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Polymeric Chiral Crown Ethers VI. Optical Resolution of α-Amino Acid by Polymers Incorporating 1,3;4,6-Di-*O*-benzylidene-D-mannitol Residues

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ABSTRACT: The optical resolution of α-amino acid was studied using chiral poly(crown ether)s **2** and **5**. The former was prepared from cyclopolymerization of 1,3;4,6-di-*O*-benzylidene-2,5-bis-*O*-[2-(2-vinyloxyethoxy)ethyl]-D-mannitol (**1**), and the latter was obtained from copolymerization of acrylonitrile and macromonomer **4** synthesized through the polymerization of **1** with 2-vinyloxyethyl methacrylate in the presence of hydrogen iodide/iodine. The optical resolution of racemic α-amino acid methyl esters through bulk chloroform containing polymer **2** from one aqueous solution to another was examined. The faster moving enantiomer was the L-isomer, which agreed with the result in the one-plate extraction experiment. On the other hand, the column packed with chiral polymer **2** gave an eluent containing a mixture enriched in the D-isomer when being used for resolution of racemic α-amino acid methyl ester. The D-isomer permeated preferentially through the membrane prepared from copolymer **5** as well. The L-isomer which forms the more stable complex is easily absorbed by the stationary phases, resulting in an excess of the D-isomer in the final mobil phases.

KEY WORDS Chiral Poly(crown ether) / Cyclopolymerization / Divinyl Ether / D-Mannitol / Macromonomer / HI/I_2 Initiator / Optical Resolution / α-Amino Acid / Membrane / Column Chromatography /

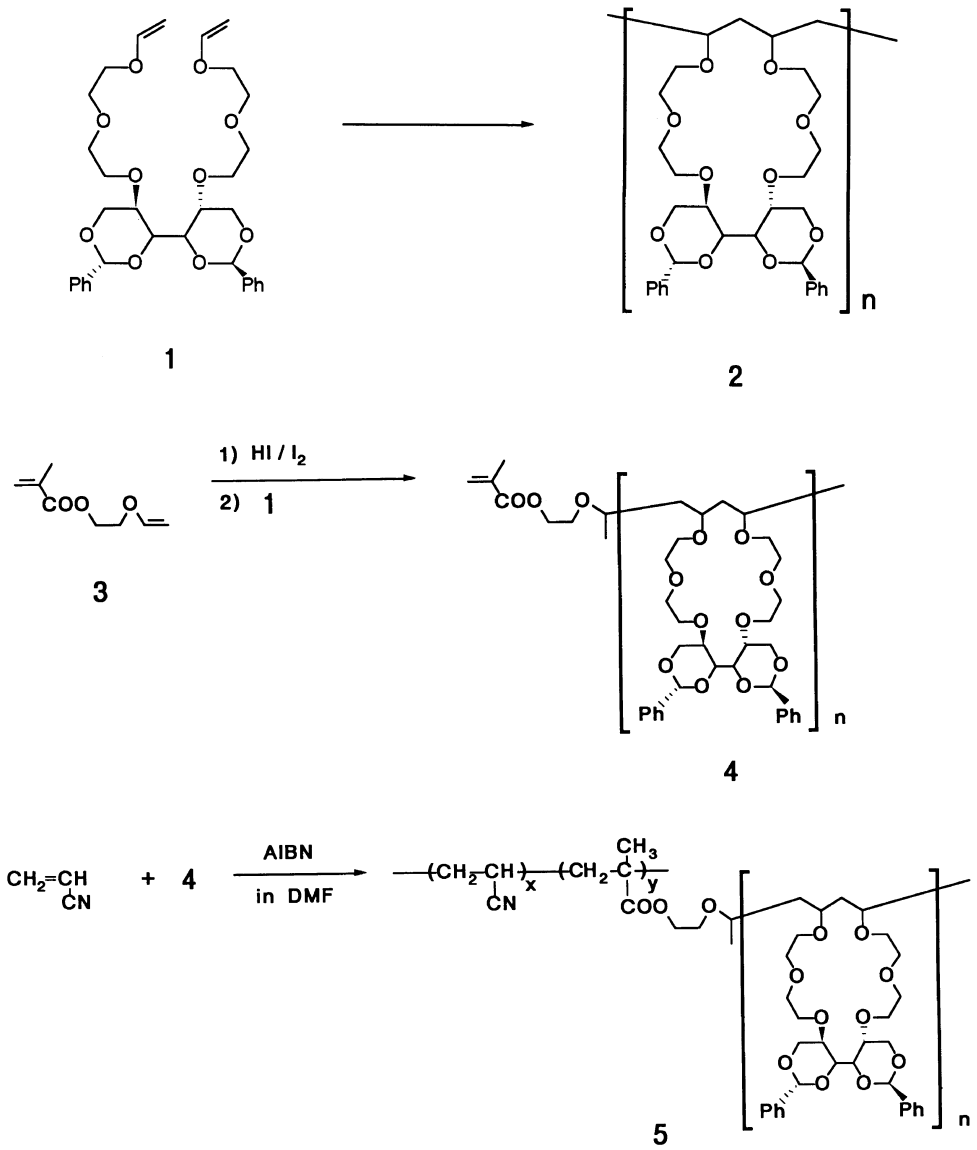
Cationic cyclopolymerization of divinyl ethers is a facile method for producing poly(crown ether)s,[1] chiral ones,[2-6] and terminally end-functional ones.[7] Optically active polymers exhibited the ability of chiral recognition toward α-amino acids in one-plate extraction experiment. The 1,3;4,6-di-*O*-benzylidene-D-mannitol residue in polymer **2** acts as a steric chiral barrier in a similar manner as 1,1′-binaphthyl one.

Chiral crown ether is one of the agents for the optical resolution of α-amino acid by one-plate extraction,[8] U- and W-tube transport,[9,10] and column chromatographic [11-13] procedures. The present aim is optical resolution using polymer **2** and its derivative.

This paper describes 1) the preparation of chiral polymer **5** through the copolymerization of macromonomer **4** with acrylonitrile (Scheme 1), 2) the enantioselective transport of α-amino acid methyl esters through bulk chloroform containing polymer **2** from one aqueous solution to another, 3) the optical resolution of amino acid methyl esters by the column packed with polymer **2**, and 4) the differential permeation of D-, L-, and DL-amino acids through the membrane prepared from copolymer **5**.

EXPERIMENTAL

General The ^1H NMR spectra were recorded with a Hitachi R 90H FT-NMR spectrometer. The IR spectra were recorded on a Jasco A-102 spectrometer. The UV spectra were recorded on a Shimadzu UV-210 spectrometer.



Scheme 1.

Optical rotation was made with a Jasco DIP-140 digital polarimeter.

Syntheses of Chiral Polymers

Polymer **2** was prepared from the polymerization of 1,3;4,6-di-*O*-benzylidene-2,5-bis-*O*-[2-(2-vinyloxyethoxy)ethyl]-D-mannitol (**1**) with $SnCl_4$ in dichloromethane at 0°C and purified by reprecipitation from methanol–chloroform.

Macromonomer **4** was prepared by the procedure reported in the previous paper.[7] To a solution of 2-vinyloxyethyl methacrylate (**3**) in dichloromethane was added a solution of hydrogen iodide (HI) in toluene at −78°C ([**3**]/[HI]=1). The polymerization was initiated by adding prechilled solutions of **1** in dichloromethane and of iodine (I_2) in toluene at

$-78°C$ ([**1**]/[**3**]=5, [HI]/[I_2]=2). After 2 h, the reaction was terminated with dry methanol. The mixture was washed with a 10% aqueous solution of sodium thiosulfate and then with water. The organic layer was dried and poured into *n*-hexane. After removal of solvent the residue was dried under vacuum to give macromonomer **4** as a viscous material. $[\alpha]_D^{25} = -29.0°$ ($c = 1.07\,g\,dl^{-1}$, $CHCl_3$).

Copolymerizations of acrylonitrile and macromonomer **4** were carried out with AIBN in DMF. After an appropriate polymerization time, the mixture was poured into methanol. The powdery copolymers obtained were purified by reprecipitation from DMF–methanol. The mole fraction of macromonomer **4** in the copolymers was determined by elemental analysis.

Preparation of Membrane

The membrane was obtained by casting the solution of copolymer **5a** in DMF, but copolymers **5b** and **5c** were unsuitable for the membrane because of their brittleness. A 200 $g\,dm^{-3}$ -DMF solution of copolymer **5a** was spread out on a glass plate using a glass rod and a *ca.* 1 mm spacer. After evaporating solvent at 40°C for 3 h, the glass plate was soaked in a cold water to give a membrane with a thickness of 0.53 mm.

Enantioselective Transport through Bulk Chloroform Containing Polymer **2**

The U-tube transport was carried out by a procedure similar to that reported by Cram *et al.*[2] In a U-tube of 14 mm i.d. was placed 10 cm^3 of 0.03 M host solution in chloroform. In the α arm of the tube, floating on the $CHCl_3$ pool, was placed water, 5 cm^3 of aqueous solution, whose concenration is 0.8 M in $LiPF_6$, 0.08 M in HCl, and 0.1 M in racemic guest salt. The β arm contained 5.0 cm^3 of 0.1 M HCl solution in water. The chloroform was mixed by a small magnetic stirrer. The rate of transport and the optical purity of the guest transferred from the α to β phase were determined by monitoring the absorbance of the UV spectrum and by measuring the specific rotation of the solutions in the β phases.

Optical Resolution through the Column Packed with Polymer **2**

Polymer **2** (2.0 mmol), which was finely powdered by agate mortar and pesttle, was packed in a glass tube of 5 mm i.d.. Through the column, 1.5 cm^3 of 0.33 M amino acid methyl ester and 1.0 M $LiPF_6$ in water were passed under a reduced pressure of 10—15 mmHg. The eluent was diluted with water, brought to pH 9 with aqueous ammonium hydroxide, and extracted with CH_2Cl_2. Through the extract, after being dried, dry HCl gas was bubbled to form the salt. The solvent was removed and the optical rotation of the resulting salt was measured in methanol.

Permeation through the Membrane of Copolymer **5**

The differential permeation of amino acid was carried out in a U-tube of 15 mm i.d. with a membrane of copolymer **5a** as a diaphragm. In the α arm of the tube, 10 cm^3 of 0.1 M amino acid perchlorate salts in water were placed, and 10 cm^3 of water in the β arm. The amounts of amino acids permeated from the α to the β phase were determined by monitoring the absorbance of the UV spectrum of the solution in the β phase.

RESULTS AND DISCUSSION

Synthesis and Copolymerization of Macromonomer **4**

Cyclopolymerization of divinyl ether with hydrogen iodide/iodine (HI/I_2) was previously reported.[7] This polymerization was living-like, when the molar ratio of divinyl ether and HI was below 10. For preparation of macromonomer **4**, the polymerization of monomer **1** was carried out with the initiator prepared from 2-vinyloxyethyl methacrylate (**3**), HI, and I_2 in dichloromethane at $-78°C$; [**1**]/[**3**]=5 and

[3]/[HI]=1. The reaction proceeded homogeneously, and the resulting polymer, even obtained in 100% conversion, was soluble in chloroform and THF. The GPC trace of macromonomer **4** was narrow and unimodal. Characteristic absorbances due to the methacrylate groups and crown ether units were observed in the IR and the ^{1}H NMR spectra of polymer, as shown in Figures 1b and 2, respectively. The number of crown ether units (n) in macromonomer **4** is $n=5$, estimated from the relative areal ratio of methacrylic methylene and acetal methine protons in the ^{1}H NMR spectrum.

The results of copolymerization of acrylonitrile (M_1) with macromonomer **4** (M_2) are listed in Table I. Characteristic absorbances due to acrylonitrile and macromonomer **4** units except for vinylic groups were observed in the IR spectrum of copolymer **5c**, as shown in Figure 1. In this copolymerization, the parameter r_1 was determined by use of the equation $d[M_1]/d[M_2]=r_1[M_1]/[M_2]$. Plots of the results in Table I yielded a straight line, giving $r_1=1.19$. This value is in good agreement with the parameter in the system of acrylonitrile–methyl methacrylate ($r_1=1.16$, $r_2=0.13$).[14]

Optical Resolution by Polymeric Chiral Crown Ethers

The results for the optical resolution of α-amino acid methyl esters through bulk chloroform containing polymer **2** are listed in Table II. The amount of phenylglycine (Ph-Gly) transported from the α to β phase was 10.6% at 30 h after the operation, and was higher than those of phenylalanine (Ph-Ala), valine (Val), and methionine (Met). Optical purities were 13.5% for Ph-Ala and 19.5% for Val, but lower for Ph-Gly and Met. The faster moving enantiomer was the L-isomer.

The ability of optical resolution is estimated by the ratio of rate constants for faster moving

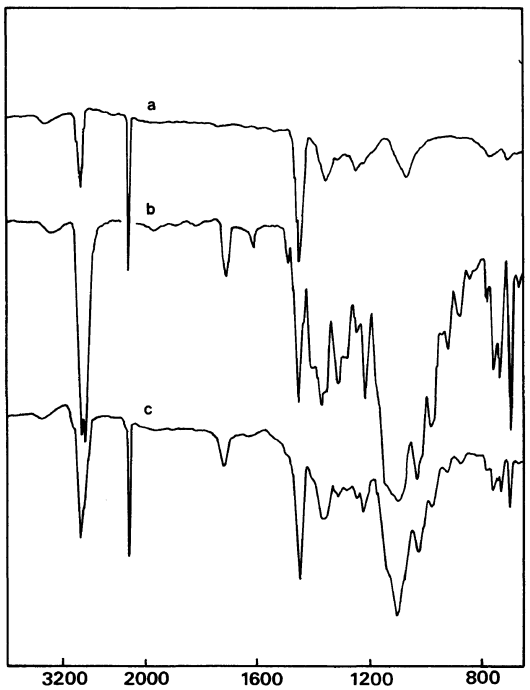


Figure 1. The IR spectra of (a) poly(acrylonitrile), (b) macromonomer **4**, and (c) copolymer **5c**.

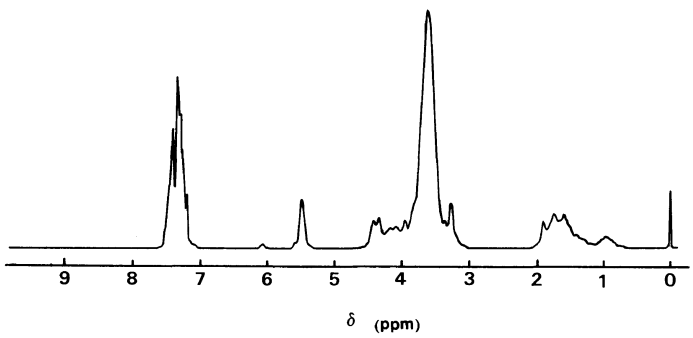


Figure 2. The ^{1}H NMR spectrum of copolymer **5c**.

Table I. Copolymerization of acrylonitrile (M_1) and macromonomer **4** (M_2) with AIBN in DMF at 50°C[a]

Copolymer	M_2 mole fraction in monomers	Time h	Yield %	M_2 mole fraction in copolymer[b]	Crown ether units in polymer meq g^{-1}
5a	0.013	13	45	0.01	0.57
5b	0.078	69	53	0.06	1.28
5c	0.144	38	46	0.14	1.46

[a] $[M_1+M_2]=40$ wt%; $[AIBN]/[M_1+M_2]=0.015$.
[b] Determined by elemental analysis.

Table II. Enantioselective transport of DL-$RCH(CO_2CH_3)NH_3^+PF_6^-$ through the bulk chloroform membrane containing polymer **2**[a]

R	Guest in final β phase: Transported[b] %	Optical purity %	Faster moving enantiomer	k_A^*/k_B^*	EDC[c]
Ph	10.6	6.8	L	1.15	1.66
$PhCH_2$	7.9	13.5	L	1.31	1.15
$(CH_3)_2CH$	7.6	19.5	L	1.48	1.48
$CH_3SCH_2CH_2$	5.1	7.9	L	1.17	1.34

[a] 10 cm^3 of chloroform containing 0.03 M host polymer in water were placed in a 14 mm i.d. U-tube; the α arm of the tube contained the aqueous solution (5 cm^3) whose concentrations were 0.8 M in $LiPF_6$, 0.08 M in HCl, and 0.1 M in racemic guest salt; the β arm, 5.0 cm^3 of 0.1 M HCl solution in water.
[b] Transported time, 30 h.
[c] Reference 4.

enantiomer A and the slower moving enantiomer B (k_A^*/k_B^*) in transport experiment and by the value of enantiomer distribution constant (EDC) in one-plate extraction experiment. Cram *et al.* derived the relationship of $k_A^*/k_B^*=$EDC on the basis of some assumption.[9]

In this experiment, however, the k_A^*/k_B^* values differ from the EDC ones, and thus the distinction is found between Cram's and polymeric crown ethers; Val > Ph-Ala > Met > Ph-Gly for k_A^*/k_B^* and Ph-Gly > Val > Met > Ph-Ala for EDC. The complexation between host and guest at the $CHCl_3$–H_2O interface reaches an equilibrium state in the one-plate extraction experiment. The [G]/[H] value for polymer **2**, which is the molar ratio of guest to crown units in the $CHCl_3$ phase, ranging from 0.6—1.5,[4] and hence the crown units in the polymer are almost occupied with complexation. As the complex becomes more crowded by increasing the steric requirements of either the host or the guest, the complexation becomes more stereoselective. On the other hand, U-tube experiments would bring about low values of [G]/[H] as a result of the transport of guest. Therefore, the steric requirement for chiral recognition of the complexing crown ether unit should be appreciably affected by the vacant ones surrounding the complex. The difference of environment for chiral recognition would cause the replacement of Ph-Gly and Ph-Ala in the order of k_A^*/k_B^* and EDC.

The results of optical resolution of methyl

Table III. Optical resolution of DL-$RCH(CO_2CH_3)NH_3^+Cl^-$ by column chromatography packed with polymer **2**[a]

R	Optical purity / %	Excess enantiomer in eluent
Ph	2.5	D
$(CH_3)_2CH$	9.0	D
$CH_3SCH_2CH_2$	3.7	D

[a] A glass tube of 5 mm i.d. packed with polymer **2** (2.0 mmol); 1.5 cm^3 of 0.33 M amino acid methyl ester and 1.0 M $LiPF_6$ in water was passed through the column under reduced pressure of 10—15 mmHg.

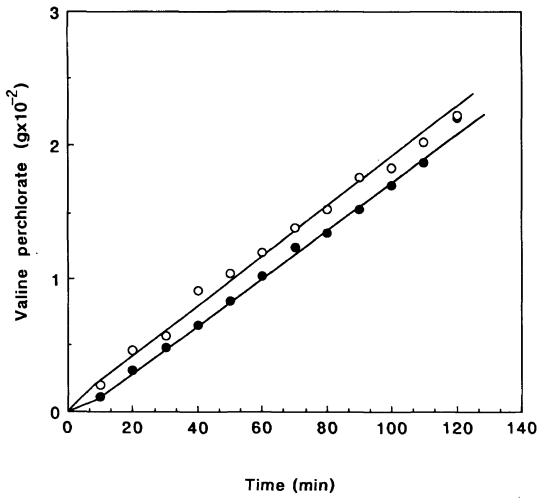


Figure 3. Time-permeation curves for D- and L-valine perchlorates through the membrane of copolymer **5a** at 30°C: [valine perchlorate]$_0$ = 0.1 M; ○, D-valine perchlorate; ●, L-valine perchlorate.

esters of racemic Ph-Gly, Val, and Met by the column packed with polymer **2** are listed in Table III. The excess enantiomer in eluent was the D-isomer for all the amino acids tested. The optical purity was 9.0% for Val, but lower for Ph-Gly and Met.

Plots of the amount of D- and L-Val permeated into the β phase *vs.* time gave a linear correlation, as shown in Figure 3. The slope gives the permeation coefficient. The good straight line was found for Ph-Gly and Ph-Ala as well.

Table IV. Permeation coefficient of L- and D-$RCH(CO_2H)NH_3^+ClO_4^-$ through a membrane of copolymer **5a** at 30°C[a]

R	$P_D \times 10^6$ / $cm^2\,s^{-1}$	$P_L \times 10^6$ / $cm^2\,s^{-1}$	P_D/P_L
Ph	3.00	2.77	1.08
$PhCH_2$	3.07	2.88	1.07
$(CH_3)_2CH$	4.36	3.90	1.12

[a] The α arm of the U-tube of 15 mm i.d. contained a 0.1 M solution (10 cm^3) of amino acid perchlorate in water; the β arm, 10 cm^3 of water.

The permeation coefficient, P, is defined as

$$P = \frac{Q \cdot L}{\Delta C \cdot A \cdot t}$$

where Q (g) is the amount of permeated amino acid, L (cm) is a thickness of membrane, ΔC ($g\,cm^{-3}$) is the difference in concentration of amino acid between the α and the β phases, A (cm^2) is an effective area of membrane, and t (s) is time. The results of the permeation coefficients for Ph-Gly, Ph-Ala, and Val are collected in Table IV. The values of P_D, P_L, and P_D/P_L are larger for Val than for Ph-Gly and Ph-Ala whose values are approximately equal. For the amino acids tested, the rate of permeation is faster in D-enantiomer than in the L-one. Thus, the crown ether units in the membrane of copolymer **5** exhibit chiral recognition toward α-amino acids, though having low ability.

The partially optical resolution of racemic amino acid was realized for DL-$C_6H_5CH(CO_2H)NH_3^+ClO_4^-$ by use of the copolymer membrane, as shown in Figure 4. The optical purity of Ph-Gly was 11% in the D-enantiomer for 40 min after the operation, and then sharply decreased to a constant value of 1.5%. The resolution of racemic amino acid, such as Ph-Ala and Val, was too small to measure the change in the optical rotatory power. In the column and solid membrane experiments, the faster moving enantiomer is the D-isomer.

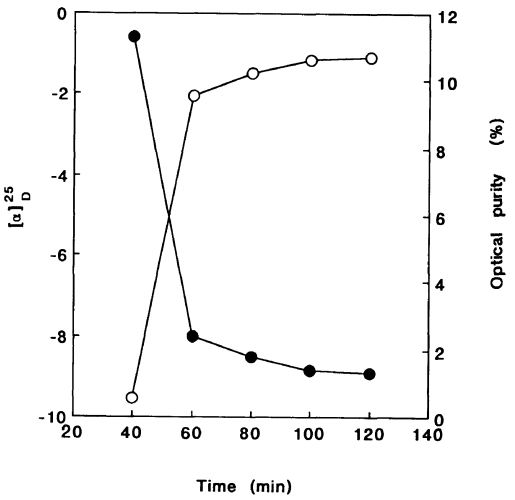


Figure 4. Optical resolution of DL-phenylglycine perchlorate through the membrane of copolymer **5a** at 30°C: [DL-phenylglycine perchlorate]$_0$ = 0.1 M; ○, optical rotation $[\alpha]_D^{25}$; ●, optical purity.

These results on the optical resolution of α-amino acid using polymer **2** and copolymer **5** are explained on the basis of a host-guest mechanism. The crown ether units in polymer **2**, 1,3;4,6-di-*O*-benzylidene-D-manno-19-crown-6 units, form a more stable complex with the L-enantiomer in one-plate extraction where polymer **2** is used as a solution in $CHCl_3$.[4] In the transport experiment, polymer **2** in the $CHCl_3$ phase formed a more stable complex with L-isomer at the H_2O–$CHCl_3$ interface, and released the isomer into the second aqueous phase after carrying it through the $CHCl_3$ phase.

On the other hand, the finally enriched enantiomer is the D-isomer, using the host polymer in the solid state, which situation differs from the results in the solution state. In the column experiment, polymer **2** absorbs dominantly the L-enantiomer to produce an excess of the D-isomer in the eluent. In the permeation of the amino acid through the solid membrane of copolymer **5**, the D-isomer that forms a less stable complex with the crown ether units permeates rapidly through the membrane, resulting in enrichment in the β phase.

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