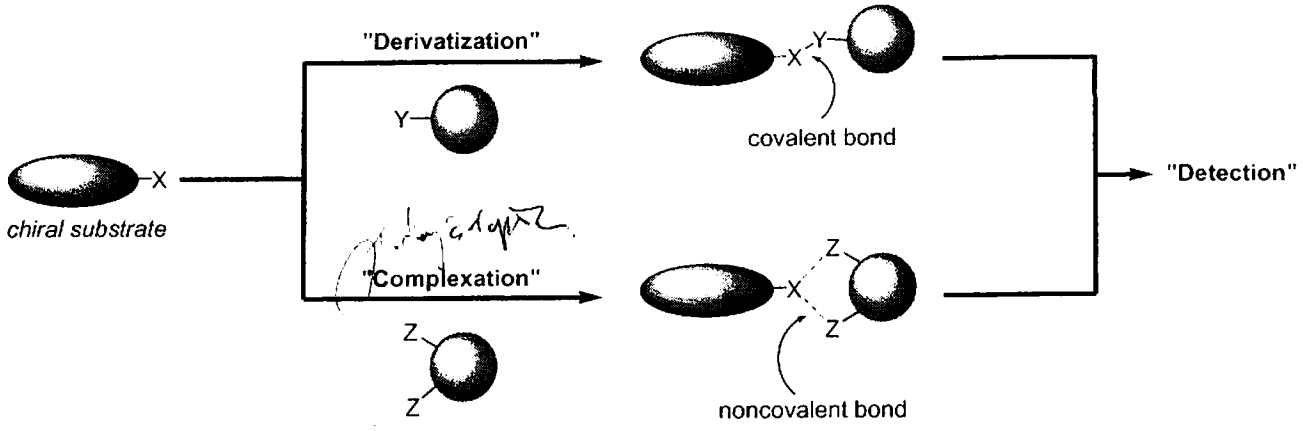
literature seminar
2006. Nov. 22nd

Yamaguchi A. (M2)

Chiral Recognition by Artificial Molecules



* derivatizations sometimes need troublesome operation
→ complexation by noncovalent interaction is much easier

* many events in living systems take place via molecular recognition process, especially "chiral recognition"
→ comprehension of phenomena in biological system?

contents

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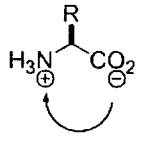
1. enantioselective liquid-liquid extraction and transport of amino acids

 # resolution of racemic amino acids by simple liquid-liquid extraction

de Mendoza et al.
J. Am. Chem. Soc. **1992**, *114*, 1511.

difficulty with "unprotected" amino acids

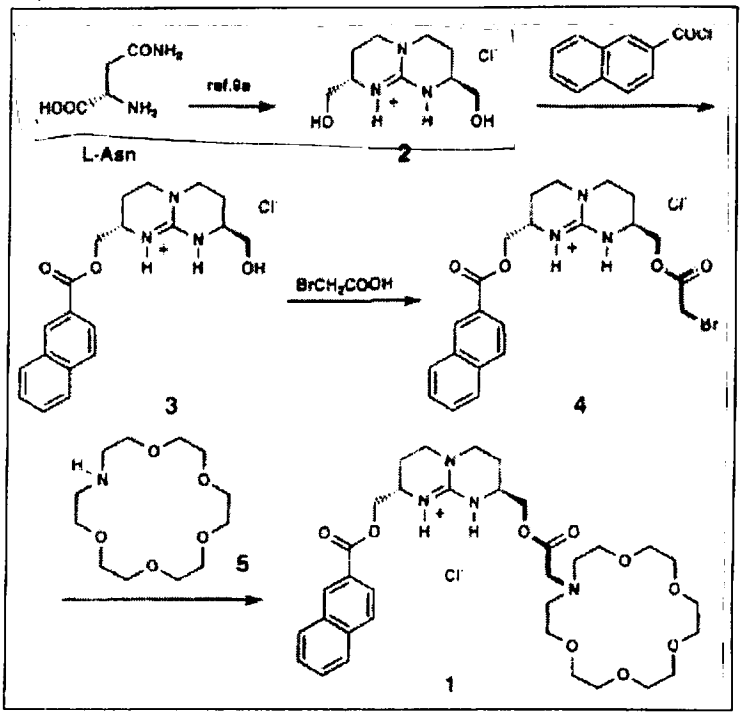


intramolecular interaction due to the vicinity

⇩

binding forces of complementary groups of receptor are made less effective

* synthesis of the receptor **1**



+ guanidinium for binding carboxylate anion

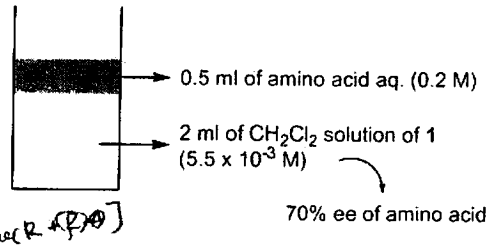
+ crown ether for binding ammonium cation

+ preventing the receptor from internal collapse

+ chiral structure for enantioselective recognition

+ **1** is scarcely soluble in water, despite its ionic structure

* liquid-liquid extraction experiment



[R-D] / [R-D + R-D]

+ the extraction efficiencies into the organic phase were ca. 40% for L-Trp and L-Phe

+ L-Val was not extracted effectively

+ extracts of racemic samples of Phe or Trp was converted to dipeptide with L-Leu
→ L-Leu-D-Phe or L-Leu-D-Trp was less than 2%,

+ however the ee of the extracts were determined to be 70% directly by chiral HPLC later

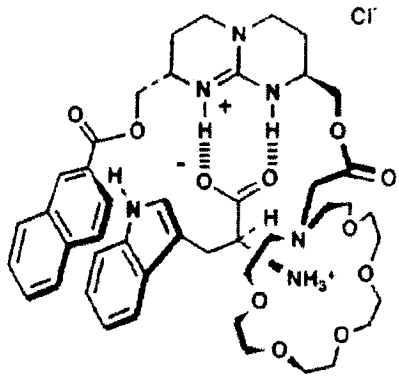


Figure 1. Proposed structure for a 1:1 complex between (*S*,*S*)-1 and L-tryptophan.

speculation.

a practical approach to the resolution of racemic N-Bn amino acids

Gennari. Piarulli et al.
Angew. Chem. Int. Ed. **2006**, *45*, 2449.

* drawbacks to be solved → low efficiency and modest selectivity

* employed substrates were "*N*-Bn" α-amino acids → might be somewhat easier than free amino acids (see previous example)

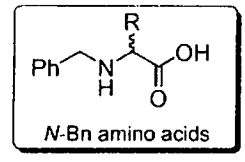


Table 1: Extraction of racemic *N*-Bn-Ala using chiral salen–cobalt(II) and –cobalt(III) complexes at 10 °C.

Entry		Host complex	Product	Equiv extracted	*ee* [%][a]
1	Co^{II}	(*R*,*R*)-[Co^{II}(**1**)]	[Co^{III}(**1**)(*N*-Bn-Ala)]	0.99[b]	55.8[c]
2	Co^{II}	(*R*,*R*)-[Co^{II}(**2**)]	[Co^{III}(**2**)(*N*-Bn-Ala)]	0.96[b]	38.9
3	Co^{II}	(*R*,*R*)-[Co^{II}(**3**)]		0[b]	
4	Co^{III}	(*R*,*R*)-[Co^{III}(**1**)(OAc)]	[Co^{III}(**1**)(*N*-Bn-Ala)]	0.92	54.8
5	Co^{III}	(*R*,*R*)-[Co^{III}(**2**)(OAc)]	[Co^{III}(**2**)(*N*-Bn-Ala)]	0.99[d]	53.6
6	Co^{III}	(*R*,*R*)-[Co^{III}(**3**)(OAc)]	[Co^{III}(**3**)(*N*-Bn-Ala)]	**0.99**	**93.0**
7	Co^{III}	(*R*,*R*)-[Co^{III}(**3**)(OAc)][e]	[Co^{III}(**3**)(*N*-Bn-Ala)]	**0.98**	**93.0**
8	Co^{III}	(*R*,*R*)-[Co^{III}(**3**)(OTf)]	[Co^{III}(**3**)(*N*-Bn-Ala)]	0.92	85.5
9	Co^{III}	(*R*,*R*)-[Co^{III}(**3**)(PF_6)]	[Co^{III}(**3**)(*N*-Bn-Ala)]	0.92	87.8

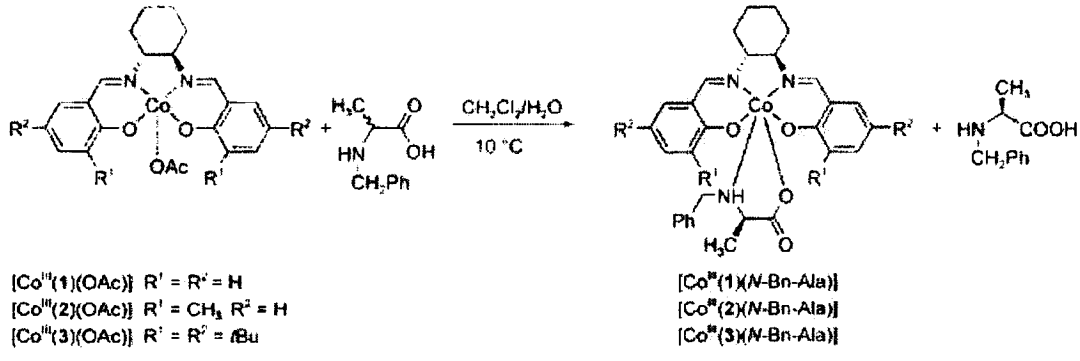
[a] Determined on uncomplexed (*S*)-*N*-Bn-Ala by chiral HPLC analysis of the aqueous phase (see the Supporting Information). [b] Extractions were run at room temperature. [c] For a comment, see Ref. [13]. [d] Extraction time of 48 h was necessary, compared to 24 h in all other cases. [e] Second cycle: (*R*,*R*)-[Co^{III}(**3**)(OAc)] was obtained from [Co^{III}(**3**)·(*N*-Bn-Ala)] after reductive cleavage and reoxidation (see text and the

+ quantitatively extracted via air oxidation of Co

+ no oxidation by air
→ facile reduction of Co^{III}(3) to Co^{II}(3) is possible?

+ high ee was achieved at 10 °C

+ second cycle (after reductive cleavage of salen complex and reoxidation with AcOH/air)



[Co^{III}(**1**)(OAc)] R' = R'' = H
[Co^{III}(**2**)(OAc)] R' = CH_3 R'' = H
[Co^{III}(**3**)(OAc)] R' = R'' = *t*Bu

[Co^{III}(**1**)(*N*-Bn-Ala)]
[Co^{III}(**2**)(*N*-Bn-Ala)]
[Co^{III}(**3**)(*N*-Bn-Ala)]

Scheme 2. Resolution of a racemic mixture of *N*-benzylalanine by liquid–liquid extraction using salen–cobalt(III) complexes.

Method A	simple extraction
Method B	recovery of uncomplexed amino acid by filtration
Method C	without water, recovery of uncomplexed amino acid by filtration

+ water-soluble *N*-Bn-Thr was extracted smoothly

+ *N*-Bn-Val and Leu are essentially insoluble in neutral water and CH_2Cl_2 due to their lipophilicity, however, their extraction proceeded selectively

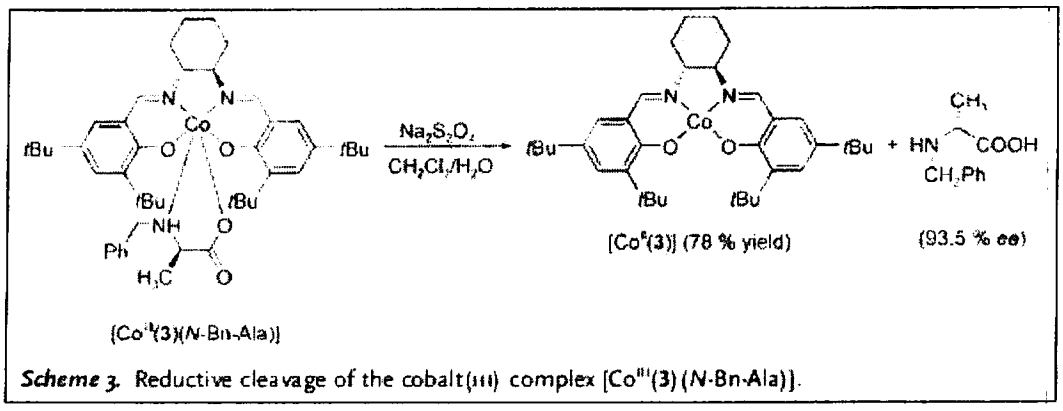
+ method C represents a more practical procedure for less hydrophilic amino acids

+ treatment with reductant is needed to release the bound amino acids (Scheme 3), this is one of the drawbacks though sodium dithionite is cheap

Table 2: Resolution of racemic *N*-Bn-amino acids using (*R,R*)-[Co^{III}(3)·(OAc)] at 10 °C.

Entry	Substrate	Meth.[a]	Product	Equiv extracted	*ee* [%][b]
1	*N*-Bn-Thr	A	[Co^{III}(3)(*N*-Bn-Thr)]	0.94	96.3[c]
2	*N*-Bn-Val	A	[Co^{III}(3)(*N*-Bn-Val)]	0.98	90.1
3	*N*-Bn-Leu	A	[Co^{III}(3)(*N*-Bn-Leu)]	0.99	99.0
4	*N*-Bn-Phe	B	[Co^{III}(3)(*N*-Bn-Phe)]	0.99	93.3
5	*N*-Bn-Val	C	[Co^{III}(3)(*N*-Bn-Val)]	0.99	94.2
6	*N*-Bn-Phe	C	[Co^{III}(3)(*N*-Bn-Phe)]	0.98	92.7
7	*N*-Bn-Ala	C	[Co^{III}(3)(*N*-Bn-Ala)]	0.98	16.3
8	*N*-Bn-Ala	C	[Co^{III}(3)(*N*-Bn-Ala)]	0.98[d]	65.8

[a] Method A: biphasic water/dichloromethane extraction; method B: biphasic water/dichloromethane treatment and recovery of the uncomplexed amino acid by filtration; method C: stirring a suspension of the racemic *N*-Bn-amino acid with a solution of (*R,R*)-[Co^{III}(3)(OAc)] in dichloromethane and recovery of the uncomplexed amino acid by filtration. [b] Determined on the uncomplexed (*S*)-*N*-Bn-amino acid by chiral HPLC analysis. [c] Determined by chiral HPLC analysis on (*R*)-*N*-Bn-Thr, following treatment of [Co^{III}(3)(*N*-Bn-Thr)] with aqueous sodium dithionite. [d] Performed at −10 °C; a reaction time of 72 h was necessary, compared to 24 h in all other cases.



Scheme 3. Reductive cleavage of the cobalt(III) complex [Co^{III}(3)(*N*-Bn-Ala)].

enantioselective transport of amino acids across liquid membranes

Gago, de Mendoza et al.
J. Am. Chem. Soc. **2003**, *125*, 8270.

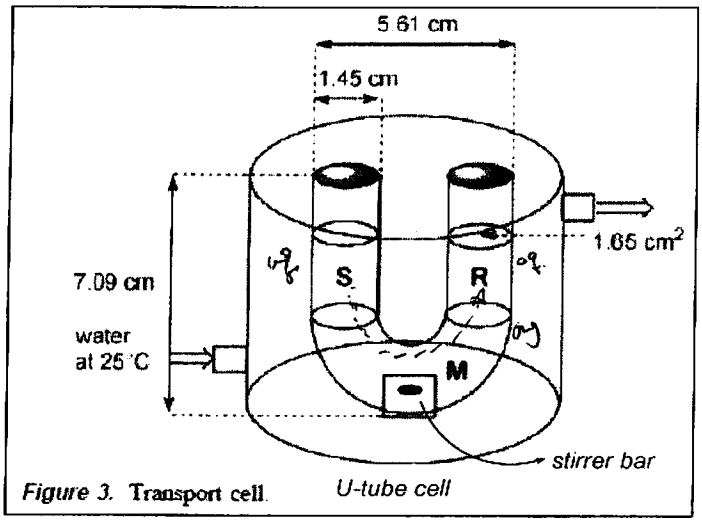
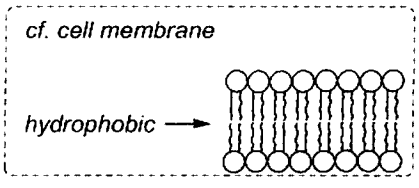


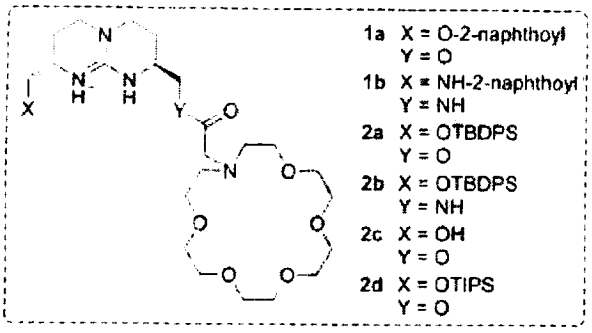
Figure 3. Transport cell.

S = source phase, 3ml of saturated amino acid solution

R = receiving phase, 3ml of deionized water

M = membrane phase, 10 ml of receptor solution (1.5 mM) in dichloromethane or dichloroethane





1a X = O-2-naphthoyl, Y = O
1b X = NH-2-naphthoyl, Y = NH
2a X = OTBDPS, Y = O
2b X = OTBDPS, Y = NH
2c X = OH, Y = O
2d X = OTIPS, Y = O

+ after investigation with many receptors and Trp or Phe, PF_6 salt of **1a** was found to be best

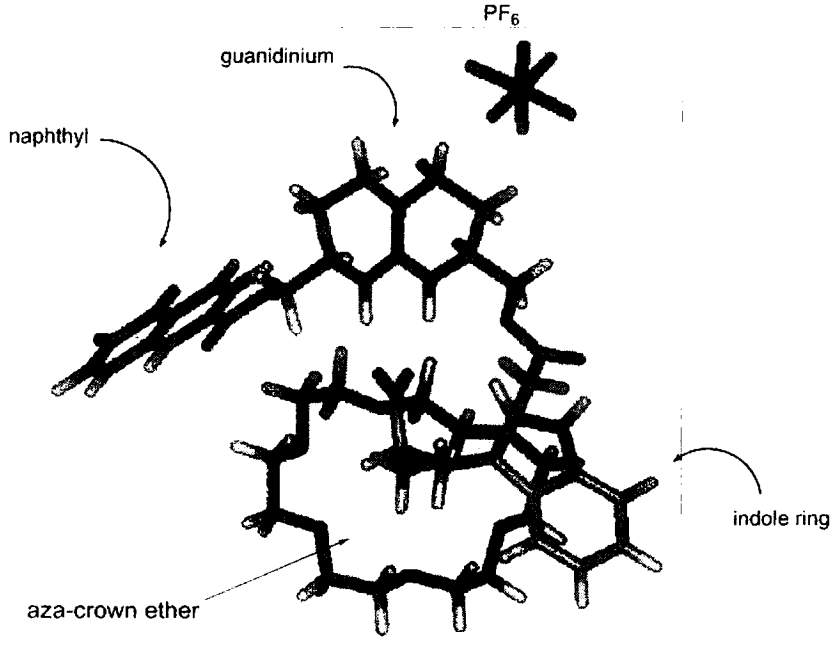
Table 2. Influence of the Concentration of Receptor **1a** on the Transport Results

[1a] (mM)	time (h)	% Trp	% ee
0.125	1.5	1.2	79
	2.0	2.2	73
	3.0	4.0	66
	5.0	7.1	62
	6.5	9.8	60
0.25	1.0	1.4	76
	1.5	2.4	69
	2.0	3.7	66
	3.0	6.7	60
	4.5	9.7	56
0.5	0.5	1.2	59
	1.0	4.3	50
	2.0	9.6	41
	3.0	14.1	38
1.0	0.5	1.7	35
	1.0	5.3	28
	2.0	11.8	20
	3.0	16.8	16

+ enantioselectivity decreases as more amimo acid was transported (enrichment of "wrong" enantiomer in source phase)

+ remarkably, when transport experiments were performed reducing the receptor concentration in the membrane phase, ee of amino acid in receiving phase increased (Trp was used)

[computational calculation of **1a**-L-Trp complex]



+ ammonium group is facing the midpoint center of the aza-crown ether

+ carboxylate is directed to the guanidinium moiety

+ the arm with naphthalene ring seems not to interact with L-Trp

+ surprisingly, **1a**-D-Trp complex is similar to this complex

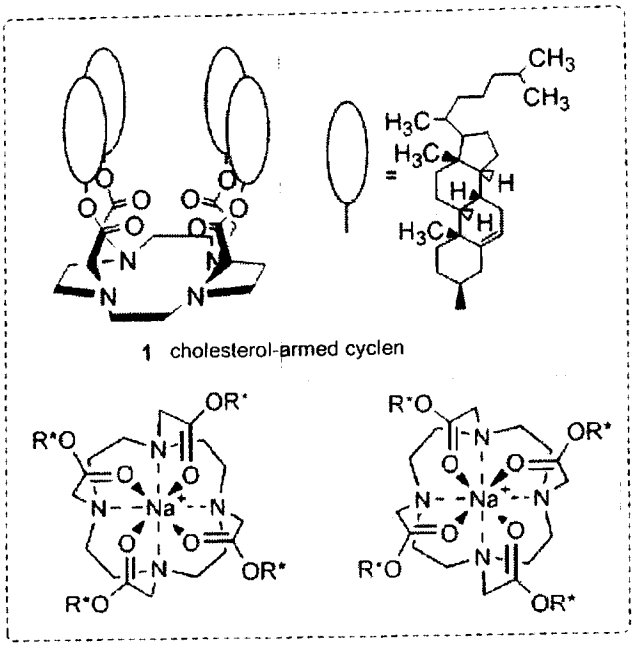
2. mechanical control of enantioselectivity in amino acid recognition

Michinobu, Tsukube, Ariga et al
J. Am. Chem. Soc. **2006**, *128*, 14478

many biological processes occur in cell membrane

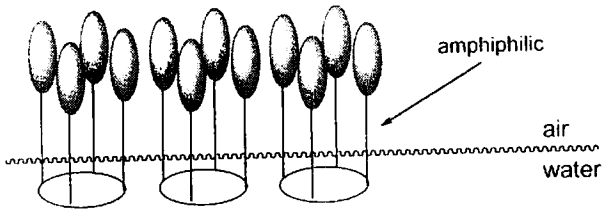
↓

more appropriate medium than *solution* is required for a deeper understanding of molecular recognition phenomena in living systems → "air-water interface constructed with cholesterol-armed cyclen"



1 cholesterol-armed cyclen

air-water interface



+ cyclen **1** forms host monolayer

+ helicity of cyclen is influenced by the chirality of the side arms especially when ordered or aggregated at the supramolecular level

* 1 was originally used for chirality sensing using dansyl amino acids
Tsukube et al. *J. Org. Chem.* **2005**, *70*, 1835.

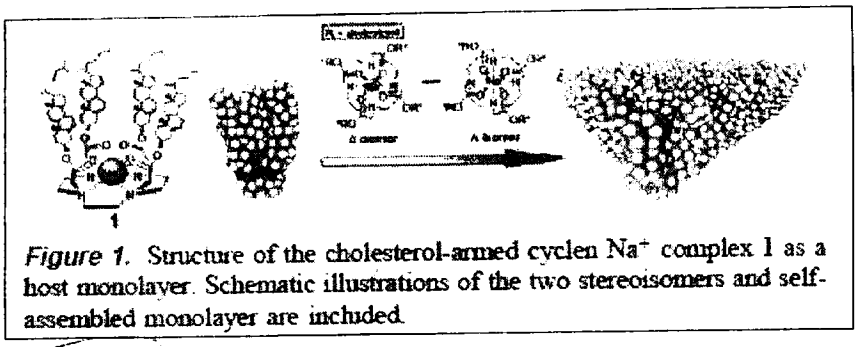
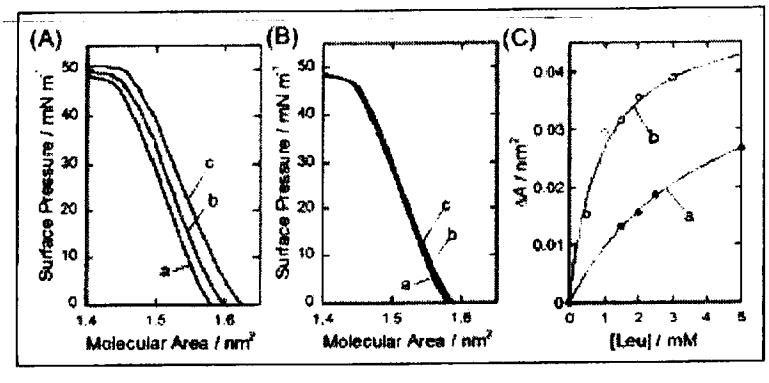


Figure 1. Structure of the cholesterol-armed cyclen Na^+ complex **1** as a host monolayer. Schematic illustrations of the two stereoisomers and self-assembled monolayer are included.

* the state of monolayer can be described with π-A isotherm
等温線

2-dimension
π = surface pressure (N/m)
A = molecular area



(A) a; on pure water
b; on 1.5 mM L-Leu
c; on 1.5 mM D-Leu
→ the isotherms were shifted to larger molecular area with amino acid
⇒ chiral recognition was detected by mechanical compression

(B) a; on pure water
b; on 1.5 mM L-Val
c; on 1.5 mM D-Val
→ insignificant differnce

(C) surface pressure is constant (20 mN m^{-1})
a; L-Leu
b; D-Leu
ΔA represents the difference in the molecular area values between on aqueous leucine and on pure water

L-valine L-leucine

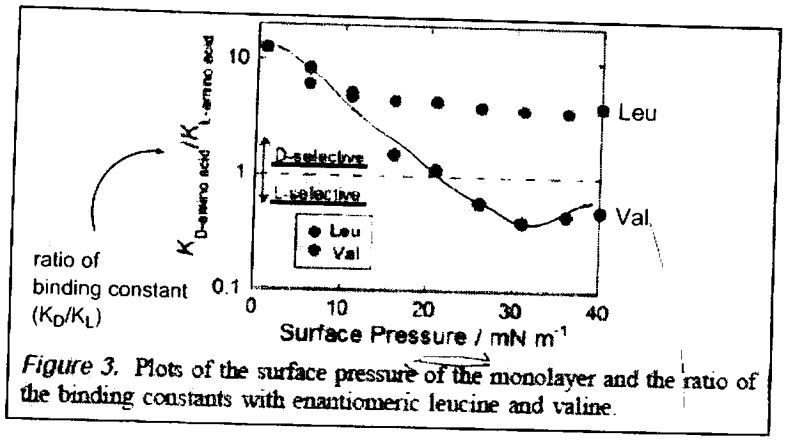


Figure 3. Plots of the surface pressure of the monolayer and the ratio of the binding constants with enantiomeric leucine and valine.

+ even for valine, the binding constant (K) estimated from Langmuir-type equation indicate that chiral descrimination of amino acids is remarkable

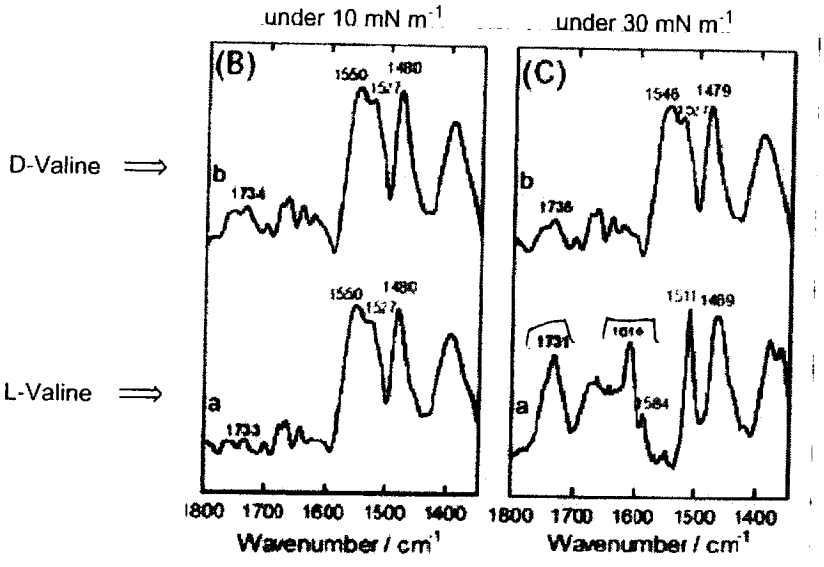
+ the K values of D-Leu are always greater than those of L-Leu

→ monolayers of **1** have a stronger interaction with D-Leu

+ chiral recognition in monolayers of **1** with valine change from D to L upon compression

+ small difference in the structure between Leu and Val can be distinguished by the monolayer

FT-IR spectra of LB films of monolayers



⟹ not significant difference, affinity to monolayer didn't change

⟹ additional peak (1610 and 1731 cm^{-1}) appeared, corresponding to the neutral (not zwitterionic) NH_2 and COOH

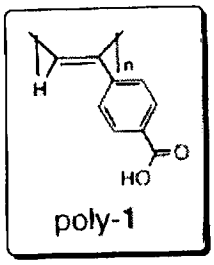
⇩

+ consistent with K values obtained from π-A isotherms

+ when amino acid is incorporated deeply in the films, they seem to exist as neutral form, consistent with Leu's result

3. macromolecular helicity induced by chiral molecules and memory of helicity

Yashima, Okamoto et al.
J. Am. Chem. Soc. **1995**, *117*, 11596.
1997, *119*, 6345.



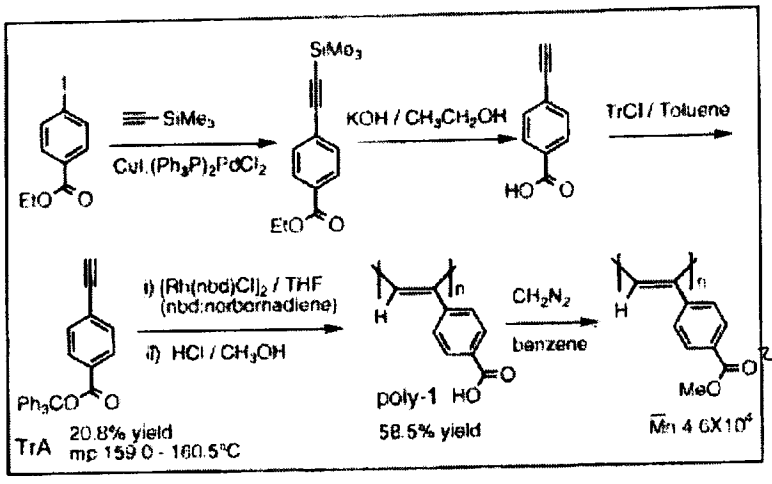
one-handed helix formation upon complexation of poly-**1** and chiral amines or amino alcohols

the complex shows induced CD (ICD) in the UV-visible region

Cotton effect signs of the ICDs can be used as a probe for chirality and stereochemical assignments

CD = circular dichroism
円二色性
correlation between wave length and ellipticity（楕円率）

Scheme 1

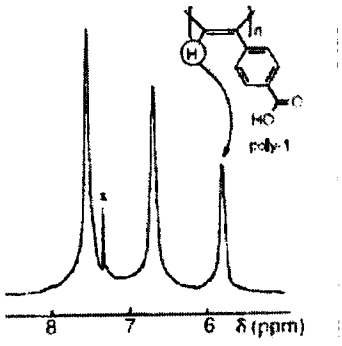


+ molecular weight (*Mn*) of poly-**1** was estimated to be 4.6 x 10^4 by gel permeation chromatography as its methyl ester

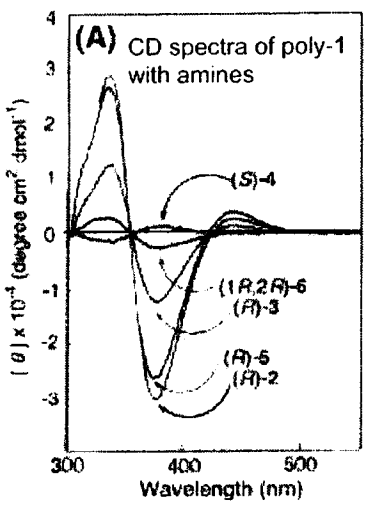
+ poly-**1** was soluble in DMSO, DMF but insoluble in $CHCl_3$, acetone, THF

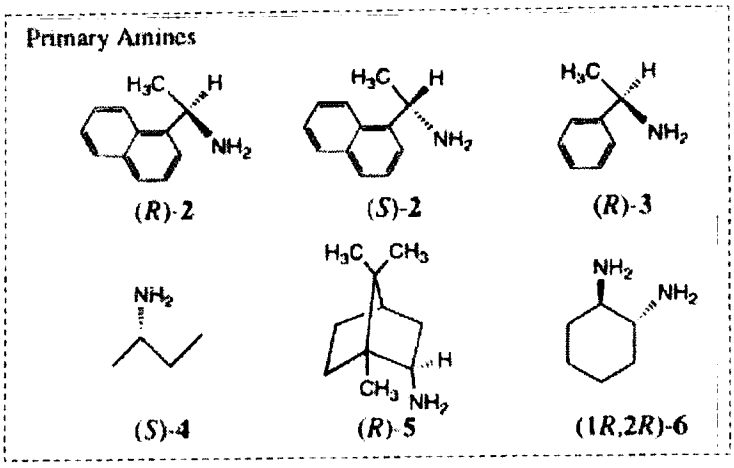
about 100% *cis* ⟶ **stereoregular**

WCl_6-*n*-Bu_4Sn and $MoCl_5$-*n*-Bu_4Sn ⟶ stereoirregular polymer



CD studies on the complexation with chiral amines and amino alcohols





+ the complex showed split-type ICD in the UV-visible region in both solution and film state

+ conjugated polyenes may be regarded as a suitable chromophore

+ the intensity of ICD increased with an increase in the concentration of chiral amine and reached an constant value at [**2**]/[poly-**1**] = 50

+ poly-**1** methyl ester didn't show ICD (acid -base interaction is important)

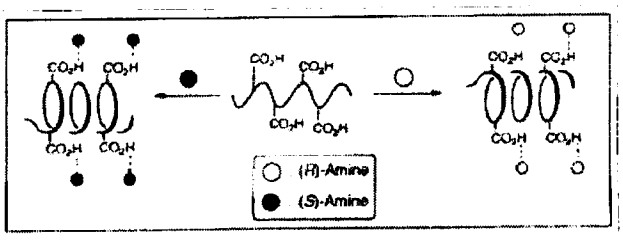
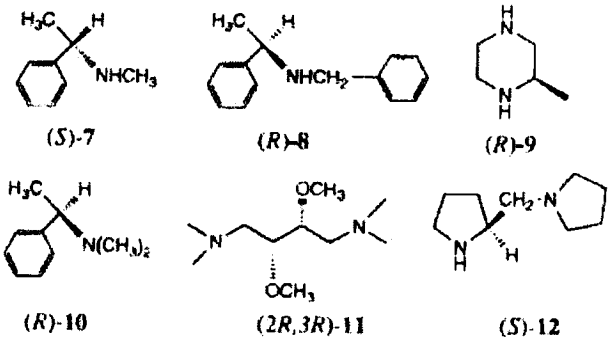


Table 1. Signs of Split Cotton Effects and Molar Ellipticities ([θ]) for Poly-1–Amine Complexes[a]

amine	first Cotton sign	first Cotton [θ] × 10⁻³ (λ)	second Cotton sign	second Cotton [θ] × 10⁻⁴ (λ)	third Cotton sign	third Cotton [θ] × 10⁻⁴ (λ)
(*R*)-2	+	2.47 (447.0)	−	3.06 (375.0)	+	2.91 (334.0)
(*S*)-2	−	2.40 (447.0)	+	2.86 (375.0)	−	2.71 (334.0)
(*R*)-2[b]	+	0.36 (447.0)	−	0.44 (375.5)	+	0.40 (334.0)
(*R*)-2[b,c]	+	1.40 (447.0)	−	1.33 (375.0)	+	0.88 (316.0)
(*R*)-3	+	1.45 (440.0)	−	1.26 (376.0)	+	1.30 (336.0)
(*S*)-4		*d*	+	0.14 (377.5)	−	0.14 (330.0)
(*R*)-5	+	3.94 (443.0)	−	2.68 (372.5)	+	2.70 (334.0)
(*R,R*)-6		*d*	−	0.30 (378.0)	+	0.28 (330.0)
(*S*)-7	+	0.89 (438.5)	−	0.85 (376.0)	+	0.89 (333.5)
(*R*)-8		*d*	−	0.113 (380.0)	+	0.099 (328.0)
(*R*)-9		*d*	−	0.11 (376.0)	+	0.10 (335.0)
(*R*)-10		*ca.* 0		*ca.* 0		*ca.* 0
(*R*)-10[e]		*d*	+	0.096 (376.0)	−	0.053 (333.0)
(*R,R*)-11		*d*	+	0.06 (386.0)	−	0.12 (334.0)
(*S*)-12	+	0.83 (435.0)	−	1.20 (374.0)	+	1.21 (341.0)

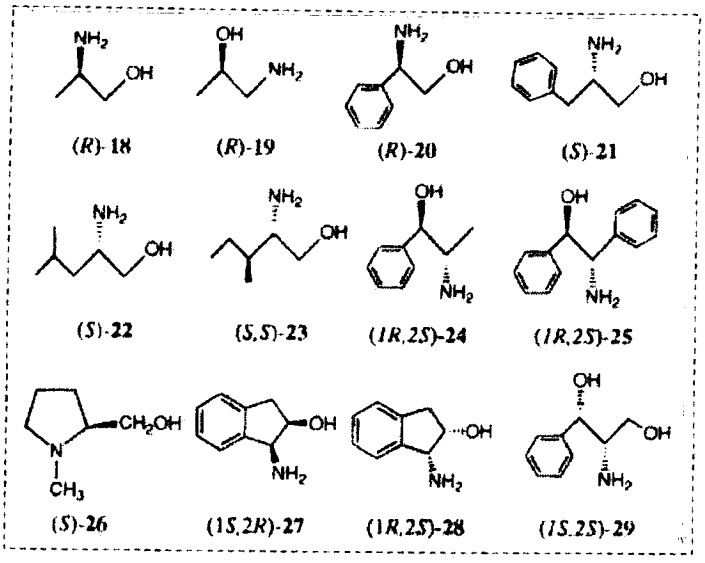
[d] very weak ICD [e] high concentration

Secondary and/or Tertiary Amines



(*S*)-7 (*R*)-8 (*R*)-9

(*R*)-10 (*2R,3R*)-11 (*S*)-12



(*R*)-18 (*R*)-19 (*R*)-20 (*S*)-21

(*S*)-22 (*S,S*)-23 (*1R,2S*)-24 (*1R,2S*)-25

(*S*)-26 (*1S,2R*)-27 (*1R,2S*)-28 (*1S,2S*)-29

Table 2. Signs of Split Cotton Effects and Molar Ellipticities ([θ]) for Poly-1–Amino Alcohol Complexes[a]

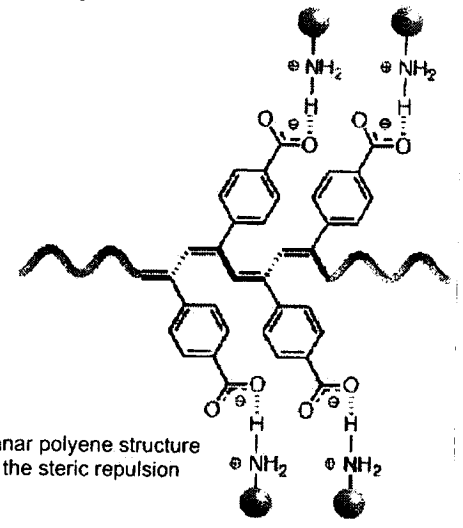
amine	first Cotton sign	first Cotton [θ] × 10⁻³ (λ)	second Cotton sign	second Cotton [θ] × 10⁻⁴ (λ)	third Cotton sign	third Cotton [θ] × 10⁻⁴ (λ)
(*R*)-18[b]	+	2.22 (437.0)	−	3.21 (373.0)	+	3.67 (330.0)
(*R*)-19	−	1.84 (442.0)	+	2.44 (374.0)	−	2.91 (331.0)
(*R*)-20	+	2.28 (444.0)	−	2.17 (374.0)	+	2.32 (333.0)
(*S*)-21	−	1.15 (444.0)	+	1.74 (374.0)	−	1.86 (334.0)
(*S*)-22[b]	−	3.06 (443.0)	+	3.30 (371.0)	−	3.65 (331.0)
(*S,S*)-23[c]	+	0.33 (422.0)	−	0.24 (352.0)	−	0.49 (317.0)
(*1R,2S*)-24	−	2.76 (439.0)	+	3.24 (372.0)	−	3.31 (331.0)
(*1R,2S*)-25	−	3.11 (439.0)	+	2.84 (374.0)	−	2.75 (332.0)
(*S*)-26	+	4.96 (429.0)	−	2.12 (374.0)		*d*

+ the split type and magnitude of the Cotton effects appear to reflect the configuration, bulkiness, and type (primary, secondary, or tetiary)

+ observed ICD increased as primary amine became bulkier

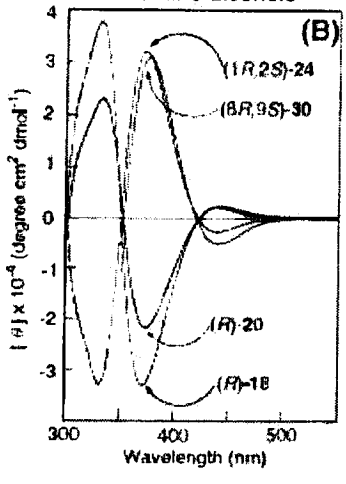
+ the magnitude of the observed ICDs likely decreases in the following order: primary(3) > secondary(7) >> tertiary(10)

+ an amino group far from the chiral center(11) may not work well for inducing a helical conformation



nonplanar polyene structure due to the steric repulsion

CD spectra of poly-1 with amino alcohols

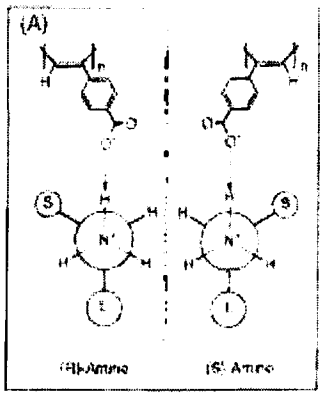


+ most chiral amino alcohols exhibited a very intense ICD irrespective of the bulkiness and type of amino alcohol

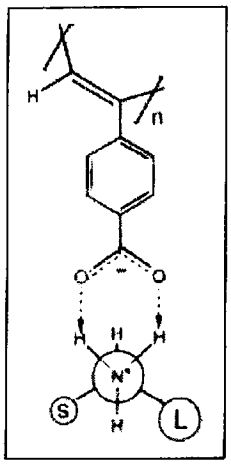
+ less bulky aminoalcohol (**18, 19**) and tertiary amino alcohol (**26**) showed significantly intense ICD

proposed complexation mode

for primary amine



or



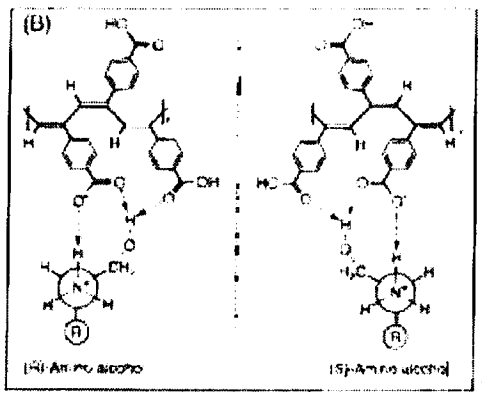
* bidentate-type ion pair model

* helical sense is controlled by the difference between "S" and "L"

* Cotton effect sign may be governed by the steric difference between "S" and H

* "L" may contributes to the extent of ICD magnitude

for amino alcohol



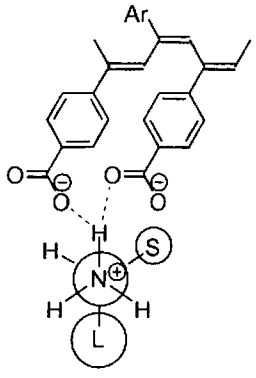
similar complexation manner was confirmed by X-ray analysis with (*1S,2R*)-ephedrinium (*R*)-mandelate ion pair (*J. Am. Chem. Soc.* **1988**, *110*, 1565.)

* hydroxy group may participate in intermolecular hydrogen bonding with -COOH together with the acid-base ion pairing of amino group

* the direction and affinity of hydroxy group to poly-1 may be the most important for controlling both the helical sense and extent of single-handedness

intense ICD independent on the bulkiness of R

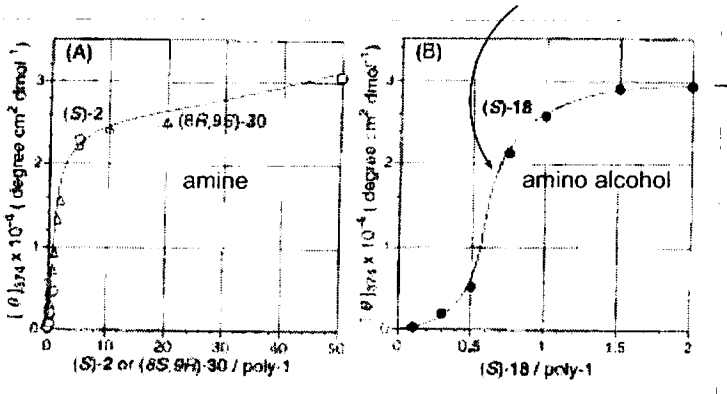
How about similar binding mode for amines??



complexation dynamics

CD titration

one-handed helical structure starts to form (ratio = 0.5-1.0)



constant value

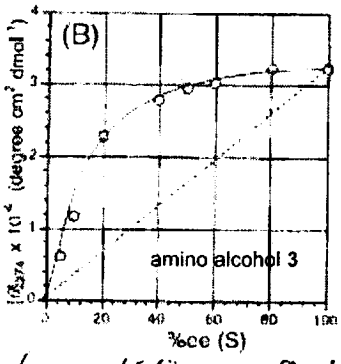
Figure 6. Titration curves of the absolute values of ICD at 374 nm in the complexation of poly-1 (1.0 mg/mL) with (*S*)-2 (○). (*8R,9S*)-30 (△) (A), and (*S*)-18 (●) (B) in DMSO at ambient temperature (*ca.* 18 – 20 °C).

memory of macromolecular helicity

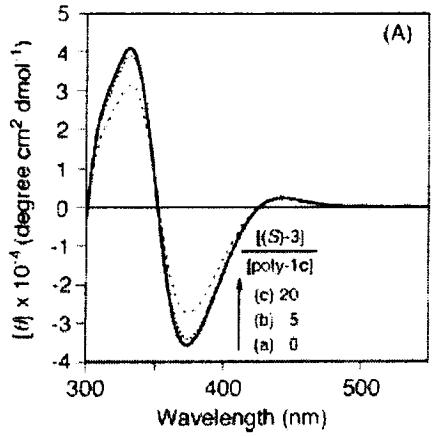
Yashima et al. *Nature*, **1999**, *399*, 449.
J. Am. Chem. Soc. **2004**, *126*, 4329.

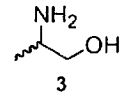
non-linear effect

(*R*) and (*S*) were premixed



addition of (*S*)-**3** to (*R*)-**3**/poly-**1** complex ((*R*)-**3**/poly-**1** = 5/1)





3

→ *significant ICD change was not observed*

two possibility
(1) slow exchange between (*R*) and (S)
(2) slow inversion of helicity after fast exchange

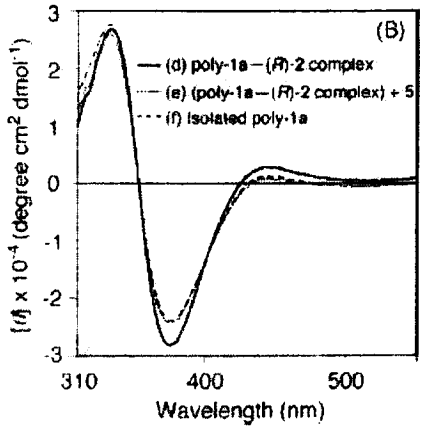
determining ee of amino alcohol in the complex

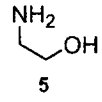
(i) collecting precipitation of the complex by adding to the poor solvent
(ii) decomplexation by 1N HCl aq. and neutralization
(iii) ee determination

→ ee was correspondent to the whole amino alcohol in the mixture

→ **inversion of helicity is slow**

addition of achiral amino alcohol **5**





5

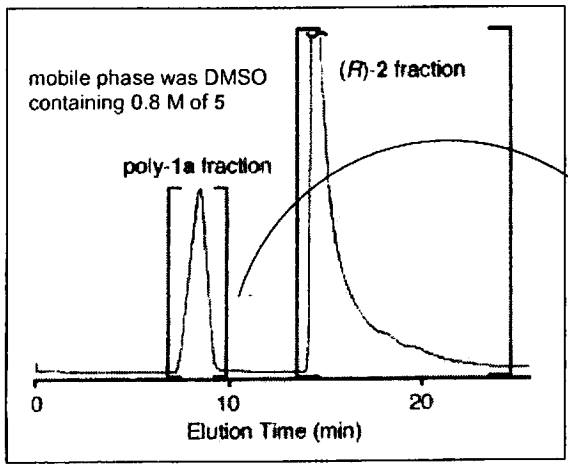
→ ICD signal was still observed with only a slight decrease in the CD intensity

→ one-handed helical conformation of poly-**1** can be retained even after the (*R*)-**2** is replaced by achiral **5**

→ *macromolecular helicity memory*

further concrete evidence (isolation of helix by chromatography)

* size exclusion chromatography (SEC) was used



→ poly-**1** fraction containing a large exess of achiral **5** showed an intense ICD comparable to that was measured before SEC fractionation

→ chiral helical macromolecule whose chirality depend on only helicity