Enantioselective Permeation of Various Racemates through an Optically Active Poly{1-[dimethyl(10-pinanyl)silyl]-1-propyne} Membrane

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ABSTRACT: Optical resolution of various racemates such as (±)-tryptophan and (±)-1,3-butanediol was achieved by permeation through a self-supporting membrane of (+)-poly{1-[dimethyl(10-pinanyl)silyl]-1-propyne} [(+)-poly(DPSP)] prepared by homopolymerization of (−)-1-[dimethyl(10-pinanyl)silyl]-1-propyne [(−)-DPSP]. Almost complete optical resolution (% ee of the permeate = 81−100% ee) was achieved at an initial period of concentration-driven permeation, and stable permeation with moderate permselectivity (% ee of the permeate = 12−54% ee) continued for more than 600 h. In addition, by permeation of vapor permeant such as evapomeation and pervaporation, higher permeation rates were attained maintaining high enantioselectivity. The sign of the enantiomer that predominantly permeated through a (+)-poly(DPSP) membrane was opposite to that through a (−)-poly(DPSP) membrane. In the permeation through a (+)-poly(DPSP) membrane of a solute or a solvent having a high affinity for (+)-poly(DPSP) and in the permeation through a membrane from the copolymer of (−)-DPSP with a small amount of 1-(trimethylsilyl)-1-propyne, their enantioselectivities were much lower. These findings suggest that the permeating route surrounding chiral pinanyl groups in a (+)-poly(DPSP) membrane that can enantioselectively separate various racemates was easily deformed by using a solute or solvent having a high affinity for (+)-poly(DPSP) or by removing a small amount of pinanyl groups.

Introduction

Optical resolution is a very important separation process and will become much more important in the field of medicine and agricultural chemicals, because the use of these chemicals in optically pure form is effective and safe. Conventional optical resolution methods, including preferential crystallization, chemical modification by an optical resolution agent, and high-performance liquid chromatography (HPLC) with a chiral stationary phase, have the common drawback that only a low amount of material can be treated in one operation.[1] On the other hand, optical resolution by membrane permeation is very promising because a large amount of racemates can be handled in a single treatment.

Optical resolution membranes reported so far[2−8] are divided into two groups. One is membranes containing enantiomer-recognizing carriers,[2,3] and the other is prepared by using a polymer of a chiral stationary phase in HPLC.[4−8] Liquid membranes containing enantiomer-recognizing carriers such as a chiral crown ether show highly enantioselective permeability[2] but low durability because losses of the liquid and carriers cannot be avoided. In the case of solid membranes containing enantiomer-recognizing carriers, their durability becomes high but the enantioselectivity is observed only at an initial period owing to saturation of the carriers with permeants. The saturation may occur because the carriers are not mobile but fixed and the contents of the carriers in self-supporting membranes are limited. For example, through a poly(chiral crown ether) membrane, racemic phenylglycine perchlorate was separated in 11% ee at the initial period but the selectivity almost disappeared after the initial period (1.5% ee).[3] On the other hand, the interaction of a polymer of a HPLC chiral stationary phase with permeants is thought to be too weak to separate permeating racemates in the very short permeation path. Moreover, most of these polymers are crystalline and have no self-membrane-forming ability or their membranes are brittle. For example, since a chiral poly(amino acid) derivative[4] and cellulose carbamate[6] require a porous supporting membrane when they are used for membrane permeation, the polymers may be easily lost from the supporting membrane by applying pressure to enhance permeation rate or by using solvent having only a weak affinity for the polymers. Therefore, in this type of membrane, permeation rates are low and it is difficult to maintain stability of the permeation performance.

In order to realize optical resolution by membrane permeation with high enantioselectivity, high permeation rates, and continuously stable performance, polymers having the ability to form self-supporting solid membranes are suitable. Since self-supporting solid membranes are fabricable to various forms and highly durable, they are expected to be easily incorporated into various practical producing processes.

In this study, we propose a new design for an optical resolution solid membrane that has a chiral permeating space. In order to obtain such a membrane, a silylpropyne that has bulky chiral pendant groups (Figure 1) was synthesized and polymerized and the resulting polymer was fabricated to a self-supporting solid membrane. Optical resolution of various racemates by using this membrane was tried and the enantioselective permeation mechanism will be discussed.

Experimental Section

Materials. (−)-*β*-Pinene {$[\alpha]_D^{25}$ −22° (neat)} and (+)-*β*-pinene {$[\alpha]_D^{20}$ +21° (neat)} were obtained from Aldrich and were used without further purification. Chloroplatinic acid hexahydrate ($H_2PtC_6 \cdot 6H_2O$) and $TaCl_5$ and Ph_3Bi were purchased from Wako Chemicals Co. 1-(Trimethylsilyl)-1-propyne (TMSP) was prepared from propyne.[9] Racemic solutes used for enantioselective permeation experiments were as follows: tryptophan (Trp, from Junsei Chemical Co.), phenylalanine (Phe, from Junsei Chemical Co.), valine (Val, from Junsei

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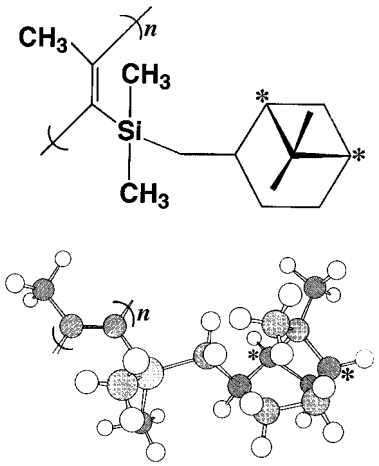

Figure 1. Chemical structure of (+)-poly(DPSP): (top) 2D; (bottom) 3D.

Chemical Co.), mandelic acid (Man, from Junsei Chemical Co.), 2-phenethyl alcohol (Phn, from Aldrich Chemical Co.), 1,3-butanediol (1,3-BD, from Tokyo Chemical Industries Co.), 1,3-diacetoxybutane (DAc-1,3-BD, from Aldrich Chemical Co.), 2-butanol (2-BuOH, from Junsei Chemical Co.), and (phenylthio)-2-butanol (PhT-2-BuOH, from Nippon Soda Co.).

Monomer Synthesis.[10] Synthesis of Optically Active (10-Pinanyl)chlorodimethylsilane (1) (Scheme 1). Chloroplatinic acid hexahydrate (46.5 mg, 89.6 mmol) was dissolved in toluene (24.5 mL) at 80 °C. To this solution was added chlorodimethylsilane (8.49 g, 90 mmol) at 40 °C, and then (−)- or (+)-β-pinene (10.9 g, 80.0 mmol) was added at 80 °C. Finally the mixture was stirred for 24 h. All the above procedures were performed in nitrogen. The product was purified by distillation at 68 °C (0.30 mmHg). Yields: 89.2% from (−)-β-pinene and 71.4% from (+)-β-pinene. ^{1}H NMR ($CDCl_3$): δ 0.48 [s, 6H, $ClSi(CH_3)_2$], 0.92 and 1.26 [2s, 6H, *gem*-$(CH_3)_2$], 1.07−2.68 ppm [m, 11H, CH and CH_2 in pinane].

Synthesis of Optically Active 1-[Dimethyl(10-pinanyl)-silyl]-1-propyne [(−)- or (+)-DPSP] (Scheme 1). *n*-Butyllithium hexane solution (1.60 M, 7.00 mL) was dropped into liquid propyne (2.00 g, 50 mmol) at −78 °C. After stirring for 1 h at room temperature, **1** from (−)-β-pinene (11.6 g, 50 mmol) was added dropwise at 0 °C and the ether solution (30 mL) was stirred for 2.5 h at the refluxing temperature. This ether layer was washed with water (50 mL). The ether solution was concentrated and distilled at 98 °C (3.0 mmHg). Yields: 55.9% for (−)-DPSP and 71.4% for (+)-DPSP. ^{1}H NMR ($CDCl_3$): δ 0.13 [s, 6H, $Si(CH_3)_2$], 0.83 and 1.18 [2s, 6H, *gem*-$(CH_3)_2$], 1.88 ppm [s, 3H, $CH_3C{\equiv}$]; IR (NaCl): 2188 cm^{-1} (C≡C); $[\alpha]_D^{20}$ −3.49 (*c* 38.1, toluene) for (−)-DPSP and +3.39 (*c* 13.0, toluene) for (+)-DPSP. Anal. Calcd for $C_{15}H_{26}Si$: C, 76.92; H, 11.11. Found: C, 76.38; H, 11.45.

Polymerizations and Copolymerizations[10] (Table 1). Homopolymerization of (−)- or (+)-DPSP. To $TaCl_5$ (140 mg, 0.380 mmol) in toluene (6.00 mL) was added (−)- or (+)-DPSP (3.00 g, 12.8 mmol) in toluene (4.50 mL) at 100 °C under nitrogen. The mixture was stirred for 24 h and was poured into methanol. The polymer was purified by reprecipitation from toluene solution into methanol. Yields: 30.2% for (+)-poly(DPSP) and 43.2% for (−)-poly(DPSP). ^{1}H NMR ($CDCl_3$): δ 0.24 [b, 6H, $Si(CH_3)_2$], 0.84 and 1.20 [2b, 6H, *gem*-$(CH_3)_2$], 1.70 ppm [b, 3H, $CH_3C{=}$]; $[\alpha]_D^{20}$ +9.03 (*c* 0.940, toluene) for (+)-poly(DPSP) and −8.94 (*c* 0.917, toluene) for (−)-poly(DPSP). Anal. Calcd for $C_{15}H_{26}Si$: C, 76.92; H, 11.11. Found: C, 73.04; H, 11.19. This polymer was soluble in chloroform, toluene, and THF, swelled in 1-butanol and 2-butanol, and was insoluble in methanol and water. For other characterization data, see Table 1.

Copolymerization of (−)-DPSP with TMSP (Feed Ratio 50/50). To $TaCl_5$ (198 mg, 0.549 mmol) in toluene (7.50 mL) were added (−)-DPSP (1.26 g, 5.38 mmol) and TMSP (0.600 g, 5.38 mmol) in toluene (1.88 mL) at 100 °C under nitrogen. The mixture was stirred for 24 h and was poured into methanol. The polymer was purified by reprecipitation from toluene solution into methanol. Yield: 60.7%. The composition of the copolymer was determined by ^{1}H NMR measurement. $[\alpha]_D^{20}$ +6.90 (*c* 0.390, toluene). Other copolymers were similarly synthesized, and other characteristics are summarized in Table 1.

Membrane Preparation.[10] A 6−9 wt % (w/v) solution of a polymer in toluene was cast on a poly(tetrafluoroethylene) sheet, and the solvent was evaporated for 24 h at room temperature. The resulting solid membrane was detached from the sheet and dried in vacuo for 24 h. Thickness (L), 61.9−90.3 μm; area (A), 3.14 × 10^{-4} m^2 for concentration-driven permeation (see below), 7.04 × 10^{-4} m^2 for pervaporation and evapomeation (see below).

Concentration-Driven Permeation of the Solution of Racemates (CP).[10] A disproportionate two-chamber cell whose chamber volumes on the feed side and permeate side were 150 and 20 cm^3, respectively, was used. The polymer membrane was placed between the chambers with silicone-rubber packings. A 0.05−0.5 wt % aqueous or methanol solution of a racemate and water or methanol was supplied in the feed- and permeate-side chambers, respectively. The permeation experiment was carried out at room temperature with stirring. To maintain constant the difference of the concentration (ΔC) between the feed and permeate sides, the solution in the permeate-side chamber was exchanged by the pure solvent before more than 3% of the solute in the feed had permeated. After a permeation period the water or methanol of the permeate was removed by evaporation, and the resulting solute was weighed (q (g)). The normalized quantity (Q (g·m/m^2)) was calculated from $Q = qL/A$, where L and A are the thickness and area of the membrane. The permeation rate (P (g·m/m^2·h)) was estimated from the slope of the Q−permeation time (t (h)) plot. The permeability coefficient (P_c (m^2/h)) was calculated by dividing P by ΔC. Since these membranes were nonporous, the diffusion coefficient (D (m^2/h)) and solution coefficient (S (cm^3/cm^3)) were estimated by using the following equations: $D = L^2/6\theta$ and $S = P_c/D$, where θ (h) was the time lag. The enantioselectivity in the permeation, i.e., the optical purity of the permeate (% ee) was directly determined by HPLC with an optical resolution column (CHIRALCELL-OD, CHIRALCELL-OB, CHIRALPAK-WH, and CROWNPAK-CR manufactured by Daicel Chemical Co.) except for 2-BuOH and 1,3-BD.

In the case of 2-BuOH and 1,3-BD, they were carbamoylated and acetylated, respectively, and the derivatives were used for the determination of the % ee with HPLC. *Carbamoylation of 2-BuOH*: 2-BuOH in the permeate was extracted with ether (2 mL). To the ether layer containing 2-BuOH (10 mg, 0.14 mmol) were added pyridine (0.2 mL, 2.5 mmol) and then phenyl isocyanate (0.2 mL, 1.8 mmol). The solution was stirred for 3 min at 50 °C, and the solvent was removed. The resulting product was dissolved in hexane, and the solution was used for HPLC measurement (CHIRALCELL-OD). *Acetylation of 1,3-BD*: The solvent of the solution of the permeate was removed and to the resulting 1,3-BD (5.0 mg, 0.055 mmol) was added acetyl chloride (0.2 g, 2.8 mmol) at 0 °C. After the solution was allowed to stand for 10 min at room temperature, distilled water (2 mL) was added to the solution at 0 °C. The solution was neutralized with sodium hydrogencarbonate. The acetate formed was extracted with hexane (2 mL). The hexane solution was used for HPLC measurement (CHIRALCELL-OB).

Evapomeation of Racemates (EV).[11] A racemic liquid was supplied to the feed side of a glass cell and the membrane was set apart from the liquid. The feed side was evacuated and filled with the vapor of the racemate. The permeate side was connected with a cold trap in dry ice−methanol and was evacuated. Evapomeation was carried out at room temperature. The P, P_c, D, and S values were determined similarly to the above-mentioned concentration-driven permeation.

A figure of the apparatus can be found in the supplementary materials.

Pervaporation of the Solution of Racemates (PV).[11] The feed side of a stainless steel cell was filled with a 3.00−7.00 wt % methanol or an aqueous solution of a racemate. The permeate side was connected with a cold trap in dry ice−methanol and was evacuated at 0.1 mmHg. Pervaporation was carried out at 25 °C. The P, P_c, D, and S values were

Scheme 1. Synthetic Route to (+)- and (−)-Poly(DPSP)

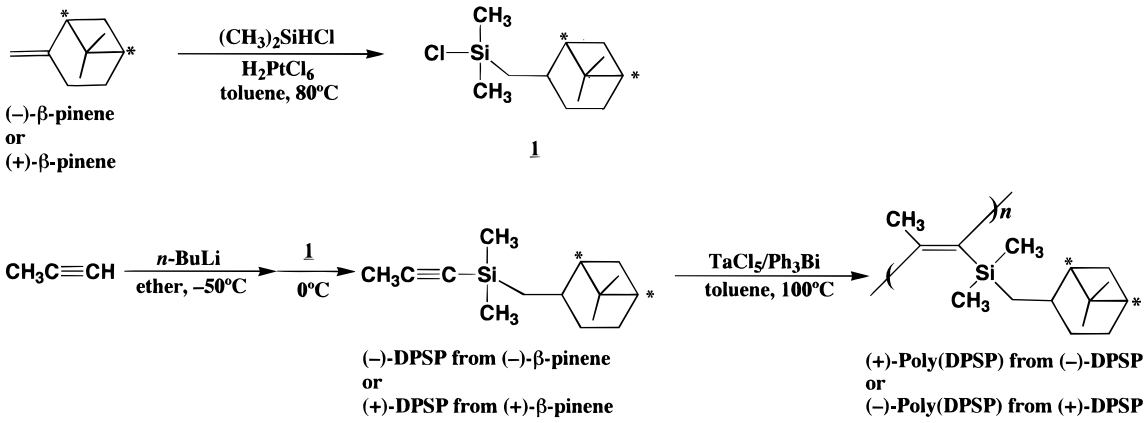

Table 1. Preparation and Characterization of (+)- and (−)-Poly(DPSP), Poly(TMSP), and Their Copolymers

no.	polymer code[a] (composition)	monomer/comonomer (feed molar ratio)	cat./cocat.	yield (%)	10^{-5} $\bar{M}_w/\bar{M}_n$[b]	$[\alpha]_D^{20}$[c] (deg)	tensile strength[d] (kg/mm²)	P_{O_2}[e]	α[f]	P_{H_2O}[g]	d[h] (g/cm³)	T_g[i] (°C)
1	(+)-poly(DPSP)	(−)-DPSP	$TaCl_5/Ph_3Bi$	30.2	1.50 1.88	+9.03	3.85	16.0	4.35	3.55	0.979	148
2	(+)-copoly(DPSP/TMSP) (82/18)	(−)-DPSP/TMSP (66/34)	$TaCl_5/Ph_3Bi$	67.1	2.62 1.93	+7.24					0.949	
3	(+)-copoly(DPSP/TMSP) (77/23)	(−)-DPSP/TMSP (50/50)	$TaCl_5$	60.7	2.41 2.57	+6.90	3.26	336	2.90			
4	(+)-copoly(DPSP/TMSP) (56/44)	(−)-DPSP/TMSP (33/67)	$TaCl_5/Ph_3Bi$	52.6	4.84 1.89	+5.89	2.76				0.938	
5	(−)-poly(DPSP)	(+)-DPSP	$TaCl_5/Ph_3Bi$	43.2	0.585 1.41	−8.94	1.38					
6	poly(TMSP)	TMSP	$TaCl_5$	87.5	6.42 3.04		3.87	1110	1.97	157000	0.910	>200

[a] DPSP, 1-[dimethyl(10-pinanyl)silyl]-1-propyne; TMSP, 1-(trimethylsilyl)-1-propyne. [b] Estimated by GPC correlating to standard polystyrene. [c] c 0.390−0.940, toluene. [d] At a strain rate of 5 mm/min. [e] Oxygen permeability coefficient in barrer at 25 °C. [f] $\alpha = P_{O_2}/P_{N_2}$. [g] Water pervaporation rate in $\times 10^8$ g·m/m²·h. [h] Density determined by the floating method. [i] Glass transition temperature determined by DSC.

determined similarly to the above-mentioned concentration-driven permeation.

Adsorption of the Solution of Racemates.[12] (+)-Poly(DPSP) powder was added to a solution of a racemate, and the mixture was stirred for 24 h. The (+)-poly(DPSP) containing the adsorbed compound was filtered and then washed with the solvent for 24 h to desorb the compound from the (+)-poly(DPSP). Enantioselectivity of the (*R*)-isomer to the (*S*)-isomer (α_S^R) was determined by a method similar to that for the permeation described above.

Calculation of the Hydrophobic Fragmental Constant (ΣF).[13] The ΣF value is a measure of the hydrophobicity of a compound and is calculated by summing the F values for each chemical group such as CH_3, CH_2, CH, and OH.[13] For example, the ΣF of 2-BuOH was calculated as follows: $\Sigma F(CH_3CH_2CH(OH)CH_3) = 2F(CH_3) + F(CH_2) + F(CH) + F(OH) = 2 \times 0.695 + 0.528 + 0.260 + (-1.44) = 0.738$.

Instruments for Characterization. ^{1}H NMR (200 MHz) spectra were recorded on a Varian Gemini-200 spectrometer. Relative molecular weights of polymers correlated to polystyrene standards were determined by gel permeation chromatography (GPC; Hitachi 655A-11 with a GL-A100M column using a UV detector, THF as solvent). SEPA-200 (Horiba Co. Ltd.) and J-720 (JASCO Co. Ltd.) polarimeters were used for the measurements of the specific rotation $[\alpha]_D$ and CD spectra, respectively. The tensile strengths of the membranes were measured by using a TOM-5 (Minebea Co. Ltd.). Oxygen and nitrogen permeability coefficients (P_{O_2} and P_{N_2} (cm³ (STP) cm²/cm·s·cmHg)) were measured by a gas chromatographic method using a YANACO GTR-10. Water permeation rate (P_{H_2O} (g·m/m²·h)) was measured by a gas chromatographic method using a YANACO GTR-12L at 25 °C.

Results

Synthesis and Membrane Preparation. Optically active poly{1-[dimethyl(10-pinanyl)silyl]-1-propyne}s [(+)- and (−)-poly(DPSP)] were synthesized by homopolymerization of optically active 1-[dimethyl(10-pinanyl)-silyl]-1-propyne [(−)- and (+)-DPSP] prepared from (−)- and (+)-*β*-pinene, respectively, as shown in Scheme 1. In spite of the bulky pendant groups, the monomers were able to be polymerized by using $TaCl_5/Ph_3Bi$ as a catalyst to give high molecular weight polymers (Table 1, nos. 1 and 5). In the CD spectra of these polymers, Cotton effects were observed in the absorption region of the backbone chromophore (Figure 2). The polymers were fabricated to self-supporting membranes by the solvent-casting method. Judging from the oxygen permeation behavior (P_{O_2} and α), the water permeation rate (P_{H_2O}), and the density (Table 1), a (+)-poly(DPSP) membrane (Table 1, no. 1) was nonporous and much denser than a poly(TMSP) membrane (Table 1, no. 6). (−)-DPSP with bulky pendant groups showed a high polymerizability, while the polymerizability of (+)-((2-methylbutyl)dimethylsilyl)propyne [(+)-MBSP] with no bulky pendant groups was very low. In copolymerization of (−)-DPSP with TMSP, (−)-DPSP also showed a higher polymerizability than TMSP in comparison between the feed molar ratio and the composition (Table 1, nos. 2−4).

Enantioselective Permeation. Figure 3 shows the normalized quantity (Q) of permeated (*R*)- and (*S*)-tryptophan (Trp) versus permeation time through a (+)-poly(DPSP) membrane in concentration-driven permeation (CP) when an aqueous solution (■,□) of racemic Trp was supplied. The permeation through this membrane was enantioselective for (±)-Trp after an initial period.[14] Especially at the initial period of this membrane permeation, the % ee of permeated Trp was enhanced to 81% ee in the permeate from 0% ee in the feed. After the initial period, a moderate enantioselective permeation of 45% ee followed and continued stably for more than 600 h. By changing the solvent from water to methanol, the permeation rate (P) was enhanced 3.5 times (Figure 3, ●,○, and Table 2, nos. 1 and 2).[15] A similar enantioselective permeation behavior was observed in other racemates such as phenylalanine (Phe), valine (Val), and mandelic acid (Man). That is to say, almost complete optical resolution occurred at

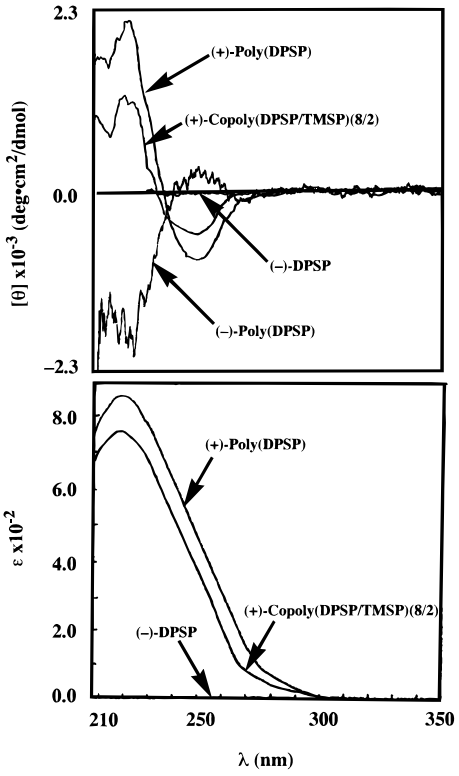

Figure 2. (Top) CD and (bottom) UV spectra of (+)- and (−)-poly(DPSP), (+)-copoly(DPSP/TMSP), and (−)-DPSP in THF (concentration = (2.86−3.40) × 10^{-3} g/dL).

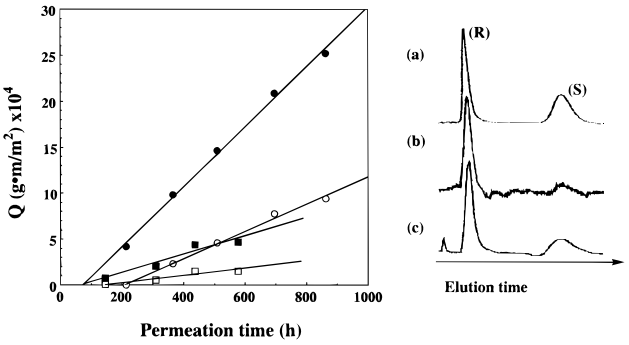

Figure 3. (Left) Plots of normalized quantity (*Q*) of permeated (*R*)- and (*S*)-Trp from a racemate vs permeation time through a (+)-poly(DPSP) membrane in concentration-driven permeation (CP): (■,□) feed = 0.500 wt % aq; (●,○) 0.0500 wt % methanol solution; (■,●) (*R*)-isomer; (□,○) (*S*)-isomer. (Right) HPLC chromatogram of Trp methanol solution: (a) racemic Trp (feed); (b and c) Trp in the permeate at an initial period (0−214 h) and after the period, respectively. Column, CHIRALPAK-WH; eluent, $CuSO_4$(aq).

the initial period after an induction period (Table 3, nos. 1, 2, and 4−6) and stable permeations with moderate enantioselectivity were observed after the initial period (Table 2, nos. 1, 2, and 4−6). Moreover, this membrane could separate (±)-2-butanol (2-BuOH) enantioselectively as shown in Table 2, no. 12. Since 2-BuOH is a small and less polar molecule and the direct separation of the racemate by chiral HPLC is impossible at present, this result is valuable and shows good enantioselective ability of this membrane. In summary, this solid membrane was found to be able to separate enantioselectively several kinds of racemates—α-amino acids, α-hydroxy acids, and alcohols—by concentration-driven permeation (CP).

However, the permeation rates (*P*) in CP were very low and especially *P* of hydrophilic (±)-1,3-butanediol (1,3-BD) was nearly zero (Table 2, no. 7). In order to

Table 2. Enantioselective Permeation through the (+)-Poly(DPSP) Membrane at Room Temperature

no.	racemate[a] ($\sum F^b$)	method[c]	solvent[d]	concn (wt %)	$10^7 P^e$ (g•m/m^2•h)	% ee[f]
1	Trp (2.31)	CP	w	0.50	13.6	45
2	Trp (2.31)	CP	m	0.050	47.2	38
3[g]	Trp (2.31)	CP	w	0.50	9.79	17
4	Phe (2.24)	CP	m	0.10	16.5	54
5	Val (1.46)	CP	m	0.10	1.02	48
6	Man (1.46)	CP	w	0.10	35.3	12
7	1,3-BD (−0.865)	CP	w	3.0	∼0	
8	1,3-BD (−0.865)	EV[h]	none	neat	13500	5.0
9	1,3-BD (−0.865)	EV[i]	none	neat	9210	17
10	1,3-BD (−0.865)	PV	m	3.0	1150	18
11	DAc-1,3-BD (0.879)	EV[j]	none	neat	4500	15
12	2-BuOH (0.740)	CP	w	3.0	70.3	10
13	2-BuOH (0.740)	EV[k]	none	neat	4240	9.3
14	2-BuOH (0.740)	EV[l]	none	neat	40300	2.7
15	2-BuOH (0.740)	PV	w	3.0	8370	45
16	PhT-2-BuOH (1.98)	EV[m]	none	neat	1410	2.4
17	PhT-2-BuOH (1.98)	PV	m	3.0	7240	4.7
18	Phn (1.43)	EV[n]	none	neat	3470	0.0

[a] Man, mandelic acid; 1,3-BD, 1,3-butanediol; DAc-1,3-BD, 1,3-diacetoxybutane; PhT-2-BuOH, 4-(phenylthio)-2-butanol; Phn, 2-phenethyl alcohol. [b] The hydrophobic fragmental constant. From ref 13. [c] CP, concentration-driven permeation; EV, evapomeation; PV, pervaporation. [d] w, H_2O; m, CH_3OH. [e] Permeation rate. [f] Enantiomeric excess of the permeate when a racemate was supplied in the feed. [g] In the presence of NaN_3. [h] Feed: 10 mmHg. [i] Feed: 50 mmHg at 100 °C. [j] Feed: 20 mmHg. [k] Feed: 10 mmHg. [l] Feed: 35 mmHg. [m] Feed: 5 mmHg. [n] Feed: 15 mmHg at 100 °C.

Table 3. Enantioselective Permeation through the (+)-Poly(DPSP) Membrane at the Initial Period

no.[a]	racemate[b] ($\sum F^c$)	method[d]	solvent[e]	$10^7 P^f$ (g•m/m^2•h)	% ee[g]
1	Trp (2.31)	CP	w	5.75	81
2	Trp (2.31)	CP	m	20.5	96
4	Phe (2.24)	CP	m	6.06	97
5	Val (1.46)	CP	m	0.523	100
6	Man (1.46)	CP	w	31.0	83
9	1,3-BD (−0.865)	EV	none	5100	42
10′	1,3-BD (−0.865)	PV	m	2250	89
11	DAc-1,3-BD (0.879)	EV	none	4170	30

[a] Numbers correspond to those in Table 2. [b−g] See Table 2.

enhance the *P* value, permeations in the vapor state, i.e., evapomeation (EV) and pervaporation (PV), were tried. By means of EV at 100 °C, 1,3-BD permeated enantioselectively (42% ee at an initial period) with high *P* (=5.1 × 10^{-4}) as shown in Figure 4[16] and Table 3, no. 9. It is interesting that enantioselective permeation occurred in the case of a vapor permeant. The *P* values in EV and PV were 2 orders of magnitude higher than those in CP. Since 1,3-BD is important as a chiral synthon and direct separation of it by chiral HPLC is impossible,[17] the achievement of this separation is of great value. After the initial period, the permeate of 17% ee with high *P* (=9.2 × 10^{-4}) was also obtained (Table 2, no. 9). PV of 1,3-BD showed a higher enantioselectivity of 89% ee at the initial period (Table 3, no. 10) and the *P* was high (=1.1 × 10^{-4}) and lower than that of EV (Figures 4 and 5[16] and Table 2, nos. 8 and 10).

The acetate of 1,3-BD, 1,3-diacetoxybutane (DAc-1,3-BD), was also separated by EV to give a permeate with 30% ee at the initial period (Table 3, no. 11). It is noteworthy that the *P* value of 2-BuOH was increased about 60 times, maintaining the selectivity by changing CP into EV (Table 2, nos. 12 and 13). However, hydrophobic (phenylthio)-2-butanol (PhT-2-BuOH) and phenethyl alcohol (Phn) were hardly separated by EV and PV (Table 2, nos. 16−18).

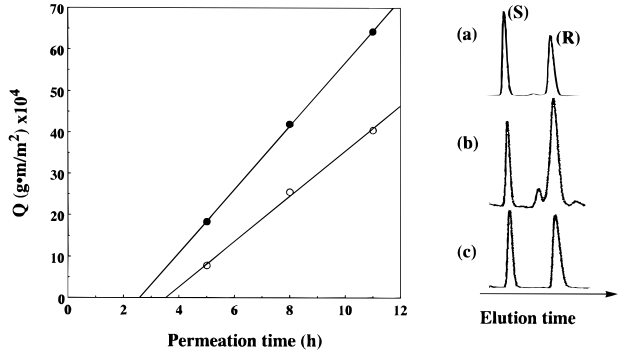

Figure 4. (Left) Plots of normalized quantity (Q) of permeated (R)- and (S)-1,3-butanediol (1,3-BD) from a racemate vs permeation time through a (+)-poly(DPSP) membrane in EV at 100 °C: (●) (R)-isomer; (○) (S)-isomer. (Right) HPLC chromatogram of diacetylated 1,3-BD: (a) racemic 1,3-BD (feed); (b and c) 1,3-BD in the permeate at the initial period and after the initial period, respectively. Column, CHIRALCELL-OB; eluent, hexane/2-propanol = 19/1 (v/v).

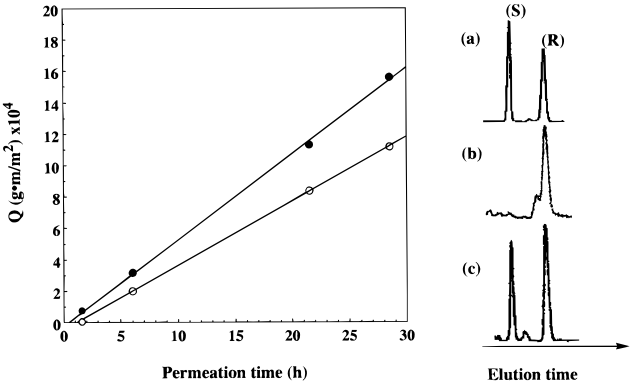

Figure 5. (Left) Plots of normalized quantity (Q) of permeated (R)- and (S)-1,3-butanediol (1,3-BD) from a racemate vs permeation time through a (+)-poly(DPSP) membrane in PV: (●) (R)-isomer; (○) (S)-isomer. (Right) HPLC chromatogram of diacetylated 1,3-BD: (a) racemic 1,3-BD (feed); (b and c) 1,3-BD in the permeate at an initial period (0−1.7 h) and after the period, respectively. Column, CHIRALCELL-OB; eluent, hexane/2-propanol = 19/1 (v/v).

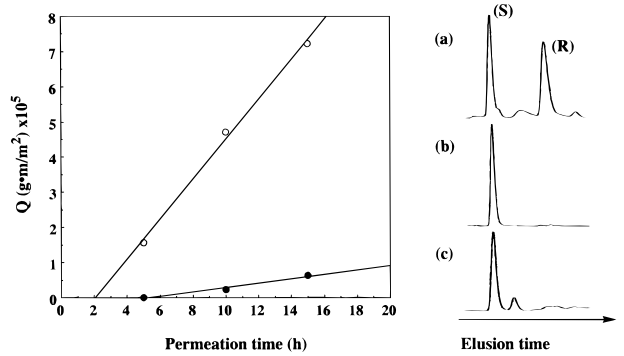

Figure 6. (Left) Plots of normalized quantity (Q) of permeated (R)- and (S)-1,3-butanediol (1,3-BD) from a racemate vs permeation time through a (−)-poly(DPSP) membrane in PV: (●) (R)-isomer; (○) (S)-isomer. (Right) HPLC chromatogram of diacetylated 1,3-BD: (a) racemic 1,3-BD (feed); (b and c) 1,3-BD in the permeate during 0−5 and 5−10 h, respectively. Column, CHIRALCELL-OB; eluent, hexane/2-propanol = 19/1 (v/v).

In the case of PV of racemic 1,3-BD, (R)-1,3-BD permeated preferentially through a (+)-poly(DPSP) membrane (Figure 5), while (S)-1,3-BD permeated preferentially through a (−)-poly(DPSP) membrane (Figure 6).[18] Therefore, a desired enantiomer can be concentrated by selecting the chirality of poly(DPSP).

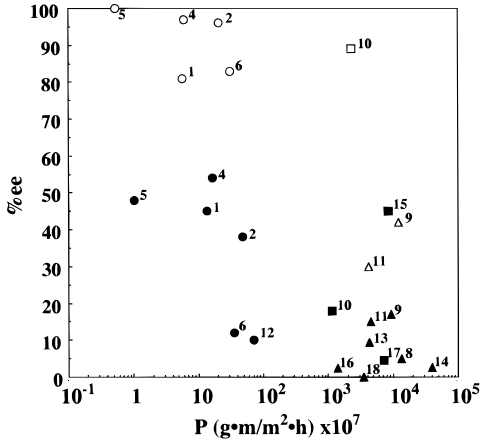

Figure 7. Plot of % ee in the permeate vs logarithmic P for various racemates. Numbers correspond to those in Table 2: (○,●) CP; (△,▲) EV; (□,■), PV; (open symbol) an initial period; (solid symbol) after the period.

Figure 7 is a plot of % ee of the permeates versus logarithmic P. The (+)-poly(DPSP) membranes were able to separate various racemates enantioselectively. The % ee values increase with a decrease in log P after an initial period (solid symbols). The % ee values are higher in CP and lower in EV and PV, while P values are higher in EV and PV and lower in CP.

In the conditions used for CP of aqueous solutions of α-amino acids described above, it is possible that microorganisms which contaminated the solution from air consume one enantiomer selectively. In order to eliminate this undesirable effect, a permeation experiment was carried out in the presence of sodium azide as an antiseptic.[19] In this condition also, enantioselective permeation was observed (Table 2, no. 3). In addition, since enantioselective permeations were observed in the condition where the influence by microorganisms is very unlikely, that is, in PC of a methanol solution of α-amino acid and in vapor permeation at high temperature (EV and PV), it was found that the influence of microorganisms on enantioselective permeation through a chiral poly(DPSP) membrane was negligible.

Discussion

Nature of Racemates Separated by the (+)-Poly(DPSP) Membrane. In the preceding section, it was shown that this membrane can separate enantioselectively various kinds of racemic compounds having a different functional group and molecular size. This finding suggests the enantioselective recognition is not caused by specific interaction between a certain functional group of a permeating racemate and that of the polymer.

The permselectivity was dependent on their hydrophobicity (ΣF). In EV (using neat racemate), the permselectivity increased with decreasing ΣF from 1.98 (PhT-2-BuOH) to −0.865 (1,3-BD) (Figure 8). Since hydrophobic PhT-2-BuOH has a higher affinity for hydrophobic (+)-poly(DPSP) (ΣF = 6.97) (in fact, this polymer was swelled in PhT-2-BuOH), it may tend to enlarge the space among chiral pinanyl groups in the (+)-poly(DPSP) membrane. In permeation through such an enlarged space, no enantioselective permeation is thought to be observed. Therefore, the enantioselectivity of this membrane disappeared for more hydrophobic (=less hydrophilic) compounds which have a higher affinity for (+)-poly(DPSP). In other words, compounds with less affinity for the polymer can be

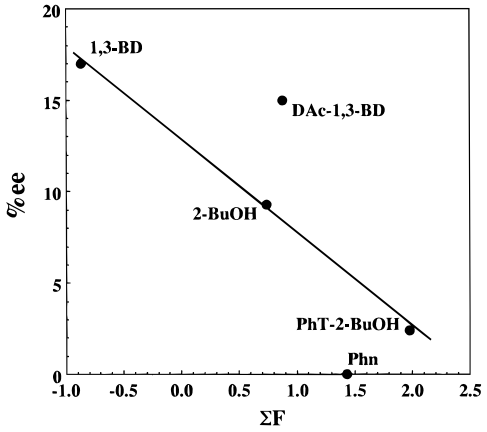

Figure 8. Dependence of % ee of the permeate on $\sum F$ of the permeant in EV: $\sum F$ is the sum of the hydrophobic fragmental constants.[13]

separated by this membrane. This fact suggests the separation mechanism of this membrane is essentially different from that of HPLC.

This membrane is dense and nonporous as described above, and therefore bulky chiral pinanyl groups should be packed densely. Racemic permeants seem to permeate through a space surrounded by the bulky chiral pinanyl groups. Since permeants should contact strongly with the bulky chiral pinanyl groups during the permeation through the space, the enantioselectivity is thought to occur in this diffusion process. The reason for the enantioselective permeation for the wide range of the size of compounds may be variability in size of the space among the chiral groups by molecular motion of the pendant groups. Accordingly, when suitable conditions not to enlarge the space are selected, optical resolution is achieved by the membrane.

Methods and Conditions of Permeation. In EV of 2-BuOH, the enantioselectivity almost disappeared on enhancing the pressure of the feed from 10 to 30 mmHg (Table 2, nos. 13 and 14). This may be because a higher pressure of 2-BuOH, which has a sufficiently high affinity to swell poly(DPSP), enlarged the space among the pinanyl groups to a higher degree. The enantioselectivity of an aqueous solution of 2-BuOH in PV (Table 2, no. 15) was much higher than that of neat 2-BuOH in EV. The higher selectivity in PV of the aqueous solution may be because the enlargement of the space by adsorption of 2-BuOH was suppressed by the water solvent, which has no affinity for poly(DPSP).

In Trp solution permeation, a high permselectivity was achieved by using water and methanol as a solvent as shown in Figure 3, while the enantioselectivity disappeared when ethanol or propanol with a higher affinity for the polymer was used as a solvent. In the permeation of aqueous 2-BuOH solution, the enantioselectivity disappeared also with increasing concentration from 3 wt % (Table 2, no. 12) to 7 wt %. These disappearances may be due to enlargement of the space by solvent or solute with high affinity for the polymer.

Enantioselective Adsorption. As mentioned above, the mechanism was suggested to be different from that of HPLC. To confirm this hypothesis, enantioselectivity in adsorption to a (+)-poly(DPSP) powder was examined for various racemates which could be enantioselectively separated by the permeation. As a result, no enantioselective adsorption was detected. Therefore, it was confirmed that the reason for the enantioselective permeation was not selective adsorption or dissolution at the membrane surface and the mechanism was different from that of HPLC.

Table 4. Analysis for Enantioselective Permeation through the (+)-Poly(DPSP) Membrane by the Solution-Diffusion Mechanism

no.[a]	racemate	solvent[b]	method[c]	P_R/P_S[d]	D_R/D_S[d]	S_R/S_S[d]
1	Trp	w	CP	2.6	2.5	1.0
4	Phe	m	CP	3.3	3.6	0.9
5	Val	m	CP	2.9	2.4	1.2
9	1,3-BD	none	EV	1.4	1.3	1.1
10	1,3-BD	m	PV	1.4	1.2	1.1
12	2-BuOH	w	CP	1.2	1.3	1.0

[a] Numbers correspond to those in Table 2. [b] See Table 2. [c] CP, concentration-driven permeation; EV, evapomeation; PV, pervaporation. [d] P_R and P_S, D_R and D_S, and S_R and S_S are the permeation rate, diffusion coefficient, and solution coefficient for the (*R*)- and (*S*)-isomer, respectively.

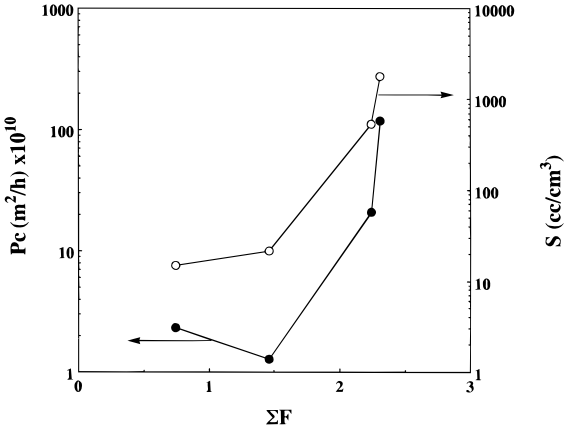

Figure 9. Dependence of the permeability coefficient (P_c) and the solution coefficient (S) on $\sum F$ of permeant in CP: $\sum F$ is the sum of the hydrophobic fragmental constants.[13]

Analysis by the Solution-Diffusion Mechanism. Since this membrane is nonporous, it is possible to analyze the enantioselective permeation by the solution-diffusion mechanism, i.e., $P_c = DS$, where P_c is the permeation coefficient, D is the diffusion coefficient, and S is the solution coefficient. Table 4 summarizes the results of the analysis. The S ratios of the (*R*)-isomer to the (*S*)-isomer (S_R/S_S) are about unity, while the D ratios of the (*R*)-isomer to the (*S*)-isomer (D_R/D_S) are close to the P_c ratios (P_{c_R}/P_{c_S}). Since the P_{c_R}/P_{c_S} values are governed by the D_R/D_S values, the enantioselectivity occurred not in the solution process but in the diffusion process. In other words, the enantioselective permeation was achieved not by selective dissolution at the membrane surface but by selective diffusion through the chiral space formed by the pinanyl groups in the membrane. This result is consistent with the lack of enantioselective adsorption described above.

On the other hand, the P_c value was governed not by the D value but by the S value. In the case of CP, the P_c and S values increased with an increase in $\sum F$ as shown in Figure 9, indicating that racemates with higher affinity for the polymer permeated more rapidly. The factor of determining the selectivity was different from that of determining the permeation rate in this permeation.

Effect of the Bulky Pinanyl Group on the Membrane Performance. Table 1 shows characteristics of (+)-poly(DPSP) together with poly(TMSP), which has the same main chain as that of (+)-poly(DPSP) and is known to be the highest oxygen permeable membrane (having the highest P_{O_2}) of all nonporous membranes owing to its large space between the macromolecules. The average molecular weight and strength of (+)-poly(DPSP) are similar to those of poly(TMSP) but permeability coefficients for oxygen (P_{O_2}) and water (P_{H_2O}) are

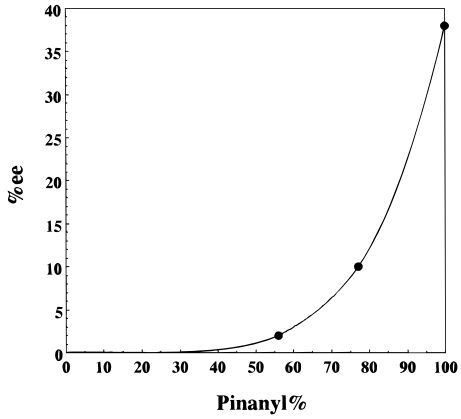

Figure 10. Dependence of the content (mol %) of pinanyl groups in the (co)polymer on the enantioselectivity (% ee in the permeate).

much lower than those of poly(TMSP). The membrane performance of the (+)-poly(DPSP) membrane is found to be fully distinct from that of the poly(TMSP) membrane. In addition, the density of (+)-poly(DPSP) was higher than that of poly(TMSP). Therefore, the bulky pinanyl groups of (+)-poly(DPSP) may be densely packed into the intermolecular spaces.

In Trp permeation through the copolymer of (−)-DPSP with a small amount of TMSP, the enantioselectivity significantly decreased as shown in Figure 10. This finding indicates the space among the bulky pinanyl groups was enlarged by removing a small amount of the bulky chiral pinanyl groups. Therefore, the achievement of enantioselective permeation through this membrane needs a great number of the chiral pendant groups packed densely. In order to enhance the density of the group, the introduction of additional chiral pinanyl groups was attempted by the cross-coupling reaction of lithiated α-methyl groups of (+)-poly(DPSP) with chiral pinanyldimethylchlorosilanes but was unsuccessful. Therefore, (+)-poly(DPSP) has insufficient additional space to introduce additional chiral pinanyl groups. Consequently, the chiral pinanyl groups in (+)-poly(DPSP) were packed densely to a maximum degree, and the small spaces among the densely packed bulky chiral pendant groups may be necessary for highly enantioselective permeation.

Conclusions

Various racemates—tryptophan (Trp), 1,3-butanediol (1,3-BD), and so on—permeated enantioselectively through a (+)-poly{1-[dimethyl(10-pinanyl)silyl]-1-propyne} [(+)-poly(DPSP)] membrane having a self-supporting ability. Especially in the initial period of permeation, almost perfect optical resolution was achieved for racemates of Trp, phenylalanine (Phe), valine (Val), and 1,3-BD (81−100% ee), and after the initial period, enantioselective permeation (12−48% ee) was retained for a long time. In addition, by permeation of vapor permeant such as evapomeation and pervaporation, higher permeation rates were attained, maintaining high enantioselectivity. In the case of the (+)-poly(DPSP) membrane, (*R*)-1,3-BD permeated predominantly, while the (*S*)-isomer did in the case of the (−)-poly(DPSP) membrane. It was found that the small space among many chiral pinanyl groups in this membrane caused the enantioselective permeation.

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Supporting Information Available: Procedure of the synthesis of (+)-(methylbutyldimethylsilyl)propyne [(+)-MBSP], results of adsorption experiments to (+)-poly(DPSP) (supplementary Table 1), method for estimation of *P* and *D* (supplementary Figure 1), apparatuses of PV and EV (supplementary Figure 2), results of CP for 2-butanol (supplementary Figure 3), and results of PV for DAc-1,3-BD (supplementary Figure 4) (8 pages). Ordering information is given on any current masthead page.

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(14) The values of *P* and % ee for the initial period indicate the values before or near the permeation time when one enantiomer has permeated and the other has not permeated through a membrane.
(15) We reported in our previous communication (ref 10) that the permeation under similar conditions showed an (*S*)-Trp permselectivity, opposite to the result of this paper. In the communication, the % ee was determined by using a polarimeter. After the communication was published, the % ee of the identical sample was determined by using a chiral HPLC instead of a polarimeter and the permselectivity was found to be (*R*)-Trp permselectivity, identical to the results of this paper. In addition, the (*R*)-Trp permselectivity was reproducibly observed. Therefore, *R* selectivity is true. In a later investigation, we found the observation of the opposite selectivity to be due to small amounts of some impurities in the ion-exchange water used in the polarimeter measurement. Since in the polarimeter measurement the water solvent (20 mL) was removed from the permeate and the resulting solid was dissolved in water (1 mL) again, the impurities were concentrated. In order to avoid the contamination, distilled water was used instead of the ion-exchange water in this study.
(16) Small peaks other than that of 1,3-BD were for some impurities which 1,3-BD used for the feed contains originally. In an initial period, some impurities were concentrated by the membrane permeation.
(17) Since racemic 1,3-BD cannot be separated by a chiral HPLC at present, it is derivatized to the acetate and then analyzed by the HPLC.
(18) The difference of the absolute value of the specific rotation between the permeates through a (−)-poly(DPSP) membrane and that through a (+)-poly(DPSP) membrane may be ascribed to the difference of the period of the permeation time. The former permeation was during an initial period and the latter was after the initial period.
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