Clearly, the *ee* value of the product formed in a solution reaction is not linked linearly to the *ee* of the initial solid. Nearly enantiopure proline selectively goes into solution relatively independently of the initial enantiomeric excess of the solid.



Scheme 2. α-Aminoxylation of propanal catalyzed by proline.[6]

An initial explanation for these observations was offered by Blackmond and co-workers, who carefully constructed a ternary phase diagram for proline in DMSO and determined the eutectic compositions for eight other

[*] Prof. Dr. R. M. Kellogg
Syncom BV, Kadijk 3
9474 AT Groningen (The Netherlands)
Fax (+31) 50-5757399
E-mail: r.m.kellogg@syncom.nl
Homepage: http://www.syncom.nl

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amino acids (threonine, valine, alanine, phenylalanine, methionine, leucine, histidine, and serine) in H_2O.[5] To understand the significance of their report, a simplified discussion of the properties of phase diagrams is helpful. First, some basic principles of the solid-state properties of chiral compounds must be considered. Racemic proline crystallizes as a *racemic compound* and not as a *conglomerate*. A well-known example of the latter is sodium ammonium tartrate, the enantiomeric forms of which crystallize separately and can, in principle, be separated by visual inspection of the crystals. In practice, twinning and other complications frustrate such efforts with most conglomerates. Conglomerates are relatively rare. Of the coded amino acids, threonine and asparagine crystallize as conglomerates. However, many derivatives of amino acids are conglomerates, and Lahav and co-workers have made brilliant use of these phenomena in the use of tailor-made additives.[8]

In racemic compounds, such as proline, a racemic crystalline solid (enantiomers are paired) is preferred for mixtures of enantiomers within a certain *ee* range over the crystal polymorphs for the separate enantiomers. Racemic compounds are most frequently encountered. The third, and again relatively rare, major class of crystalline chiral compounds is a *solid solution* in which there is essentially no mutual recognition of the enantiomers in the crystal.

The term "racemic compound" with reference to the nature of the crystals has led to more than a little confusion in the organic chemistry community. The confusion is compounded by the fact that there is unfortunately no practical method to predict whether a given compound will form crystals of a racemic compound, conglomerate, or solid solution. An excellent, mathematically sound, discussion of the properties of racemates and enantiomers in the solid and solution can be found in the seminal work by Jacques, Collet, and Wilen.[9]

The study of melting-point behavior, provided that the compounds have readily measurable melting points, is a common method to identify conglomerates tentatively. For conglomerates, the melting points of the pure enantiomers are always significantly higher than those of the racemate, with the difference being usually some 25–30 °C. In contrast, the melting-point differences for racemic compounds are less pronounced and often the melting point of the racemate is higher than that of the pure enantiomer. Idealized binary phase diagrams (melting-point behavior as a function of enantiomer composition) for conglomerates and racemic compounds are shown in Figure 1 a–c. The minima observed in the curves correspond to the eutectic compositions.

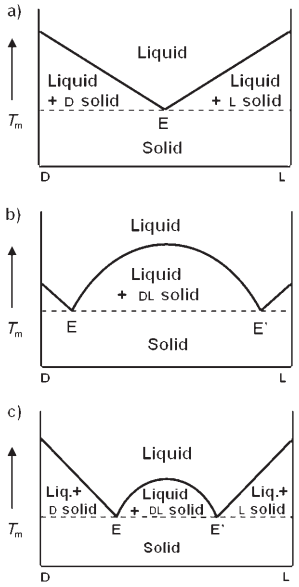

Figure 1. a) The idealized binary phase diagram for a conglomerate: the melting point (T_m) of the enantiomers is higher than that of the racemate, and the eutectic lies at 0% enantiomeric excess. b) A binary phase diagram for a racemic compound with eutectic points (E and E′, with a mirror-image relationship) at reasonably high enantiomeric excess values: the melting point of the pure enantiomers is lower than of the racemate. c) The eutectic points represent considerably lower enantiomeric excesses, and the melting points of the pure enantiomers are higher than that of the racemate.

More complicated (but at the same time more informative) phase diagrams can be constructed from solubility data (at constant temperature). The ternary solubility phase diagram for proline (only illustrative) is shown in Figure 2 b.[5] The three components include the two enantiomers (base of triangle) and the solvent (apex). Concentrations are generally expressed in mole fractions. Because proline is poorly soluble, solvent dominates the total phase diagram; thus, only the small, and interesting, area at the apex is shown in detail in Figure 2 a.

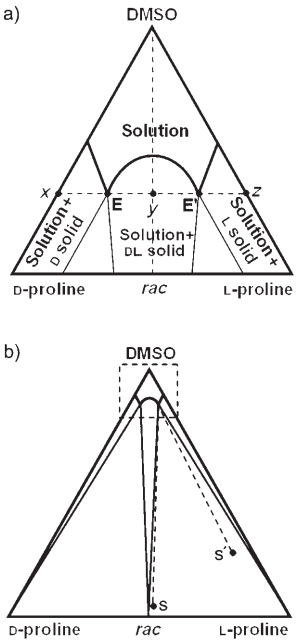

Figure 2. a) Simplified ternary phase diagram for proline in DMSO. b) The full phase diagram is clearly dominated by DMSO owing to the poor solubility of proline; the interesting small congruent triangle at the top is shown in more detail in part (a). The enantiomeric excess for L-proline at the eutectic point E′ is $(z\gamma - E'\gamma)\,(z\gamma)^{-1} \times 100\% = 50\%$ *ee*. The small unlabeled triangles under the eutectic points E and E′ (which are the top parts of the largest areas of the total phase diagram) contain solvent, D,L-configured solid, and D- or L-configured solid. Starting with sufficient material, with a small excess of L-proline, in the presence of insufficient solvent (indicated by point S in the full phase diagram), the concentration of L-proline in solution will go to the eutectic composition (50% *ee*) as indicated by the dotted line. The same is true starting from a large excess of L-proline (point S′). Note that in contrast to the behavior observed when $CHCl_3$ was used as solvent by Hayashi et al.,[6] in DMSO the pure enantiomers are slightly less soluble than the racemate.

The eutectic behavior observed in the usually more easily measured and understood binary phase diagrams often agrees with that found in ternary phase diagrams.[9] This extrapolation should, however, be made with reserve because, for example, the formation of solvates and/or polymorphs can lead to profoundly different eutectic behavior (see below).

The *phase rule*, that is, the number of degrees of freedom in the phase diagram, dictates that under equilibrium conditions, provided sufficient material is available, the solution composition will be that of the eutectic as long as three phases (racemate, excess enantiomer, and solvent) are present.[9] Depending on the starting point in the phase diagram, the end result in solution can be either an increase or a decrease in the enantiomeric excess relative to that of the solid. This powerful restriction is not generally appreciated by organic chemists. From simple (with a little practice) geometrical considerations, the composition of solid and solution at various points in the ternary phase diagram can readily be determined.

Eutectic values for racemic compounds vary tremendously. For conglomerates, the eutectic value should ideally be 0% *ee*. For the extremely important case of amino acids that form racemic compounds, eutectic values are apparently not available through the open literature. Blackmond and co-workers determined the eutectic composition for threonine to be 0% *ee* (in H_2O), which is expected because threonine is a conglomerate.[5] On the other hand, for serine, a racemic compound, the eutectic composition lies at over 99% *ee* (histidine: 93% *ee*; leucine: 87% *ee*; phenylalanine: 83% *ee*; valine: 46% *ee*). As an illustration of the consequences, Blackmond and co-workers[5] reported that a mixture of solid serine with overall 1% *ee* leads at equilibrium in H_2O to a solution of more than 99% *ee*. Breslow and Levine recently showed that slow evaporation of a solution of phenylalanine with 1% enantiomeric enrichment of the L enantiomer in water leads to a solution with 40% *ee* of L-phenylalanine and racemic solid.[10] Most likely, the solution *ee* had not reached the eutectic value of 83% *ee*.

Why is there an inconsistency between the results reported by Hayashi et al. and those reported by Blackmond and co-workers, with regard to the magnitude of the enantiomeric excess of proline found in solution under conditions of equilibrium? For 10% enantioenriched proline in DMSO, Blackmond and co-workers observed 41% *ee* in solution (approach to eutectic value of 50%; see Figure 2 caption) whereas Hayashi et al. reported values of up to 99% *ee* when $CHCl_3$/EtOH was used as solvent. The explanation was provided in another recent article from Blackmond's group.[11] However, to understand it, we must first return to the solubility properties of conglomerates and racemic compounds.

In 1904, Meyerhoffer suggested that the solubility of the racemate of a conglomerate should be twice that of the pure enantiomers.[12] A simplified explanation given by Jacques, Collet, and Wilen[9] proceeds as follows: The vapor pressure of an ideal gas is the sum of its components. If solid enantiomers in a neutral solvent are considered in a similar fashion, then in analogy one would expect the solubility of the conglomerate to be equal to the sum of its components, namely the enantiomers. This is known as the "double solubility" rule, and it works remarkably well for neutral conglomerates, in particular.[9] Reported values of α, the ratio (on a molar basis) of the solubilities of racemate to enantiomers [Eq. (1)], lie remarkably close to the ideal value of 2.

$$\alpha = \frac{\text{solubility of racemate}}{\text{solubility of pure enantiomer}} \qquad (1)$$

In their second article, Blackmond and co-workers extended this concept to the considerably more complicated situation of racemic compounds.[11] With the assumption of ideal behavior and use of the authors' empirical observation that the concentration of the major enantiomer at the eutectic is essentially equal to the solubility of the pure enantiomer, they arrived at Equation (2) to predict the enantiomeric composition of the eutectic (ee_{eut}). For an ideal conglomerate ($\alpha = 2$), the limiting *ee* value for the eutectic is the expected 0%. If $\alpha > 2$, the model does not work owing to assumptions in the derivation.

$$ee_{eut} = \frac{1-(\alpha^2/4)}{1+(\alpha^2/4)} \times 100\,\% \qquad (2)$$

This is a useful equation that can readily be applied in the laboratory. From relatively simple solubility measurements on racemate and pure enantiomers (assuming that these are available), the eutectic point can quickly be estimated without the time-consuming construction of a full ternary phase diagram. It was shown that the approximation of Equation (2) works very well for amino acids in water and many other compounds including binol, binap, and taddol ligands. Measured values of α range from 10^{-2} to 2. There are a few failures, of course; for example, the values reported in the literature for mandelic acid and benzylidene camphor fail to fit the theoretical curve.

Equation (2) provides a smooth curve with limits of 0% *ee* for the eutectic solution ($\alpha = 2$, ideal conglomerate) and 100% *ee* for the eutectic solution as α approaches zero. In other words, the enantiomeric excess of the eutectic solution (for racemic compounds) will increase as the solubilities of the pure enantiomers increase relative to that of the racemates. This can be a useful rule of thumb to establish whether or not one has a conglomerate or a racemic compound.

Now we return to proline and the discrepancy in the results of Hayashi et al. (99% *ee* in $CHCl_3$/EtOH) and Blackmond and co-workers (40% *ee* in DMSO). Blackmond and co-workers found that the eutectic value of proline in $CHCl_3$ is indeed 99% and not 50% *ee* as found in DMSO or in water, and provided a demonstration of the cause. On crystallization of racemic proline from $CHCl_3$/EtOH, they were able to isolate a solvate that contains one $CHCl_3$ molecule with each racemate pair of proline molecules. Hydrogen-bonding effects in this solvate effectively reduce the solubility of the racemate relative to enantiopure proline, which crystallizes from $CHCl_3$ without incorporation of solvent. The authors emphasized the exciting prospect of engineering the eutectic position by judicious choice of a small achiral molecule that can influence solubility behavior, for example, by means of hydrogen-bonding interactions.

It is clear that both Blackmond and Hayashi have shown through use of enantioenriched solid proline (as well as other amino acids) in a heterogeneous system that the enantiomeric excess in solution may differ dramatically from that in the solid. As Blackmond and co-

workers demonstrate, there are perfectly reasonable thermodynamic explanations for this.[13]

What about kinetic effects? How quickly is equilibrium established and how does the enantiomeric excess change on the way there? Data from Hayashi et al. for enantioenriched proline indicate that over a period of several hours the *ee* in solution changes from very low to the ultimate very high value found. In a third paper, Blackmond and co-workers have studied this phenomenon carefully and provide a rationalization and explanation why nonlinear behavior in proline-catalyzed reactions is sometimes observed.[14] If one begins with unequal amounts of enantiopure solid proline, the *ee* value in DMSO solution rises over a period of 3–4 h from 0% to the final eutectic value of 50%. They confirm that for a proline-catalyzed aldol reaction, the enantiomeric excess of the condensation product even for strongly enriched solid proline can be very low during the equilibration period. The authors suggest that a "kinetic conglomerate" is involved. In other words, solid, enantiomerically pure prolines mixed together in the beginning stages of dissolution in effect form a conglomerate, and, as expected, the eutectic composition (the situation towards which the system first tends) is 0% *ee*. As equilibrium is reached, the poorly soluble racemate of proline (a racemic compound) begins to precipitate and the system proceeds then towards the final eutectic composition of 50% *ee* in DMSO. This is a fascinating idea that invites further experiments in the engineering of solution enantiomeric excesses in heterogeneous catalysis.

Blackmond and Hayashi both point out that their results can have implications for the generation of homochirality in nature. Highly enantioenriched solutions can be obtained from slightly enantioenriched solids. Catalytic asymmetric synthesis could then lead to a variety of homochiral biomolecules. The suggestion is certainly plausible.

Further application of these observations in heterogeneous catalysis and other areas such as enantiomeric separations or kinetic resolutions should be possible. Combination of thermodynamic and kinetic considerations may lead to even better models for the generation of homochirality during evolution. Perhaps interactions of chiral molecules are indeed stronger in the solid state. If communication between solid and liquid can be established, the possibilities are limited only by the imagination of the chemist.

In 1981, Jacques, Collet, and Wilen[9] observed in the introduction to their treatise that "*If there is one central theme to this book, it is that the properties of mixtures of enantiomers, particularly those affecting the solid state, are special and even different from those of achiral molecules*". How true this observation is.

[1] See, for example: a) B. List, *Acc. Chem. Res.* **2004**, *37*, 548; b) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580; A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**, chap. 6–7; B. List, *Modern Aldol Reactions*, *Vol. 1*, (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2005**, chap. 4.

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[4] For example, see: S. P. Mathew, H. Iwamura, D. G. Blackmond, *Angew. Chem.* **2004**, *116*, 3379; *Angew. Chem. Int. Ed.* **2004**, *43*, 3317.

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[8] See, for example: I. Weissbuch, M. Lahav, L. Leiserowitz, *Cryst. Growth Des.* **2003**, *3*, 125.

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[10] Eutectic behavior likely is involved in a recent brief report of enantiomeric enrichment of phenylalanine in solution on concentration and precipitation of the racemate; see: R. Breslow, M. S. Levine, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 12979.

[11] M. Klussmann, A. J. P. White, A. Armstrong, D. G. Blackmond, *Angew. Chem.* **2006**, *118*, 8153; *Angew. Chem. Int. Ed.* **2006**, *45*, 7985.

[12] W. Meyerhoffer, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 2604.

[13] If the reader's appetite for phase diagrams has been whetted, 14 phase diagrams for amino acids and other compounds can be found in the supplementary material to Ref. [11]. A phase diagram for proline in $CHCl_3$ is also included therein.

[14] M. Klussman, S. P. Mathew, H. Iwamura, D. H. Wells, Jr., A. Armstrong, D. G. Blackmond, *Angew. Chem.* **2006**, *118*, 8157; *Angew. Chem. Int. Ed.* **2006**, *45*, 7989.

