S0032-3861(96)00630-1

Polymer Vol. 38 No. 1, pp. 235–238, 1997

0032-3861/97/$17.00 + 0.00

Enantioselective permeation of racemates through a solid (+)-poly{2-[dimethyl(10-pinanyl)silyl]norbornadiene} membrane

Toshiki Aoki*, Makoto Ohshima, Ken-ichi Shinohara†, Takashi Kaneko, and Eizo Oikawa

Graduate School of Science and Technology, Niigata University, Ikarashi 2-8050, Niigata 950-21, Japan

(Received 29 March 1996; revised 17 May 1996)

A novel norbornadiene polymer having optically active pinanyl groups in the pendant groups was synthesized as an optical resolution membrane material. The resulting polymer membrane showed highly enantioselective permeability for racemic propranolol used as a medicine. The permeability of tryptophan was much higher than that of a (+)-poly{1-[dimethyl(10-pinanyl)silyl]-1-propyne} membrane we reported previously. Copyright © 1996 Elsevier Science Ltd.

(Keywords: pinanyl group; optical resolution membrane; propranolol)

Introduction

Since optically active compounds are closely related to biological and pharmacological activity, the development of an effective method for producing them is very important. Conventional optical resolution methods, such as preferential crystallization, chemical modification to a diastereomer with an optical resolution agent, and high-performance liquid chromatography (h.p.l.c.)[1], can produce only very low amounts of optically active compounds in one operation.

On the other hand, optical resolution through a solid membrane is expected to realize the treatment of a large amount of racemic compounds. Several optical resolution solid membranes have been reported by us[2–6] and other groups[7–9]. However, they had several disadvantages, for example low selectivity, low permeability, and/or low mechanical strength. In particular, a (+)-poly{1-[dimethyl(10-pinanyl)silyl]-1-propyne}((+)-poly(DPSP), *Scheme 1*) membrane showed enantioselective permeability with high enantioselectivity (max. 89% e.e.) for various racemates, for example, 1,3-butanediol, 2-butanol, and tryptophan[4–6]. However, the permeation rate was low, and the membrane was not able to separate hydrophobic racemates such as *sec*-phenethyl alcohol and phenylthio-2-butanol[6] because the polymer membrane was swelled by hydrophobic racemates. In addition, this membrane was a little brittle and was not durable for pressure-driven permeation[4].

In this study, we synthesized (+)-poly{2-[dimethyl-(10-pinanyl)silyl]norbornadiene} ((+)-poly(DPSN), *Scheme 1*) which had the same optically active pendant groups as that of (+)-poly(DPSP), and a more flexible main chain than that of (+)-poly(DPSP), and then we measured enantioselective permeability for (RS)-propranolol (Prp, *Scheme 1*) and (RS)-tryptophan (Trp) through this polymeric membrane.

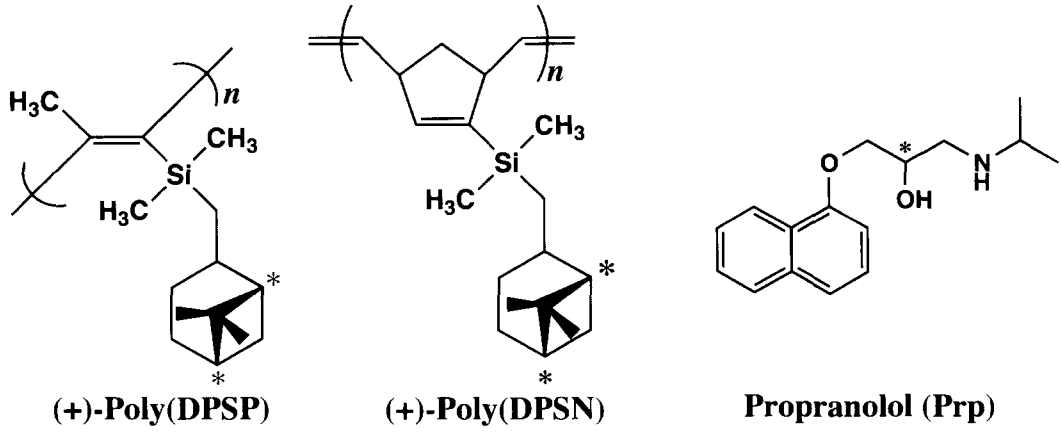
* To whom correspondence should be addressed

† Research Fellow of the Japan Society for the Promotion of Science (No.19961758)

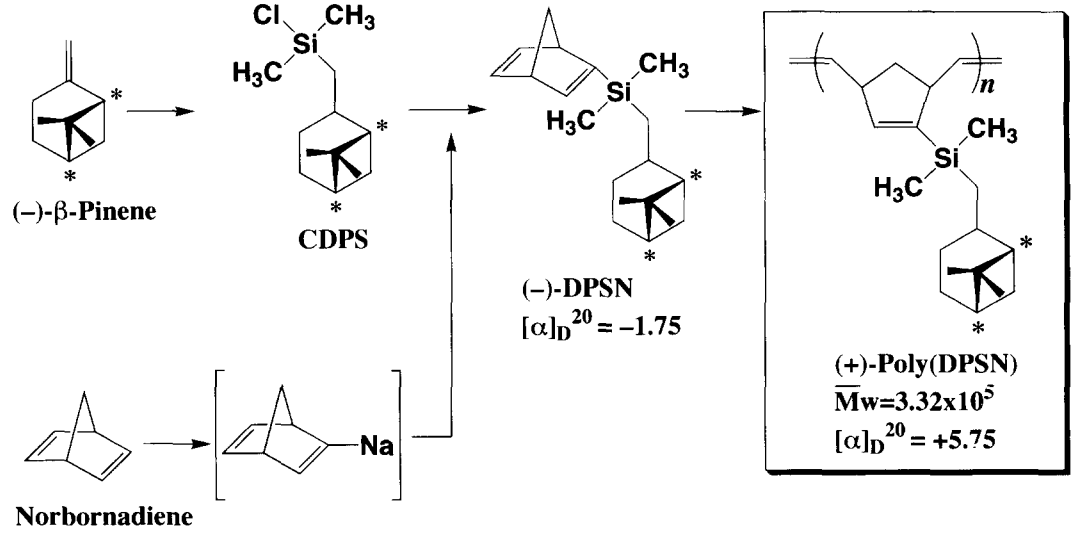
Experimental

Materials. (−)-β-Pinene and 2,5-norbornadiene were obtained from Aldrich Inc. and were used without further purification. Chloroplatinic acid hexahydrate ($H_2PtCl_6 \cdot 6H_2O$), WCl_6, and $(CH_3)_4Sn$ were purchased from Wako Chemicals Co. Racemic solutes used for enantioselective permeation and adsorption experiments were as follows: propranolol (Prp, Daicel Chemical Co.), tryptophan (Trp, Junsei Chemical Co.), *sec*-phenethylalcohol (Aldrich Inc.), and mandelic acid (Junsei Chemical Co.).

Synthesis (Scheme 2). *Chlorodimethyl(10-pinanyl)silane (CDPS).* CDPS was prepared by hydrosilylation of (−)-β-pinene with dichlorodimethylsilane according to our previous paper[4]. *(−)-2-[(10-pinanyl)silyl]norbornadiene [(−)-DPSN]*[10]. Tetrahydrofuran (THF) (50.0 ml), sodium *t*-butoxide (7.65 g, 79.5 mmol), and 2,5-norbornadiene (8.36 g, 90.7 mmol) were added slowly to 1.57 mol l^{-1} *n*-butyllithium THF solution (50.0 ml, 78.5 mmol) under stirring at −90°C. This solution was kept at −50°C for 15 h and CDPS (16.5 g, 71.6 mmol) was added and the solution was stirred for 1 h. After usual work-up, the product was purified by vacuum distillation. Yield 33.4%; b.p. 95°C (0.20 mmHg); ^{1}H nuclear magnetic resonance (n.m.r., $CDCl_3$): δ (ppm) 0.06 (s, 6H, $Si(C\underline{H}_3)_2$ 0.80 and 1.18(2s, 6H, *gem*-$(C\underline{H}_3)_2$ in pinane), 0.60–2.03 (m, 11H, C<u>H</u> and $C\underline{H}_2$ in pinane), 2.05 (m, 2H, $C\underline{H}_2$ in norbornadiene), 3.67 (m, 2H, 2C<u>H</u> of norbornadiene bridgehead), 6.68 (m, 2H, <u>H</u>C=CH), 7.00 (d, 1H, SiC=C<u>H</u>); I.r. (NaCl, cm^{-1}): 1252 (Si–CH_3), 1576 (C=C), 2912 (C–H); $[\alpha]_D^{20}$ −1.75 (*c* 0.970 g dl^{-1}, CCl_4). *(+)-Poly{2-[dimethyl(10-pinanyl)silyl]norbornadiene} [(+)-poly(DPSN)]*[11]. To WCl_6 (21.3 mg, 5.37×10^{-2} mmol) and $(CH_3)_4Sn$ (20.0 μl, 1.44×10^{-1} mmol) in toluene (23 ml) was added (−)-DPSN (610 mg, 2.13 mmol) at room temperature in nitrogen. After stirring for 4 h, the mixture was poured into methanol. The polymer was purified by reprecipitation from the toluene solution into methanol. Yield



Scheme 1 Chemical structures of (+)-poly(DPSP), (+)-poly(DPSN), and propranolol



Scheme 2 Synthetic route to (+)-poly(DPSN)

98.3%; ^{1}H n.m.r. ($CDCl_3$): δ (ppm) 0.08 (s, 6H, $Si(C\underline{H}_3)_2$), 0.84 and 1.18 (2s, 6H, *gem*-$(C\underline{H}_3)_2$ in pinane), 0.65–2.35 (m, 13H, C<u>H</u> and $C\underline{H}_2$ in pinane and norbornadiene), 3.28 (b, 1H, C<u>H</u>C=C of bridgehead), 3.70 (b, 1H, C<u>H</u>C(Si)=C of bridgehead), 5.25 (b, 1H, C<u>H</u>=C), 5.85 (b, 1H SiC=C<u>H</u>); $[\alpha]_D^{20}$ +5.75 (*c* 1.10 g dl^{-1}, CCl_4); T_g 42°C. *2-(Trimethylsilyl)norbornadiene (TMSN)*[10]. TMSN was synthesized from 2,5-norbornadiene and chlorotrimethylsilane according to the literature[10]. Yield 59.6%; b.p. 52°C (12.0 mmHg); ^{1}H n.m.r. ($CDCl_3$): δ (ppm) 0.08 (s, 9H, $Si(C\underline{H}_3)_3$), 1.88 (m, 2H, $C\underline{H}_2$), 3.66 (m, 1H, C<u>H</u>C(Si)=C of bridgehead), 3.73 (m, 1H, C<u>H</u>C=C of bridgehead), 6.70 (m, 2H, <u>H</u>C=CH), 7.03 (d, 1H, SiC=C<u>H</u>). *Poly[2-(trimethylsilyl)norbornadiene[poly(TMSN)]*[11]. TMSN was polymerized according to the literature[11]. Yield 45.6%; ^{1}H n.m.r. ($CDCl_3$): δ (ppm) 0.07 (s, 9H, $Si(C\underline{H}_3)_3$), 1.54 and 2.33 (2s, 2H, $C\underline{H}_2$), 3.23 (b, 1H, C<u>H</u>C(Si)=C of bridgehead), 3.60 (b, 1H, CHC=C of bridgehead), 5.27 (b, 2H, <u>H</u>C=CH), 5.80 (b, 1H, SiC=C<u>H</u>).

Membrane preparation. A 10% (w/v) THF solution of (+)-poly(DPSN) was cast on a polytetrafluoroethylene 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.

Permeation measurements. The membrane with 3.00 cm diameter was placed in the glass cell. A 0.500 wt% of (RS)-Prp methanol solution or a 0.100 wt% (RS)-Trp aq. solution was used as a feed solution. The permeability coefficient (P in m^2 h^{-1}) was calculated from the slope of a Q–t plot where Q is quantity of the solute in the permeate and t is permeation time. The enantiomeric excess (%e.e.) was determined using h.p.l.c. (Tosoh Co.) with chiral columns (Daicel Chemical Co.): CROWNPAK CR® (for Trp) and CHIRALCELL OD® (for Prp).

Adsorption experiments. (+)-Poly(DPSN) powder (39.0 mg) was added to a 0.100 wt% aq. solution of a racemate (40.0 ml) and the mixture was stirred for 24 h. The (+)-poly(DPSN) containing the adsorbed compound was filtered and then washed with water for 24 h to desorb the compound from the (+)-poly(DPSN) powder. Enantioselectivity (% e.e.) was determined by a method similar to that for the permeation described above.

Measurements. For gel permeation chromatography (g.p.c.) measurements, a Hitachi 655A-11 liquid chromatograph (Column: polystyrene gel) was used. ^{1}H n.m.r. spectra were recorded on a Varian Gemini 200H (200MHz) n.m.r. spectrometer. Thermal analysis was made on a Shimadzu DSC-50.

Table 1 Characteristics of (+)-poly(DPSN), (+)-poly(DPSP), and poly(TMSN)

Polymer[a]	$\overline{M}_w$[b] ($\times 10^5$)	T_g[c] (°C)	Membrane[d] forming ability
(+)-Poly(DPSN)	3.32	42	++
Poly(TMSN)	1.43	115	−
(+)-Poly(DPSP)	1.80	148	+

[a] (+)-Poly(DPSN), (+)-poly{2-[dimethyl(10-pinanyl)silyl]norbornadiene}; poly(TMSN), poly[2-(trimethylsilyl)norbornadiene)]; (+)-poly(DPSP), (+)-poly{1-[dimethyl(10-pinanyl)silyl]-1-propyne}, see ref. 4
[b] By g.p.c. correlated to polystyrene standard
[c] By d.s.c., heating rate: 10°C min^{-1}
[d] ++, excellent; +, good; −, poor

Results and discussion

(−)-DPSN, synthesized from (−)-β-pinene and 2,5-norbornadiene, was polymerized by using WCl_6 as a catalyst and $(CH_3)_4Sn$ as a cocatalyst (*Scheme 2*). *Table 1* summarizes the characteristics of (+)-poly(DPSN) together with poly(TMSN) having the same main-chain structure and (+)-poly(DPSP) having the same pendant group (*Scheme 1*). (+)-Poly(DPSN) had a high molecular weight similar to poly(TMSN) and (+)-poly(DPSP), and showed the best membrane-forming ability of three. It is worth noting that, in spite of the very bulky substituent, a high-molecular-weight polymer capable of forming a tough membrane could be obtained. The glass transition temperature (T_g) of (+)-poly(DPSN) was near room temperature and much lower than those of poly(TMSN) and (+)-poly(DPSP)[4]. Indeed a (+)-poly(DPSN) membrane was more flexible and tough compared with (+)-poly(DPSP) at room temperature.

Figure 1 shows the plots of quantity of permeated (R)- and (S)-Trp from aq. racemic solution *versus* permeation time through (+)-poly(DPSN) membrane together with the result of (+)-poly(DPSP)[6]. The permeability coefficient (P 4.54×10^{-9} m^2 h^{-1}) of (+)-poly(DPSN) membrane for Trp was much higher than that (2.72×10^{-10} m^2 h^{-1}) of a (+)-poly(DPSP) membrane having higher selectivity. This may be because the main-chain of (+)-poly(DPSN) is more flexible than that of (+)-poly(DPSP).

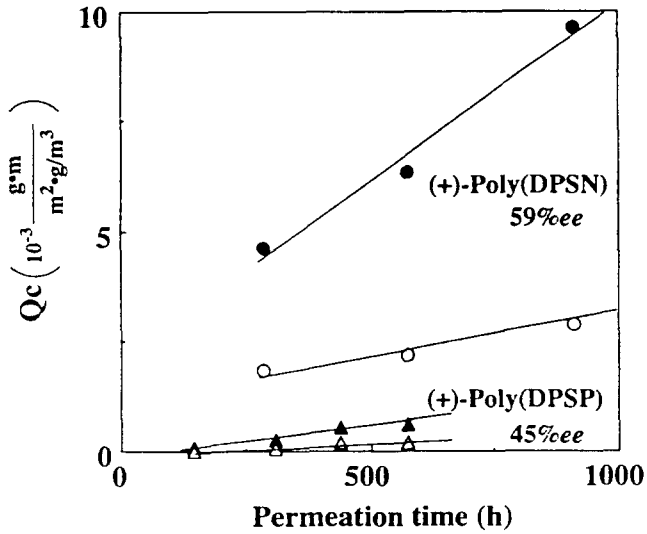


Figure 1 Plots of normalized quantity (Q_c) of permeated (R)-(●, ▲)- and (S)-(○, △)-tryptophan (Trp) from aq. racemic solution (0.100 wt%) vs permeation time through (+)-poly(DPSN) (●, ○) and (+)-poly(DPSP) (▲, △) membrane

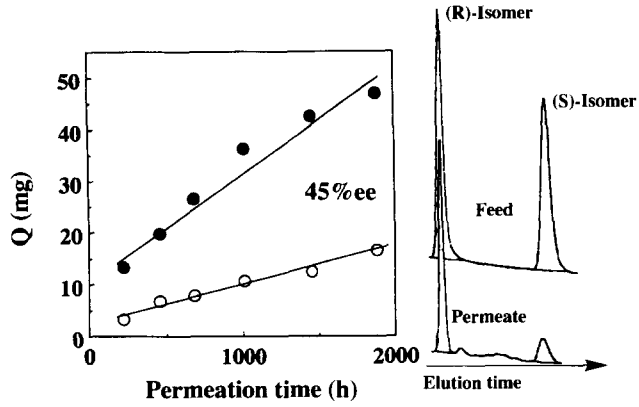


Figure 2 (Left) Plots of quantity (Q) of permeated (R)-(●)- and (S)-(○)-propranolol (Prp) from methanol racemic solution (0.500 wt%) vs permeation time through (+)-poly(DPSN) membrane. (Right) Chromatogram of h.p.l.c. of Prp: (above) racemic Prp in the feed, (below) Prp in the permeate during 650–1000 h. Column: CHIRALCELL-OD®; eluent: hexane/isopropanol = 19/1 (v/v)

Figure 2 shows the plot of quantity of permeated (R)- and (S)-Prp (*Scheme 1*) from racemic methanol solution *versus* permeation time through (+)-poly(DPSN) membrane. The (R)-(+)-isomer permeated preferentially. The % e.e. and P values were 45% and 2.80×10^{-10} m^2 h^{-1}, respectively. This means that the (R)-isomer permeated 2.7 times faster than the (S)-isomer. This is the first example of optical resolution for Prp by membrane permeation. Moreover, this enantioselective permeation was stable for 2000 h. Since Prp is useful for medicine and one of the hydrophobic compounds which could not separate (+)-poly(DPSP) membrane, this attainment is significant.

This polymer also showed enantioselective adsorption for *sec*-phenethylalcohol (66% e.e.), mandelic acid (12% e.e.), and Trp (82% e.e.). Therefore, (+)-poly(DPSN) is expected for an enantioselective adsorbent. Judging from the difference in the enantioselectivity between the permeation and the adsorption for Trp, the enantioselective permeation was suggested to be not caused only by selective dissolution into the membrane surface.

In conclusion, (+)-poly(DPSN) membrane showed enantioselective permeability for Prp which was useful and hydrophobic and higher permeability than (+)-poly(DPSP). Since this membrane was flexible and tough, attainment of much higher permeation is expected by application of pressure.

Further research into enantioselective permeation of other racemates and its mechanism is now in progress.

Acknowledgement

Partial financial support by a Grant-in-Aid for Scientific Research (No.08651049) from the Ministry of Education, Science, and Culture, Japan.

References

1 Morrison, J. D. 'Asymmetric Synthesis, Analytical Methods', 1983, Academic Press, New York
2 Aoki, T., Tomizawa, S. and Oikawa, E. *J. Membr. Sci.* 1995, **99**, 117
3 Aoki, T., Maruyama, A., Shinohara, K. and Oikawa, E. *Polym. J.* 1995, **27**, 547

4 Aoki, T., Shinohara, K. and Oikawa, E. *Makromol. Chem., Rapid Commun.* 1992, **13,** 565
5 Shinohara, K., Aoki, T. and Oikawa, E. *Polymer* 1995, **36,** 2703
6 Aoki, T., Shinohara, K., Kaneko, T. and Oikawa, E. *Macromolecules* 1996, **29,** 4192
7 Maruyama, A., Adachi, N., Takatsuki, T., Torii, M., Sanui, K. and Ogata, N. *Macromolecules* 1990, **23,** 2748
8 Ishihara, K., Suzuki, N. and Matsui, K. *Nihonkagakukaishi* 1987, **3,** 446
9 Nakagawa, T., Toyokawa, Y., Abe, M. and Higuchi, A. *Macromol. Symp.* 1994, **84,** 209
10 Stähle, M., Lehmann, R., Kramer, J. and Schlosser, M. *Chimia 1985,* **39,** 229
11 Stonish, D. A. and Weber, W. P. *Polym. Bull.* 1991, **26,** 493