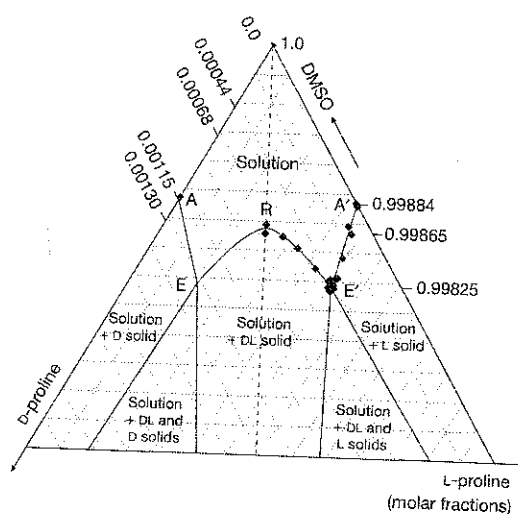


# New Models of Asymmetric Amplification in Amino Acid Catalysis



NLE of proline-catalyzed reaction

enantioenrichment  
(dropping the racemate)

the evolution of biomolecular homochirality

~ Today's Content ~

1. Background of Non-Linear Effects
2. Non-Linear Effects of Proline-catalysed Reaction
  - 2-1. Early Observation of NLE (Agami and Kagan)
  - 2-2. Explanation by Blackmond (1) Kinetic Model
  - 2-3. Explanation by Blackmond (2) Thermodynamically-controlled Model
3. Investigating the Evolution of Biomolecular Homochirality

# 1 Background of non-linear effects (NLE)

Review: Kagan et al. *Angew. Chem. Int. Ed.* **37**, 2922 (1998)

Blackmond *Acc. Chem. Res.* **33**, 402 (2000).

- In 1986, Kagan, Agami et al. considered asymmetric synthesis with a chiral catalyst that was not enantiomerically pure.

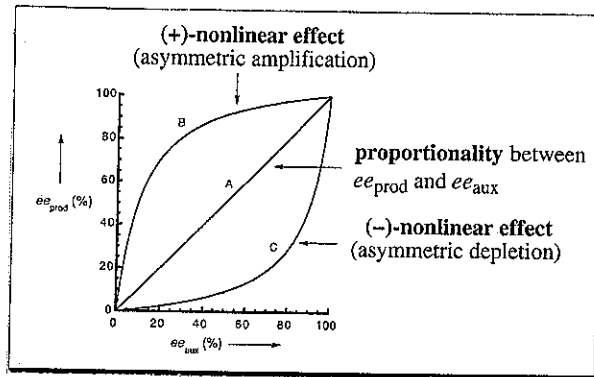
the well accepted assumption:

$$ee_{prod} = EE_0 \cdot ee_{cat} \quad (eq. 1)$$

ee of product when catalyst is enantiopure

↓ However

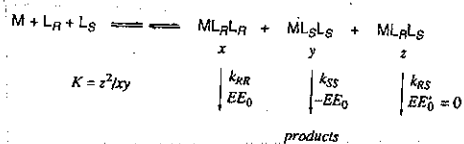
In many enantioselective reactions,  $ee_{prod}$  is not always proportional to  $ee_{cat}$ .



## < Kagan's models >

(1)  $ML_n$  model.

$n=2$



- Based on a system with a fast ligand exchange at a metal center bearing two ligands.
- Heterochiral (meso) catalyst ( $ML_RL_S$ ) generates racemic product.

$$ee_{prod} = EE_0 \cdot ee_{cat} \times \frac{1 + \beta}{1 + g\beta} \quad (2)$$

$\beta$  = relative amounts of complexes =  $\frac{N_{meso}}{N_{chiral}}$   
 $g$  = relative reactivities of complexes =  $\frac{k_{SR}}{k_{RR}}$

Model returns to linearity when  $\beta = 0$  or  $g = 1$ .

$\beta = 0$ ; no meso complex  $\rightarrow ee_{prod} = ee_0 \cdot ee_{cat} \times \frac{1+0}{1+g \cdot 0} = EE_0 \cdot ee_{cat}$

$g = 1$ ;  $k_{SR} = k_{RR}$   $\rightarrow ee_{prod} = ee_0 \cdot ee_{cat} \times \frac{1+\beta}{1+\beta} = EE_0 \cdot ee_{cat}$

$g < 1$ : (+) - NLE

meso complex is less reactive

$$\frac{1+\beta}{1+g\beta} > 1 \Rightarrow ee_{prod} > ee_{cat}$$

The reactivity become slower than that with enantio-pure catalyst.

$\beta \uparrow \Rightarrow$  The degree of NLE become larger.

$g > 1$ : (-) - NLE

meso complex is more reactive

$$\frac{1+\beta}{1+g\beta} < 1 \Rightarrow ee_{prod} < ee_{cat}$$

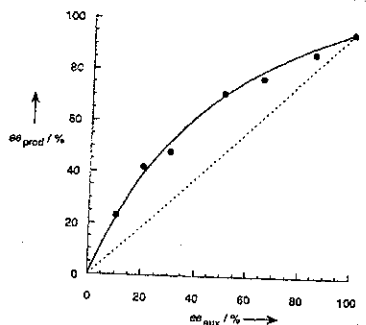
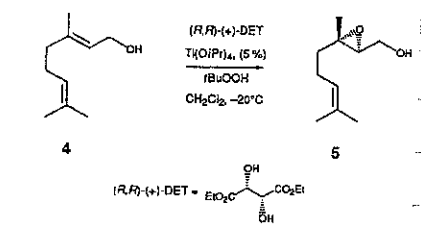
The reactivity become faster than that of enantio-pure catalyst.

example)

### Sharpless Epoxidation of Geraniol

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DATE

Kagan and Agami et al. discovered the (+)-NLE for the first time through this reaction.



$EE_0 = 95\%$   
 $\beta = \frac{k_{SR}}{k_{RR}} = 0.35$

- Involvement of less reactive dimeric meso complex and more reactive dimeric catalyst in  $ML_2$  model can explain the NLE.
- This result is consistent with the Sharpless mechanism implicating two DET's in active catalyst.

### (2) The Reservoir Effects

Formation of inactive catalyst aggregates can also explain NLE.

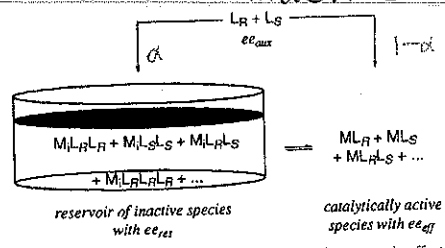


Figure 14. A large pool of unproductive complexes: the reservoir effect model.  $ee_{res}$  and  $ee_{cat}$  are for the ligands overall.

$ee_{res} \neq ee_{cat}$

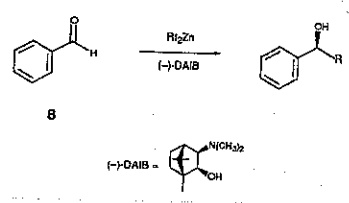
$\Rightarrow$  The ee of catalyst involved in the reaction ( $ee_{eff}$ ) will be effectively different.  
 $ee_{eff} = \frac{ee_{cat} - \alpha ee_{res}}{1 - \alpha}$  (3)

$\alpha$ : the proportion of ligand engaged in nonreactive aggregation

- Example: A catalyst of 50% ee in which 40% of material is stored in non-reactive racemic aggregates.

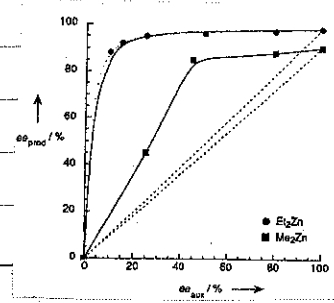
$ee_{cat} = 50(\%)$   
 $\alpha = 0.4$   
 $ee_{res} = 0(\%)$   
 $\Rightarrow ee_{eff} = \frac{50 - 0.4(0)}{1 - 0.4} = 83(\%)$

### example) Addition of organozinc reagents to aldehyde (Noyori et al.)



Reservoir  
 $ee_{res} = 0\%$   
 $\alpha = 0.88$

$ML_2$   
 $EE_0 = 98\%$   
 $\beta = \frac{k_{RS}}{k_{RR}} = 0.01$



- This NLE is explained by both models.
- This remarkable NLE was due to very stable (unreactive) heterocomplex. ( $\leftarrow$  X-ray analysis)

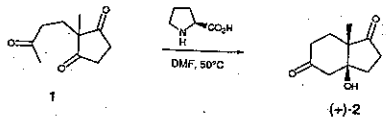
## 2. Non-Linear Effects of Proline-catalysed Reaction

3

### 2-1. Early observation of NLE (by Agami and Kagan)

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- (-)-NLE was observed slightly.
- Two molecules of proline might be involved in the reaction mechanism.

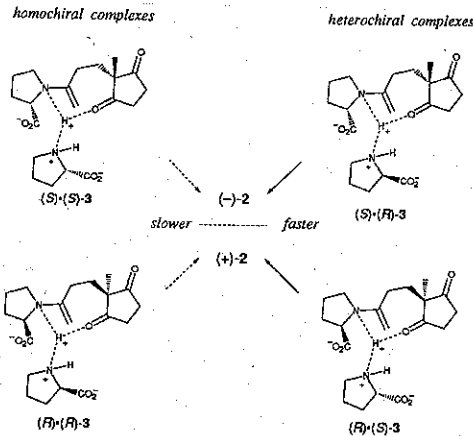
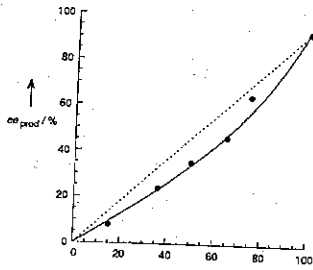


Figure 1  
Kagan proposed intermediates

• This was supported by a kinetic model based on a second-order reaction in respect to proline.

### Kinetic and Stereochemical Evidence for the Involvement of Only One Proline Molecule in the Transition States of Proline-Catalyzed Intra- and Intermolecular Aldol Reactions

Linh Hoang,<sup>†</sup> S. Bahmanyar,<sup>†</sup> K. N. Houk,<sup>†</sup> and Benjamin List<sup>\*,†</sup>

JACS 125, 16 (2003)

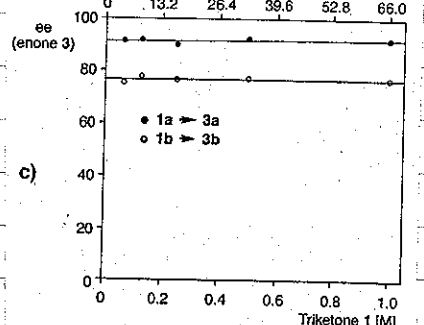
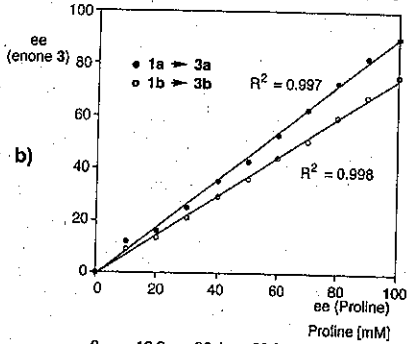
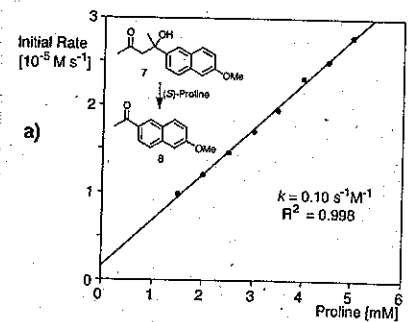
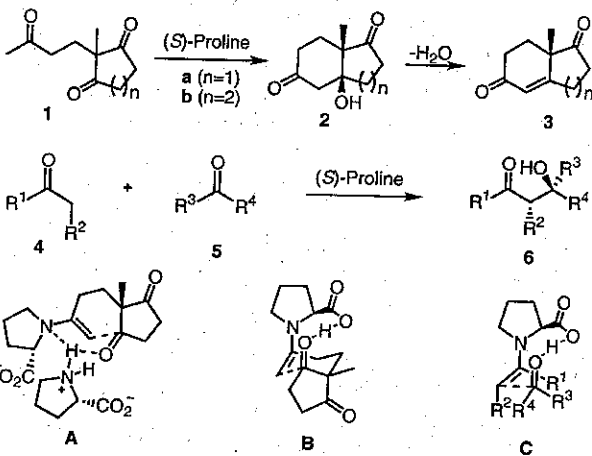


Figure 2

• B. List proposed the involvement of only one -proline molecule in the reaction mechanism.

↑ a) retro-Aldolization kinetics

( b) Linear effects

c) Absence of dilution effects

\* There are other examples of NLE in proline catalysed reaction

(Hanessian et al. OL, 2, 19, 2975 (2000), Barbas III JACS, 123, 5260 (2001))

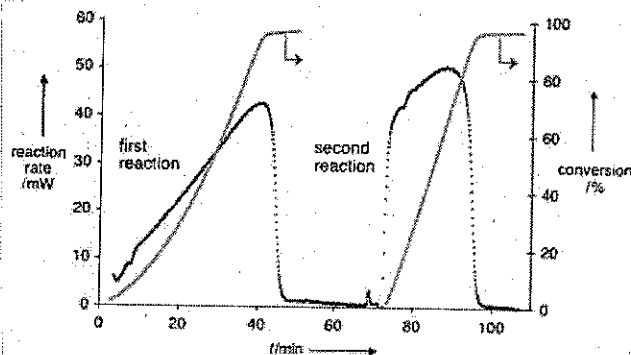
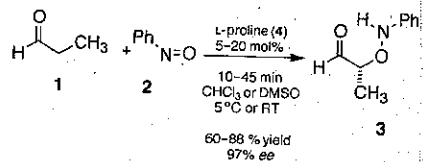
sometimes, (+)-NLE and sometimes more complex. ⇒ very confusing!

## 2-2. Explanation by Blackmond (1) Kinetic model

### Amplification of Enantiomeric Excess in a Proline-Mediated Reaction\*\*

Suju P. Mathew, Hiroshi Iwamura, and  
Donna G. Blackmond\*

Angew. Chem. Int. Ed. 43, 3317 (2004)

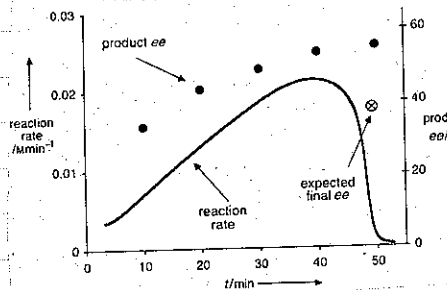
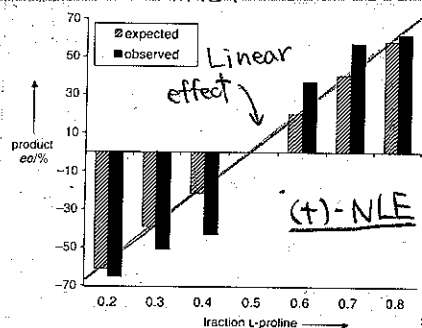


**Figure 1.** Reaction rate (filled black circles, corresponding to the left axis) and percent conversion (shaded grey line, corresponding to the right axis) versus time for a one-pot, two-consecutive-reaction sequence of the reaction shown in Equation (1) ( $\text{CHCl}_3$  solvent, 278 K). Initial concentrations of aldehyde 1 and L-proline 4 were 2.07 and 0.07 M, respectively. First reaction: 0.26 M PhNO; second reaction: 0.24 M PhNO.

- d-aminoxylation of aldehyde
- fast reaction
- $\Rightarrow$  suitable for mechanistic study

- The reaction rate rose steadily throughout the course of reaction.
- $\Rightarrow$  autocatalytic or autoinductive reaction.

- Addition of the reaction product to fresh reagents
- $\rightarrow$  no reaction
- $\Rightarrow$  not autocatalytic. It looks like autoinductive reaction.

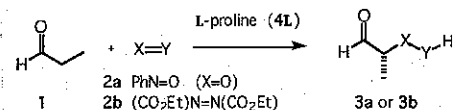


- Ee rose over the course of the reaction.
- $\Downarrow$
- (+)-NLE was observed.

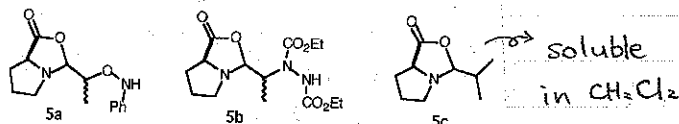
### Probing the Active Catalyst in Product-Accelerated Proline-Mediated Reactions

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

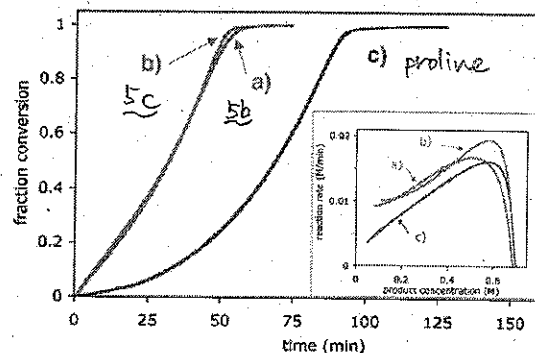
JACS 126, 16312 (2004)



- The solubility of proline is a key of explaining this autoinductive effect?

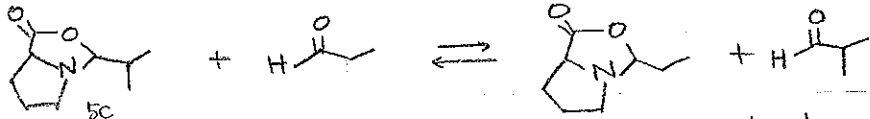


- The reaction is significantly faster with oxazoline 5b, 5c than with proline.
- The rate acceleration in the case of 5b, 5c  $\rightarrow$  not simply the solubility of catalyst was the cause of autoinductive effect.



**Figure 1.** Fraction conversion versus time for the reaction of eq 1 with 2 M propionaldehyde and 0.7 M 2b in  $\text{CH}_2\text{Cl}_2$  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.

\* NMR experiment



• Direct exchange  $\Rightarrow$  Free proline is involved in the reaction pathway.

\* DFT calculation (B3LYP/6-31G)

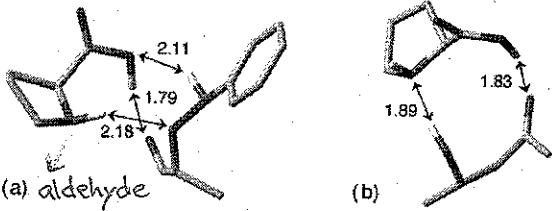
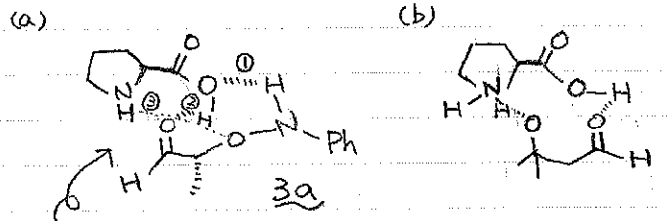
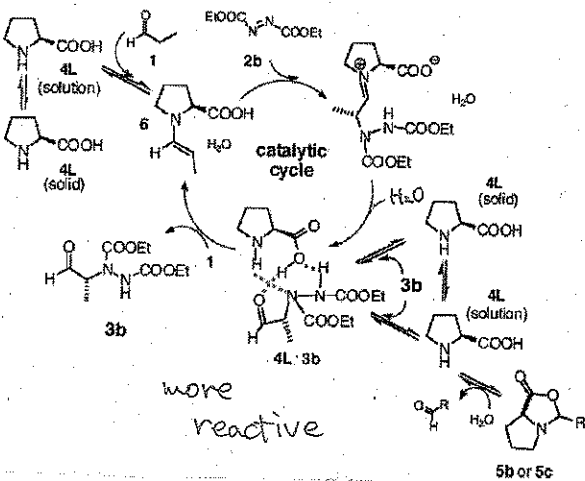


Figure 2. Calculated structures for hydrogen-bonded product-proline adducts (a) 4L-3a in the aminoylation reaction of eq 1 with X = Y as 2a, and (b) 4L hydrogen bonded to the product of the aldol reaction between acetone and acetaldehyde. Distances are given in angstroms.

Scheme 1. Proposed Autoinductive Reaction Mechanism for the Reaction in eq 1 with X = Y as 2b<sup>a</sup>



• 3 point hydrogen bonding  $\Rightarrow$  different from other proline catalysed reaction.

• proline's N can attack the free aldehyde.  $\Downarrow$  autoinductive effect!

\* Proposed mechanism

• 4L-3b complex is more nucleophilic than proline 4L.

•  $[Product] \uparrow \Rightarrow [4L-3b] \uparrow \Rightarrow$  rate acceleration  
(Product acceleration)

2-3 Explanation by Blackmond (2) Thermodynamic control model

### Thermodynamic control of asymmetric amplification in amino acid catalysis

Martin Klussmann<sup>1</sup>, Hiroshi Iwamura<sup>1†</sup>, Suju P. Mathew<sup>1</sup>, David H. Wells Jr<sup>1†</sup>, Urvish Pandya<sup>1</sup>, Alan Armstrong<sup>1</sup> & Donna G. Blackmond<sup>1,2</sup>

Nature 441, 621 (2006)

• They show an alternative mechanism for NLE.  
— the equilibrium solid-solution phase behaviour.

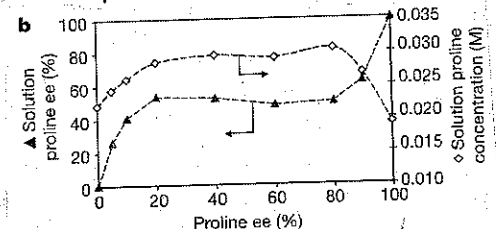
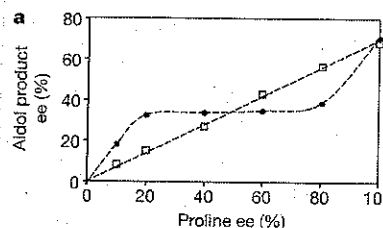
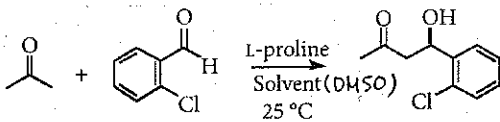
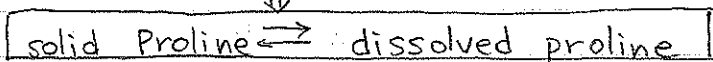


Figure 1 | Reaction and solution behaviour as a function of the overall proline enantiomeric excess. a, Product enantiomeric excess versus proline enantiomeric excess for the aldol reaction of equation (1). Squares, proline concentration 0.025 M; circles, total proline concentration 0.1 M (corresponding to ~4 mol% solution proline). b, Solution proline enantiomeric excess (left axis, triangles) and solution proline concentration (right axis, diamonds) as a function of the overall enantiomeric excess for proline at 0.1 M; all experiments in DMSO with 0.8 wt% H<sub>2</sub>O at 25 °C.

• [proline]

low  $\Rightarrow$  soluble  $\Rightarrow$  linear

high  $\Rightarrow$  not fully soluble  $\Rightarrow$  non-linear



$\Downarrow$   
catalysed the reaction with linear relationship.

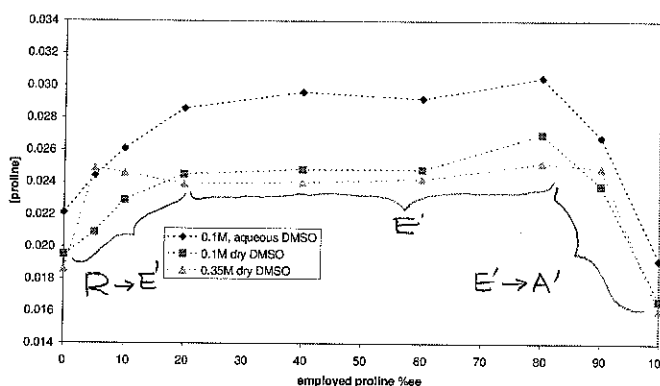
The solid-solution phase behaviour of enantiomers and racemates was fully investigated, but non-enantiopure, non-racemic mixtures have received less attentions.

\* They explored the phase behaviour of prolines of various ee.

Supplementary Table 1: Equilibrium concentrations and ee of saturated proline solutions.

#	%ee <sub>empl</sub>	[Pro]	solvent	[Pro] <sub>solution</sub>	%ee <sub>solution</sub>	%ee <sub>solid</sub>
10	0.0	0.10	dry DMSO	0.0195	-0.9	0.9
11	5.0	0.10	dry DMSO	0.0209	27.9	1.1
12	10.0	0.10	dry DMSO	0.0229	40.4	1.8
13	20.0	0.10	dry DMSO	0.0245	51.6	13.5
14	40.0	0.10	dry DMSO	0.0248	47.8	40.2
15	60.0	0.10	dry DMSO	0.0248	47.0	68.4
16	80.0	0.10	dry DMSO	0.0270	49.2	92.9
17	90.0	0.10	dry DMSO	0.0238	56.1	99.7
18	100.0	0.10	dry DMSO	0.0167	100.0	n.d.
19	0.0	0.35	dry DMSO	0.0186	-0.3	-0.4
20	5.0	0.35	dry DMSO	0.0249	50.7	3.6
21	10.0	0.35	dry DMSO	0.0246	53.5	6.7
22	20.0	0.35	dry DMSO	0.0239	54.2	21.4
23	40.0	0.35	dry DMSO	0.0240	49.9	41.0
24	60.0	0.35	dry DMSO	0.0242	48.9	62.5
25	80.0	0.35	dry DMSO	0.0252	48.1	n.d.
26	90.0	0.35	dry DMSO	0.0249	47.9	94.0
27	100.0	0.35	dry DMSO	0.0161	100.0	n.d.

Proline  $\xrightarrow[25^\circ\text{C}, >24\text{h.}]{\text{dry DMSO}}$  dissolved Proline + solid Proline



Supplementary Figure 1: Saturation concentrations of proline in dry or aqueous (0.35M water) DMSO, taken for samples of varying enantiomeric composition and different total concentrations of proline (Constructed from data in Supplementary Table 1).

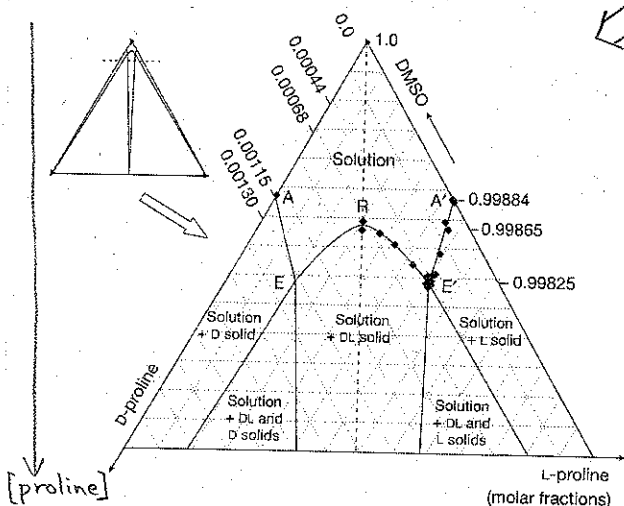
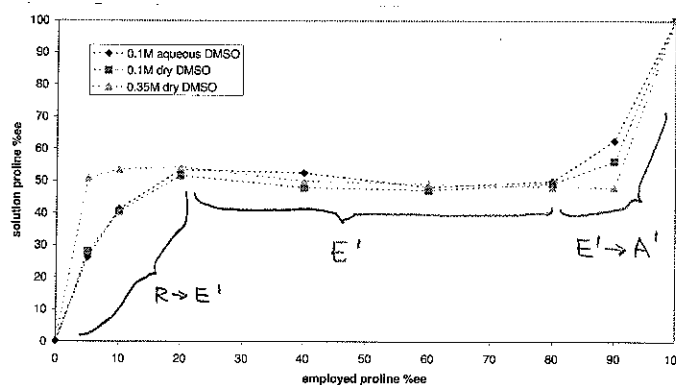


Figure 2 | Ternary phase diagram of D-proline, L-proline and DMSO at 25°C. The main figure expands the area above the dashed line in the inset (not to scale). Saturated solutions exist along the line A'E'R and AER. E and E' represent the eutectic mixture composition where three phases (solid enantiopure proline, solid racemic compound, and liquid phase) exist in equilibrium.



Supplementary Figure 2: Equilibrium solution enantiomeric excess of proline in dry or aqueous (0.35M water) DMSO, taken for samples of varying enantiomeric composition and different total concentrations of proline (Constructed from data in Supplementary Table 1).

→ This chart represents [dissolved Proline] at various ee.

- proline with moderate ee  $\Rightarrow$  E' (eutectic point)  $\Rightarrow$  dissolved proline's ee is ee<sub>eut</sub> (~const.) 共融晶点
- proline with very low ee  $\Rightarrow$  R  $\rightarrow$  E' ([major enantiomer] is too low to establish its solid phase.)
- proline with very high ee  $\Rightarrow$  E'  $\rightarrow$  A' ([minor enantiomer] is too low to form racemic solid.)

\* In the proline-catalysed aldol reaction, the ee of product is linear with the ee of dissolved proline.

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

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

Angew. Chem. Int. Ed. 45, 7982 (2006)

• Although they could explain the NLE of proline-mediated aldol reaction, the original Kagan's observation of (-)-NLE is still unsolved.

↓ to explain....

(new concept): "kinetic conglomerate" phase

This concept explain the original observation along with the one-proline reaction mechanism.

■ the phase behavior of proline under the non-equilibrium conditions

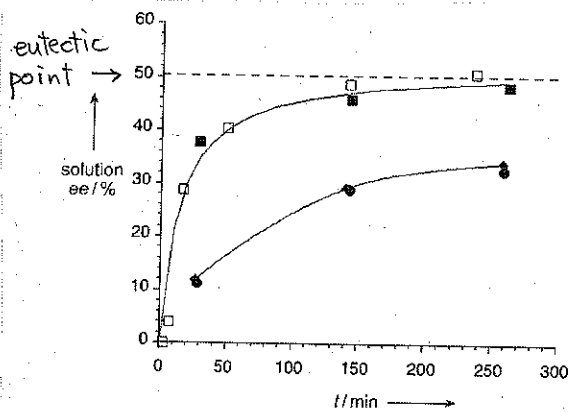
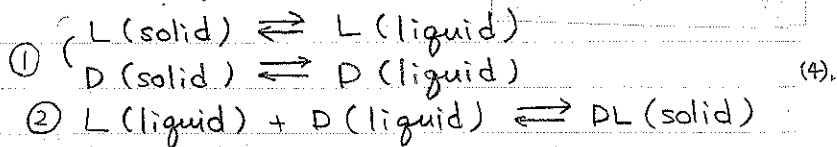


Figure 1. Solution ee values as a function of time for physical mixtures of pure D- and pure L-proline in DMSO at 25°C at different overall proline ee values. Total proline concentration: 12 mg mL<sup>-1</sup>, unless noted otherwise. Filled squares (■): 20% ee; open squares (□): 19% ee, 40 mg mL<sup>-1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

- The solution ee value for scalemic proline is near zero just after addition of proline.
- As time goes, the solution ee rises up to eutectic point.

((reason))



① First, L-Pro (solid) and D-Pro (solid) gradually dissolved. ⇒ Low ee in solution. (like conglomerate's behaviour).

② L-Pro (liq) and D-Pro (liq.) became the solid DL racemate

⇒ solid-solution equilibrium

⇒ Ee<sub>solution</sub> = eutectic point.

solid; DL racemate

L (major enantiomer)

solution; D, L (eutectic composition)

\* Until the solid proline arrive at the solid-solution equilibrium, the product ee may be lower than expected based on total proline ee.

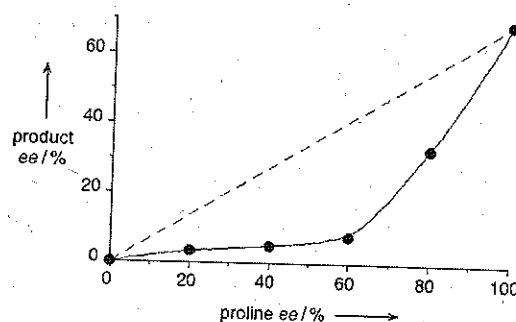
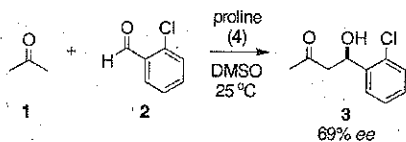


Figure 2. Product ee values versus overall proline ee for the aldol reaction of Scheme 1 carried out in DMSO at 25°C using 40 mg proline per mL of DMSO. Reaction time: 30–45 min; conversion was greater than 98% in all cases. The dashed line represents the expected linear relationship.

• In fact, (-)-NLE was observed.  
⇒ first explanation of the origin of the Kagan's original (-)-NLE.

• The sensitivity of solution ee to mixing time and water causes observed differences in reactions carried out under seemingly same conditions.



\* These phenomenon are observed even in other commonly used ligands.

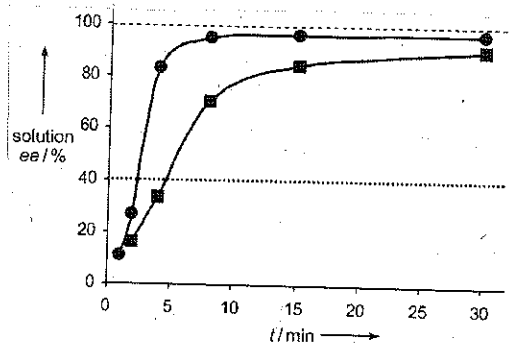
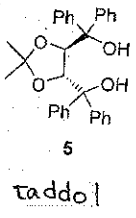


Figure 3. Solution ee values versus time for dissolution of Taddol 5 in hexane (1.76 wt%) at 21 °C (●) and 0 °C (■). Overall ee for Taddol: 40% (.....); eutectic ee for Taddol: 99% (-----).

- Taddol 5 exhibited high eutectic ee value (>99%).
- For 40% ee Taddol mixture, solution ee values are expanded from racemic to almost enantiopure.
  - ⇒ (+)-NLE
  - ⇒ (-)-NLE

\* NLE in mixed-phase systems could occur according to

- ① equilibrium
- ② kinetic behavior (like Kagan's  $ML_2$  model)

### 3. Investigating the Evolution of Biomolecular Homochirality

#### Thermodynamic control of asymmetric amplification in amino acid catalysis

Martin Klussmann<sup>1</sup>, Hiroshi Iwamura<sup>1†</sup>, Suju P. Mathew<sup>1</sup>, David H. Wells Jr<sup>1†</sup>, Urvish Pandya<sup>1</sup>, Alan Armstrong<sup>1</sup> & Donna G. Blackmond<sup>1,2</sup>

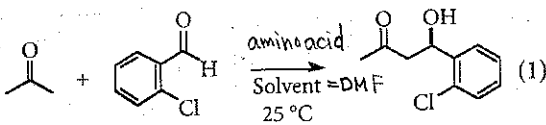
Nature 441, 621 (2006)

- They investigated not only the phase behaviour of proline but also that of other natural amino acids.

Table 1 | Solution enantiomeric excess at the eutectic point in water at 25 °C for selected amino acids

Amino acid	ee of solution at eutectic (%)	Amino acid	ee of solution at eutectic (%)
Threonine	0	Methionine	85
Valine	46	Leucine	87
Alanine	60	Histidine	93
Phenylalanine	83	Serine	>99

- Threonine, arginine, which form conglomerates exhibit 0% ee.
- Serine; ee<sub>eutectic</sub> > 99% ee enantiopure solution from a nearly racemic sample under solid-liquid equilibrium.



\* They also conducted the reaction with some amino acids of various ee.

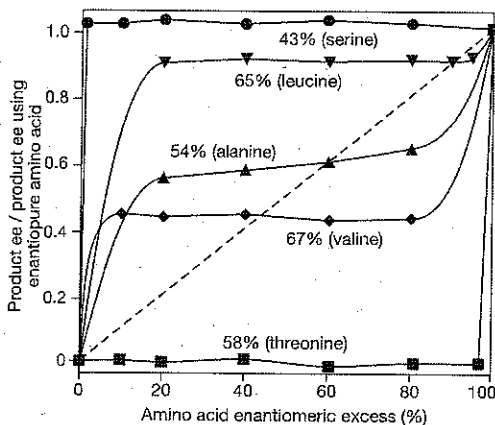


Figure 3 | Nonlinear effects in an amino-acid mediated aldol reaction. Product enantiomeric excess expressed as a fraction of that obtained using enantiopure amino acid versus amino acid enantiomeric excess in the aldol reaction of equation (1) carried out in *N,N*-dimethylformamide (DMF) at ambient temperature using serine (circles), leucine (down triangles), alanine (uptriangles), valine (diamonds), and threonine (squares). Percentage product ee values found for the enantiopure catalysts are given.

• Predictable of ee<sub>prod</sub> from ee<sub>eutectic</sub>.  
 $ee_{prod} \propto ee_{eutectic}$   
 (not ee<sub>cat</sub>)



solid-solution phase behaviour

+

amino acid catalysis

||

efficient and robust mechanism for asymmetric amplification.

• One of examples of the synthesis of sugars catalysed by amino acids

## Prebiotic Amino Acids as Asymmetric Catalysts

Sandra Pizzarello<sup>1</sup> and Arthur L. Weber<sup>2</sup>

Science 303, 1151 (2004)

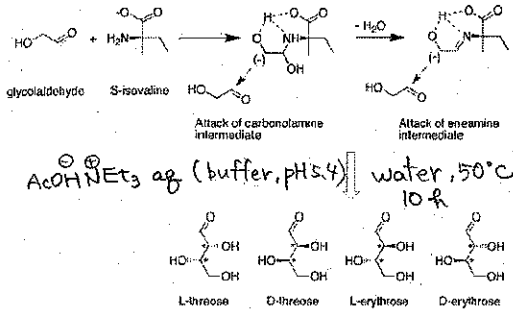
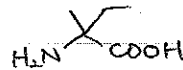


Table S1. Percent D-enantiomeric excess (ee) of tetrose sugars synthesized from glyceraldehyde in the presence of amino acid catalysis.

Catalyst (ee%)	D-Threose ee% (n)	D-Erythrose ee% (n)
DL-Ala <sup>3</sup>	0.5 ± 0.7 (13)	0.3 ± 1.3 (8)
L-Ala (100)	6.9 ± 0.4 (14)	-5.4 ± 0.6 (10)
D-Ala* (100)	-7.1 ± 0.7 (11)	4.3 ± 0.9 (12)
S-Iva <sup>4</sup> (100)	10.6 ± 0.3 (14)	-4.8 ± 0.6 (11)
R-Iva (100)	-10.7 ± 1.2 (11)	4.8 ± 0.9 (8)
R-Iva (75)	-7.9 ± 0.2 (12)	4.0 ± 0.6 (6)
R-Iva (50)	-6.1 ± 0.2 (9)	3.9 ± 1.3 (5)
R-Iva (25)	-3.5 ± 0.3 (7)	0.2 ± 1.3 (5)
R-Iva (10)	-1.4 ± 0.5 (11)	0.8 ± 0.7 (8)
R-Iva (5)	-0.7 ± 0.3 (11)	0.1 ± 0.5 (7)
L-Pro <sup>5</sup> (100)	None synthesized	None synthesized

(n) = number of statistical sample data. <sup>3</sup>Alanine. <sup>4</sup>Isovaline. <sup>5</sup>Proline.  
\* Reaction time three hours.



isovaline

Proline didn't catalyze the reaction.

Isovaline is the most abundant chiral amino acid in meteorites.

\* Amino acids have been implicated in prebiotic catalysis.

## Rationalization and Prediction of Solution Enantiomeric Excess in Ternary Phase Systems\*\*

Martin Klussmann,\* Andrew J. P. White, Alan Armstrong, and Donna G. Blackmond\*

Angew. Chem. Int. Ed 45, 7985 (2006)

\* They developed means of predicting eutectic composition.

$$ee^{eut} = \frac{1 - \frac{\alpha^2}{4}}{1 + \frac{\alpha^2}{4}} \cdot 100\%; \quad \alpha = \frac{[rac]}{[ep]}$$

Table 1: Solubility ratio ( $\alpha$ ) and eutectic ee values of selected amino acids and chiral ligands 1-4.<sup>[a]</sup>

Entry	Compound	Symbol <sup>[a]</sup>	Solvent	[rac] <sup>[d]</sup>	[ep] <sup>[d]</sup>	$\alpha$ <sup>[d]</sup>	[X] <sub>eut</sub> <sup>[e]</sup>	calcd [X] <sub>eut</sub> <sup>[e]</sup>	ee <sub>eut</sub> <sup>[f]</sup> [%]	calcd ee <sub>eut</sub> <sup>[g]</sup> [%]
1	alanine	♦	water	34.11	33.39	1.021	n.d.	42.10	60.4 <sup>[h]</sup>	58.6
2	histidine	♦	water	1.78	4.66	0.383	4.79	4.83	93.7 <sup>[h]</sup>	92.9
3	isoleucine	♦	water	5.38	4.66	1.155	6.15	6.21	51.8	50.0
4	leucine	♦	water	1.36	3.19	0.426	3.31	3.33	87.9 <sup>[h]</sup>	91.3
5	methionine	+	water	3.88	7.33	0.529	7.72	7.85	85.3 <sup>[h]</sup>	86.9
6 <sup>[i]</sup>	methionine	+	water	8.26	11.02	0.750	12.10	12.57	78.8	75.3
7	phenylalanine	♦	water	1.56	2.97	0.525	3.22	3.18	83.2 <sup>[h]</sup>	87.1
8	proline	♦	DMSO	1.33	1.15	1.155	1.73	1.53	49.6 <sup>[h]</sup>	50.0
9	proline	♦	CHCl <sub>3</sub>	0.001	0.51	0.002	0.36	0.51	99.2	100.0
10	proline	♦	CHCl <sub>3</sub> /MeOH <sup>[j]</sup>	1.21	31.49	0.038	36.07	31.50	96.4	99.9
11	proline	♦	CHCl <sub>3</sub> /MeOH <sup>[j]</sup>	7.92	63.84	0.124	67.90	64.08	93.6	99.2
12	serine	♦	water	8.64	63.74	0.130	64.81	64.03	> 99.0 <sup>[h]</sup>	99.1
13	valine	x	water	11.27	9.15	1.231	n.d.	12.62	46.7 <sup>[h]</sup>	45.1
14 <sup>[k]</sup>	valine	x	water	16.52	12.49	1.323	16.95	17.95	36.8	39.1
15	binol (1)	▲	toluene	2.29	5.66	0.405	5.95	5.89	91.0	92.1
16	binap (2)	●	toluene	0.29	5.95	0.048	5.91	5.95	99.9	99.9
17	taddol (3)	■	toluene	0.25	28.63	0.009	28.89	28.63	99.8	100.0
18	salen (4)	▼	hexane	7.03	3.42	2.057	6.97	7.03	0.0	-2.8

[a] Data measured at 25 °C unless noted otherwise. Concentrations in 10<sup>-3</sup> molar fraction. [b] See Figure 1. [c] According to Equation (1). [d] According to Equation (7). [e] According to Equation (8). [f] From Ref. [4]. [g] At 60 °C. [h] 1.0 M MeOH. [i] 2.0 M MeOH. n.d. = not determined.

• High eutectic ee

$$\alpha \ll 2; [rac] < [ep]$$

less soluble

• Possible to predict the eutectic point only by examining the concentration at racemic compound and enantiopure compound.

\* Proline was found to exhibit very different eutectic ee values in different solvents.

- DMSO → 50% ee  
- CHCl<sub>3</sub> → 99% ee

What is the reason?

• They found the solid racemate of proline in CHCl<sub>3</sub>/MeOH exhibits a novel structure.

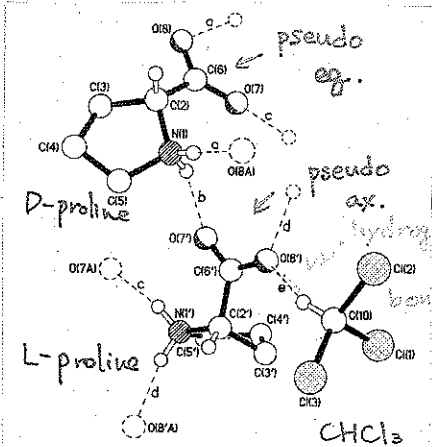


Figure 2. The asymmetric unit of D-proline/chloroform showing the hydrogen-bonding interactions between the two independent proline molecules and the included chloroform solvent molecule (ellipsoids shown at 50% probability). The hydrogen-bonding geometries (X—O [Å], H—O [Å], X—H—O [°]) are a) 2.708(2), 1.81, 178; b) 2.826(3), 2.01, 150; c) 2.809(2), 2.00, 148; d) 2.761(2), 1.88, 165; e) 3.098(3), 2.22, 152.

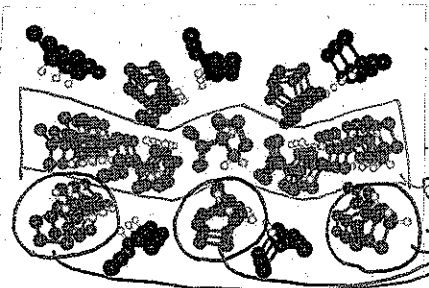


Figure 3. Structure of racemic proline crystallized from a CHCl<sub>3</sub>/CH<sub>3</sub>OH mixture, with one CHCl<sub>3</sub> molecule (black) incorporated per pair of proline molecules. The blue proline molecules correspond to one enantiomer, while the magenta proline molecules correspond to the opposite enantiomer. These conformations switch in adjacent sheets.

• proline → zwitterionic form  
extensive hydrogen-bonding network  
including CHCl<sub>3</sub>: (Fig 2)

One enantiomer  
the other enantiomer

• Fig 3  
axial ) opposite  
equatorial ) enantiomer  
these conformations switch  
in the adjacent centrosymmetrically related sheets.

Extensive hydrogen-bond network  
⇒ the significant decrease in the solubility of proline.

CHCl<sub>3</sub> found in seawater and in gases vent from solfataric volcanoes.

= existed in a prebiotic world(?)

As additive, ↓

other small molecular existing in a prebiotic era might make the eutectic point higher.

(硫氣孔)

Table 1. Soluble Organic Compounds in the Murchison Meteorite<sup>a</sup>

Class of Compounds	ppm	n <sup>b</sup>
aliphatic hydrocarbons	>85	140
aromatic hydrocarbons	15–28	57
polar hydrocarbons	<120	10 <sup>c</sup>
carboxylic acids	>300	48 <sup>c</sup>
amino acids	60	75 <sup>c</sup>
imino acids <sup>d</sup>	nd <sup>b</sup>	10
hydroxy acids	15	7
dicarboxylic acids	>30	17 <sup>c</sup>
dicarboximides	>50	2
pyridine carboxylic acids	>7	7
sulfonic acids	67	4
phosphonic acids	2	4
N-heterocycles	7	31
amides	13	20 <sup>c</sup>
amides	nd <sup>b</sup>	27
polyols	30	19

<sup>a</sup> Number of compounds identified with reference standards or with unequivocal matching of compound and library mass spectra. <sup>b</sup> Not determined. <sup>c</sup> Groups where larger number of compounds are recognized by their mass spectra in the absence of standards or library references.

**Emergence of Solution-Phase Homochirality via Crystal Engineering of Amino Acids**

Martin Klussmann,<sup>1,2</sup> Toshiko Izumi,<sup>3</sup> Andrew J. P. White,<sup>1</sup> Alan Arnström,<sup>1</sup> and Donna G. Blackmond<sup>1,1,5</sup>

JACS, 129, 7657 (2007)

Acc. Chem. Res.

39, 4, 231 (2006)

• Several small, achiral molecules of potential prebiotic relevance were examined as additive.

- urea, thiourea, heterocyclic bases (cytosine, guanine, thymine, uracil) ... no effect
- dicarboxylic acids

Table 1. Solution ee at the Eutectic for Amino Acids in Aqueous Solution in the Presence of Carboxylic Acid Additives<sup>a</sup>

amino acid	% ee at the eutectic						
	thr	val	ile	met	phe	leu	his
none	0	47	52	85	88	88	94
oxalic acid	56	66	82	43	23	98	63
malonic acid	11	50	51	69	86	91	91
succinic acid	2	93	52	42	79	89	58
maleic acid	34	69	71	60	7	51	32
fumaric acid	24	99	59	72	99	92	98
adipic acid	0	48	51	68	94	92	77

<sup>a</sup> Values for eutectic ee for amino acids in the absence of additives were reported in refs 1 and 6. The value for phe was reported to be 83% ee in those studies; further detailed studies gave the value of 88% ee shown here, in agreement with ref 10.

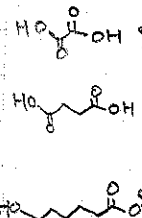
• eutectic ee can change significantly.

• threonine ; conglomerate (without acid, ee eutectic = 0)

→ up to 50% ee.

• valine ; rise from 47% ee to 99% ee!

\* solvate formation influenced solubility and eutectic composition.



additive leg. in water

\* solidocrystals in a 1:1 of racemate phenylalanine to fumaric acid

11.

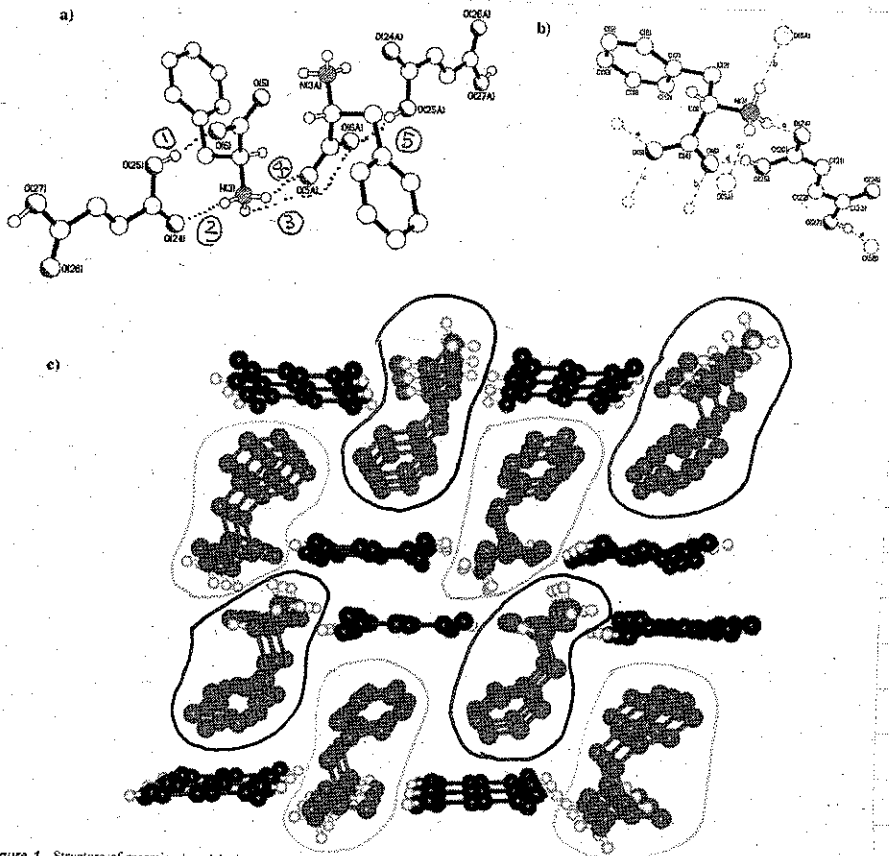


Figure 1. Structure of racemic phenylalanine co-crystallized in a 1:1 ratio with fumaric acid: (a) the contents of the unit cell, (b) the asymmetric unit showing the five unique hydrogen bonds; (c) extended structure showing opposite enantiomers in blue and magenta and fumaric acid in black (see Supporting Information).

- Five hydrogen bonding
  - 3 NH<sub>3</sub><sup>+</sup> in Phe  $\xrightarrow{2}$  COO<sup>-</sup> in Phe  
 $\xrightarrow{1}$  COOH in acid
  - 2 COOH in acid  $\rightarrow$  COO<sup>-</sup> in Phe
- ↓
- form two-molecule-thick sheets.
  - ⇒ more stable(??)

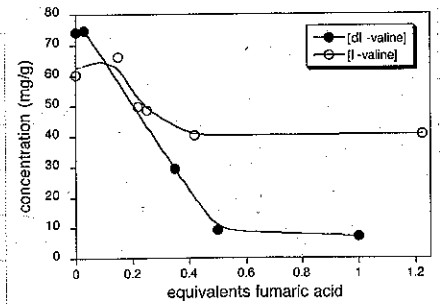


Figure 2. Solution concentration of valine as a function of the number of equivalents of fumaric acid added: (O) L-valine; (●) dl-valine.

\* Concept of the solution enantioenrichment by additives

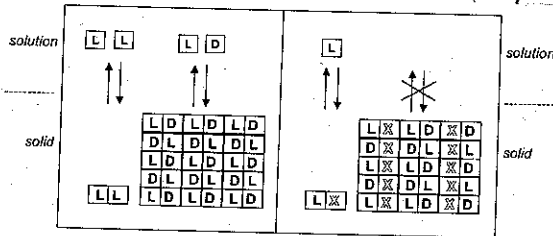


Figure 3. Pictorial representation of the solution enantioenrichment caused by an additive (shown as an open X) by incorporation into the structure of solid enantiopure and racemic compounds (enantiomers shown as L and D). The left picture shows a nearly racemic mixture of a compound exhibiting a eutectic ee of ca. 50% ee. The right picture shows that if the additive suppresses the solubility of the racemic compound more than that of the enantiopure compound, the solution ee at the eutectic will be enhanced.

• the solubility of racemate is strongly suppressed by acid.

\* the application to chiral separations should be plausible.  
 dropping the racemate  
 (=the opposite to usual enantioenrichment)

- In this system, which could occur in a prebiotic world, not only almost enantiopure serine solution but also valine, phenylalanine solution could be available.

→ Such solutions might serve as efficient asymmetric catalysts or as homochiral building blocks for construction of the complex molecules.

Introduction of the Evolution of Biomolecular Homochirality

1874 van't Hoff postulated the existence of chiral molecules

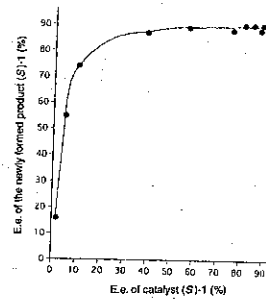
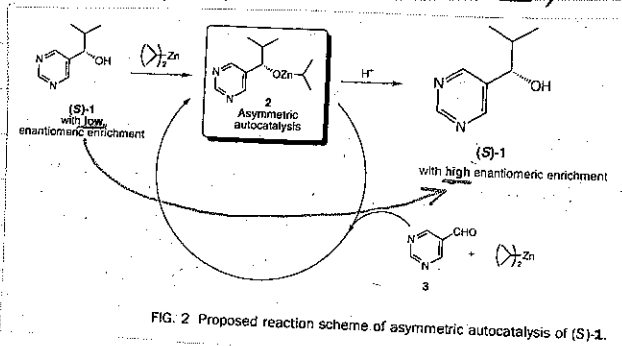
- Pasteur salts of tartaric acid as mirror image crystals.
  - In living organisms, chiral molecules existed exclusively in one enantiomeric form.
- ↓ — molecular recognition etc...

How was this exclusive chirality produced in near-racemic environment?

\* A representative model — Autocatalysis

1953 C. Frank proposed the concept of autocatalytic systems.

1995 Soai et al. Nature 378, 767 (1995) the reactions where a compound catalyzes its own formation



$$ee_{cat} < ee_{prod}$$

$$2 \times ee_{cat} < ee_{prod}$$

$$ee_{cat} < ee_{prod}$$

- This discovery provided proof of concept for Frank model.
- mechanistic study

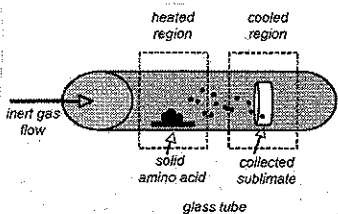
Blackmond, JACS 123, 10103 (2001)  
Brown et al. PNAS 101, 5782 (2004)

\* However, this dialkylzinc chemistry is unlikely to occur in an aqueous prebiotic environment.

Appendix 2

Cooks and Feringa independently reported chiral amplification of amino acid by the sublimation (昇華)

Chem. Commun 1071 (2007), Chem. Commun. 2578 (2007) See also Chem. World 2007 (March) 30



3% ee L-Ser  $\xrightarrow{190^\circ\text{C}, 2\text{h}}$  75% ee L-Ser  
9% ee L-Leu  $\xrightarrow[0.005\text{ mmHg}]{120^\circ\text{C}, 72\text{h}}$  89% ee L-Leu

- Blackmond suggested a model that combines the sublimation and solution-solid phase phenomena.
- in space  $\rightarrow$  sublimation
- in aqueous pools  $\rightarrow$  solution-solid equilibrium (earth) through cycles of rainfall and evaporation.



Donna G. Blackmond

Fig 4 Schematic of sublimation experiment

Chem. Commun. 3990 (2007)  
Blackmond et al.