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Non-linear effects in acyclic amino acid-catalyzed direct asymmetric aldol reactions

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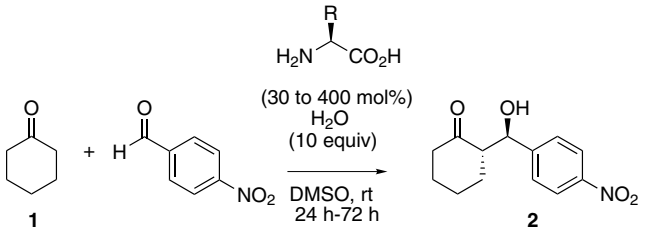
Abstract—Non-linear effects were observed in acyclic amino acid-catalyzed direct asymmetric intermolecular aldol reactions. The non-linear effects are due to the equilibrium solid–liquid phase behavior of amino acids. The results suggest that the phase behavior of amino acids linked to asymmetric catalysis may have implications to the evolution of homochirality.

The direct asymmetric aldol reaction is one of the most important C–C bond-forming reactions in Nature and in synthetic chemistry.[1–3] In particular, the development of catalytic stereoselective methods for the asymmetric directed aldol reaction has recently been the subject of intense research.[4–6] One powerful way of promoting the direct asymmetric aldol reaction is the use of proline and proline derivatives as catalysts.[7–9] More recently, acyclic amino acids and their derivatives were successfully used as catalysts for the direct intermolecular asymmetric aldol reaction.[10]

In a pioneering work, Kagan and co-workers gave an explanation for the occurrence of non-linear effects in several catalytic asymmetric organic transformations.[11] The amino acid-catalyzed asymmetric aldol reaction between ketones and aldehydes displays first-order kinetics with respect to the amino acid.[12] Thus, a single amino acid molecule is involved in the transition state of this reaction.[13] However, positive non-linear effects have been observed in proline-catalyzed direct asymmetric aldol reactions with aldehydes as nucleophiles.[14] In this case, the non-linear effect is due to in situ kinetic resolution of the amino acid by the chiral aldol product. Herein, we report non-linear effects in acyclic amino acid-catalyzed intermolecular asymmetric aldol reactions that are caused by the solid–liquid phase behavior of amino acids in solution. Serine catalyzed the reaction with a significant amplification of enantiomeric excess in aqueous media.

In initial experiments, we investigated the influence of the enantiomeric excess of the amino acid catalyst on the enantiomeric excess of the aldol product **2** for the asymmetric aldol reaction between cyclohexanone **1** and 4-nitrobenzaldehyde (Eq. 1).[15,16]



(1)

In stark contrast to alanine and valine, we found a remarkably high amplification of the enantiomeric excess of aldol product **2** in the serine catalyzed asymmetric aldol reaction (Fig. 1).

The serine-catalyzed aldol reactions were heterogeneous in wet DMSO, which is due to the lower solubility of serine as compared to the aliphatic amino acids, alanine and valine in wet DMSO. In comparison, the alanine and valine catalyzed reactions became homogeneous after 48 h of reaction time. We also found that the ee of the soluble serine was significantly higher than the starting ee of the serine catalyst. Hence, the significant asymmetric amplification of **2** could be correlated to the difference in enantiomeric excess of the serine in solution and in the solid phase.[17] Moreover, increasing the amount of (*S*)-serine (200 mol %) increased the

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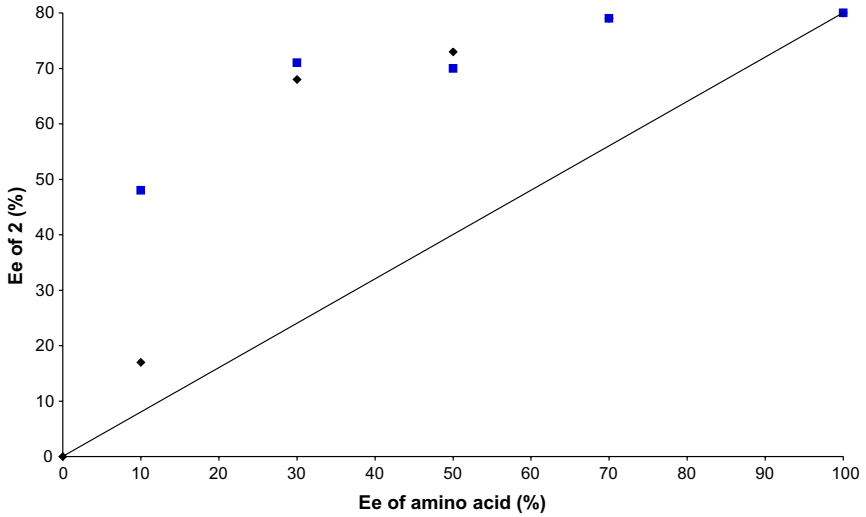

Figure 1. Relationship between the enantiomeric excess of (*S*)-serine (30 mol %) (◆) and (*S*)-serine (200 mol %) (■) and that of the newly formed **2**, respectively.

amplification of enantiomeric excess of **2** (Fig. 1). For instance, serine with 10% ee mediated the asymmetric formation of **2** with 48% ee. We also observed non-linear effects in the alanine and valine mediated reactions if the reaction mixture was heterogeneous.[15] Hence, we decided to investigate the influence of the ee of the alanine and valine mediated asymmetric aldol reactions on the ee of aldol product **2** in DMSO using an excess of amino acid (200–400 mol %) (Fig. 2). Under these conditions all the studied reactions were heterogeneous.

Interestingly, the alanine and valine mediated reactions gave simultaneous positive and negative non-linear effects (Fig. 2). We observed a significant amplification of enantiomeric excess at low enantiomeric excess of the amino acid. For instance, the aldol reaction with valine as the mediator with 10% ee gave the corresponding aldol product **2** with 61% ee. Thus, heterogeneous valine and alanine mediated aldol reactions exhibit a significant amplification of ee of the aldol product at low ee of the amino acid. The ee of **2** was almost constant even though the ee of the added scalemic amino acid was different. Hence, the eutectic points of valine and alanine had been reached in the reaction system.[10c,17,18] After the point where the straight line characterizing the absence of a non-linear effect was reached, a negative non-linear effect arises.

It is known that (*S*)-serine exhibits a higher solubility as compared to the racemic amino acid mixture in water.[19] Consequently, we investigated the solubility of scalemic serine mixtures in water and found that the solubility increased with increased enantiomeric excess of the scalemic amino acid mixture. Moreover, we established

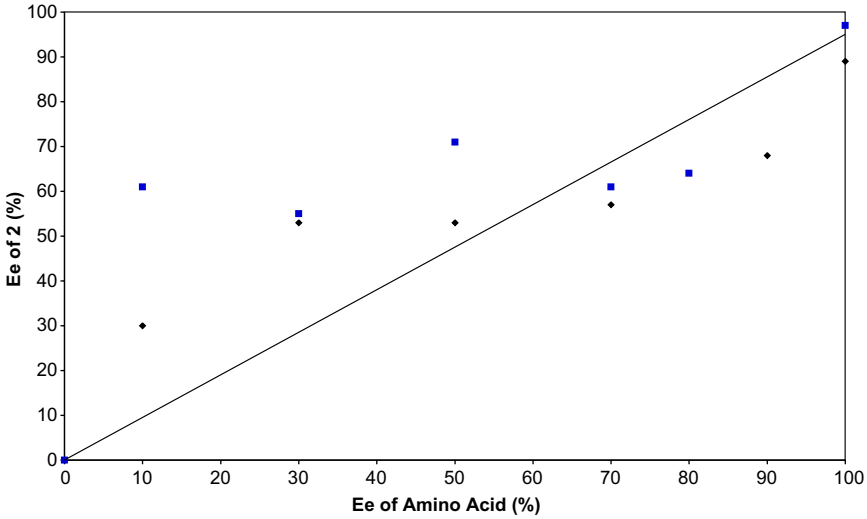

Figure 2. Relationship between the enantiomeric excess of (*S*)-alanine (400 mol %) (◆) and (*S*)-valine (200 mol %) (■) and that of the newly formed **2**, respectively.

a difference in enantioselectivity between (*S*)-serine in solution and the solid scalemic (*S*)-serine mixture in water (Fig. 3).

We next investigated the influence of the ee of the acyclic amino acid on the ee of the aldol product **2** in water. The serine-catalyzed asymmetric aldol reaction between cyclohexanone **1** and 4-nitrobenzaldehyde gave aldol product **2** with 49% ee in water. Notably, a positive non-linear effect was observed for the serine-mediated intermolecular aldol reaction in water, which was directly correlated to the enantiomeric excess of the serine in solution (Fig. 4). Moreover, the enantiomeric excess of serine in solution at the eutectic point in water was 99% ee.[17]

These results show that the heterogeneous amino acid-catalyzed asymmetric aldol reaction involves the same transition states as previously proposed.[15] Furthermore, serine derived oligopeptides also displayed significant positive non-linear effects for the intermolecular aldol reaction in water.

The equilibrium solid–liquid phase behavior of an amino acid mixture that is linked to amino acid catalysis may also be of importance for the evolution of homochirality.[20] For instance, serine can catalyze the asymmetric formation of erythrose and threose in water.[21] Thus, in a plausible prebiotic scenario, a heterogeneous amino acid mixture with low optical purity could possibly catalyze the formation of a sugar product with high asymmetric induction. Next, the optically active sugar product may have synergistically contributed to the sugar-assisted kinetic resolution of the amino acid catalyst that can lead to a nearly optically pure carbohydrate.[14a]

In summary, we have found significant positive non-linear effects in the direct acyclic amino acid- and peptide-catalyzed asymmetric aldol reaction. Serine and its peptides were unique in catalyzing the reaction with a

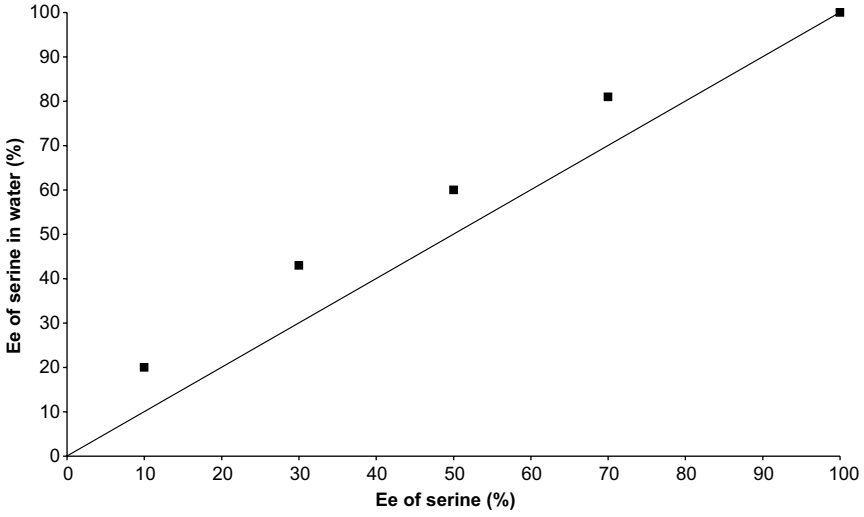

Figure 3. Relationship between the enantiomeric excess of (*S*)-serine (400 mol %) and that of the soluble serine (■) in water (1.6 mL).

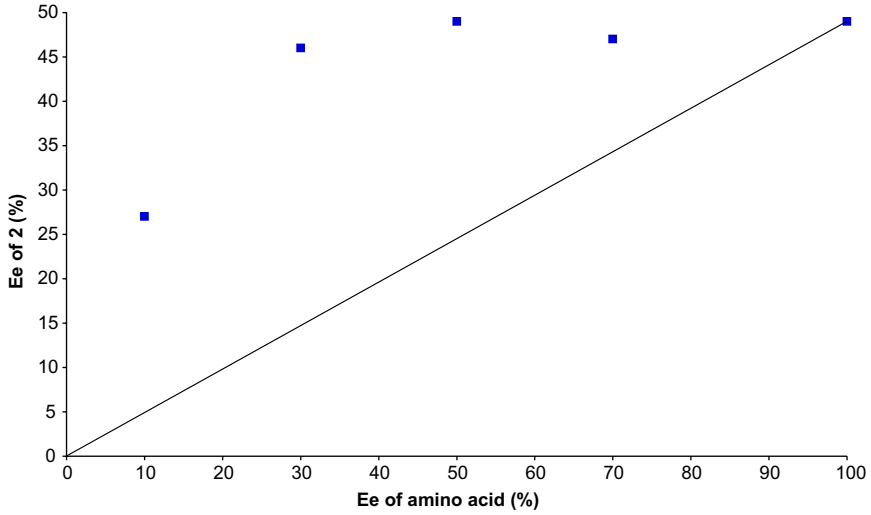

Figure 4. Relationship between the enantiomeric excess of (*S*)-serine (400 mol %) and that of the newly formed **2** (■) in water.

high positive non-linear effect. The amino acid-mediated reactions exhibited non-linear effects, which are due to the equilibrium solid–liquid phase behavior of amino acids. As a consequence, a significant imbalance of enantiomeric excess of the amino acid in the solution can be achieved, which may have implications to the evolution of homochirality. Further investigations of these systems with respect to our model for sugar-assisted kinetic resolution of amino acids, asymmetric transformations and molecular modeling studies are ongoing.

Acknowledgements

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16. (*S*)-Amino acid (30, 200 or 400 mol %) was added to a vial containing acceptor aldehyde (0.5 mmol) and donor ketone **1** (2.0 mmol) in DMSO (2 mL). After 1 day of vigorously stirring at room temperature, the reaction mixture was poured into an extraction funnel containing

brine (5 mL), which was diluted with distilled H_2O (5 mL) and EtOAc (15 mL). The reaction vial was also washed with 2 mL of EtOAc, which was poured into the extraction funnel. The aqueous phase was extracted with EtOAc (2×15 mL). The combined organic phases were dried with Na_2SO_4 and the solvent removed under reduced pressure. The reaction could also be quenched by directly pouring the reaction mixture onto a silica gel column. The crude aldol product was purified by silica gel column chromatography (EtOAc:pentane-mixtures) to furnish the desired aldol product **2**. The ee of the aldol product **2** was determined by chiral-phase HPLC analysis. Compound **2**: ^{1}H NMR ($CDCl_3$, 400 MHz): 1.52–2.14 (m, 6H), 2.33–2.52 (m, 2H), 2.59 (m, 1H), 3.15 (bs, 1H), 4.90 (d, $J = 8.6$ Hz, 1H), 7.49 (d, $J = 8.7$ Hz, 2H), 8.20 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz): $\delta = 24.6$, 27.6, 30.7, 42.6, 57.1, 73.9, 123.5, 127.8, 147.5. 148.4, 214.7; HPLC (Daicel Chiralpak AD, *iso*-hexanes/*i*-PrOH = 80:20, flow rate 0.5 mL/min, $\lambda = 254$ nm): major isomer: $t_R = 31.12$ min; minor isomer: $t_R = 24.14$ min; MALDI-TOF MS: 272.0897; $C_{13}H_{15}NO_4$ ($M+Na^+$: calcd 272.0899).

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