Enantiomer Enrichment of Oxprenolol through Cellulose Tris(3,5-dimethylphenylcarbamate) Membrane

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SYNOPSIS

Enantioselective enrichment of racemic oxprenolol dissolved in a hexane-2-propanol mixture was achieved with a solid chiral polymer membrane consisting of cellulose tris(3,5-dimethylphenylcarbamate) coated on a Teflon membrane filter. The oxprenolol obtained through the membrane was rich in (S)-isomer up to about 50% ee at initial stage and (R)-enrichment of a source phase (23% ee) was achieved. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

Separation of enantiomers through chiral membranes is an attractive process from a continuous and energetically efficient standpoint. Until now, a number of studies on optical resolution of racemic compounds through a liquid membrane containing a chiral mobile carrier such as chiral crown ethers[1-3] and their polymeric derivatives,[4] cyclodextrins,[5] and amino acid derivatives[6] have been reported. Optical resolution of an amino acid by a polymer membrane bearing an amino acid condensate was also reported.[7] However, only a few studies have been reported on the separation of enantiomers by using membranes consisting of solid chiral polymers.[8-10] Significant results were reported on the enantioselective permeation of α-amino acids through a poly(α-amino acid)-derived membrane in a water system by Maruyama and Ogata et al.[8] Permeated tryptophan was rich in (D)-isomer and almost complete resolution was attained, although enantiomer enrichment of a source phase could not be achieved due to extremely slow permeation. Analogous enantioselective permeation of tryptophan was recently carried out using optically active polyacetylene derivative membranes by Aoki et al.[9] As for the enantioselective permeation of neutral racemic compounds by using a solid chiral polymer membrane in an organic solvent system, an example was found in a patent, where cellulose tribenzoate, tris(phenylcarbamate), and tris(p-chlorophenylcarbamate) were used as solid membranes and a racemic compound such as trans-stilbene oxide was partially resolved by liquid-liquid permeation.[10] Here we wish to report an efficient optical resolution of oxprenolol, which is known as an effective β-adrenergic blocking agent (β-blocker), with a polysaccharide-derivative membrane in an organic solvent system.

Phenylcarbamate derivatives of cellulose and amylose coated on silica gel have been widely used as chiral stationary phases (CSPs) for high-performance liquid chromatography (HPLC) and they show characteristic and efficient chiral recognition to a variety of racemic compounds.[11,12] Particularly, cellulose tris(3,5-dimethylphenylcarbamate) (CTPC) is one of the most useful CSPs. Moreover, CTPC membrane possesses high enantioselective adsorption power to some racemic compounds, for instance, oxprenolol.[13] The (S)-isomer of oxprenolol, which is the second-eluted enantiomer on the CTPC column for HPLC, is preferentially adsorbed on the CTPC membrane; and the enantiomeric excess (ee) of adsorbed oxprenolol reaches 60%. These results led us to use the CTPC membrane for the enantioselective permeation process.

EXPERIMENTAL

Membrane Preparation

CTPC was prepared according to the method previously reported.[11] Because the CTPC film obtained

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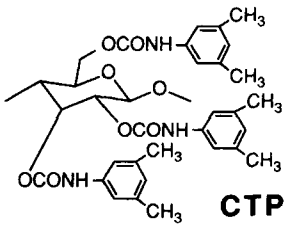
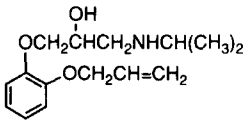


CTPC



oxprenolol

by casting a THF solution of CTPC was brittle, a Teflon membrane filter (Advantec, 25 mm ϕ, 0.10 μm pore) was used as the support. The CTPC membrane was prepared by soaking a Teflon membrane filter into a THF solution of CTPC (50 mg ml^{-1}), followed by drying on a glass plate under nitrogen at room temperature. The amount of CTPC coated on a Teflon membrane was about 18 mg. An electron microscopic analysis of the CTPC membrane showed that both sides of the Teflon membrane filter were homogeneously covered with CTPC without a pinhole. The thickness of the CTPC layer was about 30 μm.

Permeation Experiment

A pair of glass cells (U-type) illustrated in Figure 1 was used for permeation experiments. The CTPC membrane was held between the cells. Effective membrane area was 3.14 cm^2. The membrane was washed with a hexane-2-propanol (9 : 1) mixture before use. The amount and ee of oxprenolol which permeated through the CTPC membrane were estimated on an HPLC instrument (JASCO PU-980) equipped with a UV detector (JASCO UV-970) by using a CTPC column (250 × 4.6 (i.d) mm) and hexane-2-propanol–diethylamine (80 : 20 : 0.1) mixture as an eluent.[14]

Enantioselective permeation experiments were carried out at 30°C in two ways. One was the usual liquid-liquid permeation using glass cells (Fig. 1). A racemic solution of oxprenolol (12 mg) in hexane-2-propanol (9 : 1) (12 ml) was placed in one side (source phase) of the glass cells and 15 ml of hexane-2-propanol (9 : 1) in the opposite side (receiving phase). The solutions of both phases were stirred during the experiment. From the receiving phase, 100 μl or 200 μl solution was withdrawn and analyzed by HPLC at appropriate time intervals.

The other method was the modified permeation process devised in this study (Fig. 2). A racemic solution of oxprenolol (10 mg) in hexane-2-propanol (9 : 1) (10 ml) was placed in the source phase, and 3 ml of hexane-2-propanol (8 : 2) in the receiving phase. The analyte was allowed to permeate through the membrane or adsorb on the membrane for 60 min. During this procedure the source phase was stirred and the surface of the membrane on the receiving side was not contacted by the solvent of the receiving phase. After an appropriate time, the glass cell was tilted as illustrated in Figure 2 and the membrane was swept from the receiving side for 10 min to obtain oxprenolol that permeated through and was adsorbed by the membrane. During the extraction, the surface of the membrane on the source side should not contact the racemic solution of the source phase. The extraction solvent was renewed at every extraction procedure in the course of the experiment. This permeation–extraction process was carried out by using hexane containing various amounts of 2-propanol as an extraction solvent, at various permeation times.

RESULTS AND DISCUSSION

The CTPC membrane was first employed as a device for enantioseparation of oxprenolol by the usual liquid–liquid permeation technique. A pair of glass cells (Fig. 1) was used through the experiments. Oxprenolol was chosen as a racemate, which is adsorbed enantioselectively on the CTPC membrane; recovered oxprenolol by the single adsorption-desorption procedure is rich in (S)-isomer and the ee reaches 60%.[13]

In the liquid–liquid permeation experiment, (R)-isomer preferentially permeated through the membrane at the initial stage. After 10 min, the analyte in the receiving phase was (R)-rich up to 18% ee and the amount was ca. 0.15 mg (1.25% of the feed). But after that, the % ee of oxprenolol in the receiving phase decreased rapidly and became nearly racemic

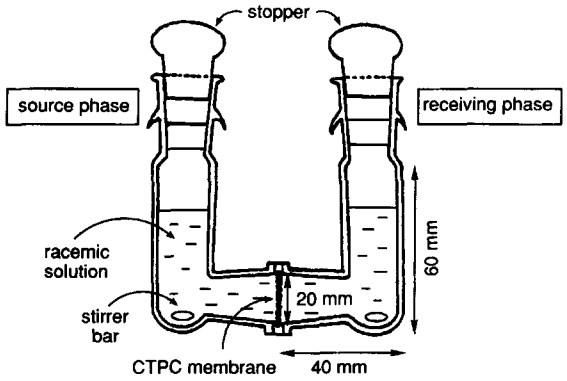


Figure 1 Illustration of the glass cells.

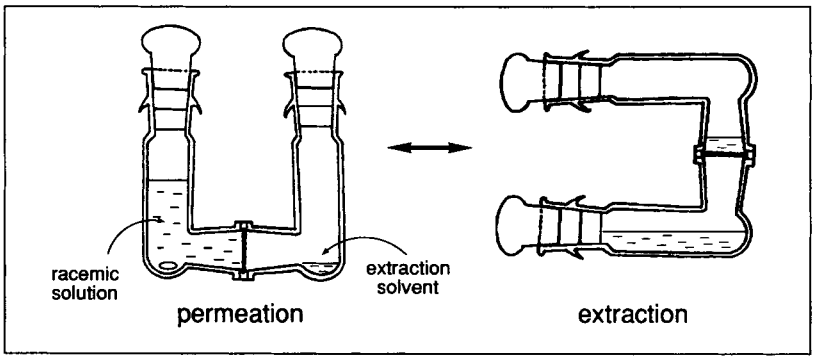


Figure 2 "Permeation–extraction" procedure in the enantioselective permeation.

within 1 h. This result indicates that almost-racemic oxprenolol permeated through the membrane, except in the initial stage. The permeation rate of (R)- and (S)-enantiomers was ca. 0.75 mg h^{-1} at initial 60 min and gradually slowed. In the optical resolution of oxprenolol on the CTPC column by HPLC, (R)-isomer elutes first, followed by (S)-isomer. This indicates that (S)-isomer interacts with the CTPC more strongly than (R)-isomer. In consideration of these results, we assumed that similar phenomena occurred in the initial stage of permeation through the membrane; (R)-isomer, which interacts weekly with the CTPC, may quickly permeate into the membrane, while the (S)-isomer may be preferentially adsorbed in the CTPC membrane to permeate slowly. After adsorption of oxprenolol in the CTPC membrane comes to equilibrium, (R)- and (S)-isomers probably diffuse through the membrane without interacting with the chiral CTPC. Moreover, the CTPC swells in hexane-2-propanol (ca. 20% swelling in hexane-2-propanol [9 : 1]). This may be another reason for the lack of success of enantioselective permeation in the liquid–liquid permeation.

Similar results were obtained by C. Linder et al.[10] In their patent, trans-stilbene oxide was enantioselectively resolved through cellulose tribenzoate and tris(*p*-chlorophenylcarbamate) membranes by liquid–liquid permeation in a hexane-2-propanol system; ee of permeated trans-stilbene oxide ranged from 30% to 10% at the initial stage. Enantioselectivity decreased as the concentration of permeated trans-stilbene oxide increased. However, Linder et al. claimed that enantioselectivity was restored by changing the receiving solution containing permeated trans-stilbene oxide to a fresh solvent.

After the liquid–liquid permeation experiment, we found that the oxprenolol adsorbed on the membrane which could not be permeated through the membrane was (S)-rich in a high ee (61%). This value is almost the same as the value observed in the enantioselective adsorption using the CTPC membrane as previously reported.[13] This implies that enantiomer enrichment is possible if oxprenolol adsorbed in the membrane in a high ee is efficiently recovered by other appropriate means.

We devised a new technique called a permeation–extraction procedure, in which the sides of the membrane were not simultaneously contacted with source and receiving solutions to avoid permeation of racemic oxprenolol through the membrane. First the source side of the membrane was contacted with the racemic solution sufficiently to permit oxprenolol to permeate into the membrane and adsorb on the CTPC. Then the glass cells were tilted and the membrane was swept from the receiving side to obtain oxprenolol permeated and adsorbed on the

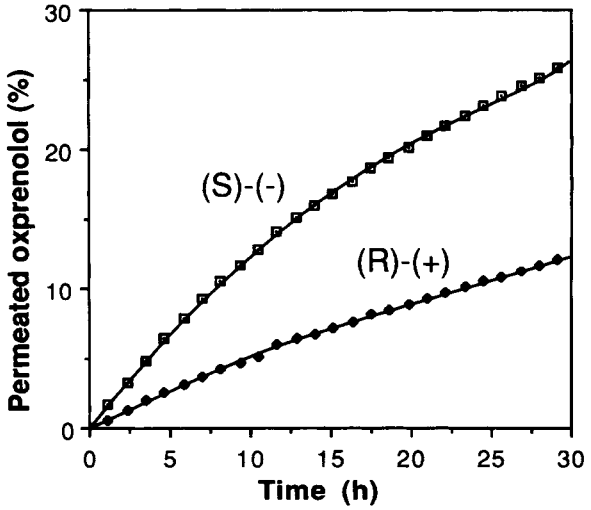


Figure 3 Permeation behavior of (RS)-oxprenolol through CTPC membrane by "permeation–extraction" procedures using hexane-2-propanol (7 : 3) as the extraction solvent at 30°C.

Table I Results of Enantioseparation of Oxprenolol through CTPC Membrane for 30 h at 30°C

	Feed	Remaining Oxprenolol	Permeated Oxprenolol
Amount (mg)	10	6.1 (61%)[a]	3.8 (38%)[a]
%ee[b]	0	22.9 (R)	36.2 (S)

[a] Parentheses show the percentage of the amount of oxprenolol.
[b] Parentheses show the configuration of the excess enantiomer.

membrane at regular time intervals (Fig. 2) as described in the Experimental section. The recovered oxprenolol was rich in (S)-isomer by about 50% ee at the initial stage. This value was close to that obtained by the enantioselective adsorption experiment (60% ee).[13]

The (R)-enrichment of the source phase was achieved by repetition of the permeation–extraction procedure. Figure 3 shows the time dependence of the amount of enantiomers of oxprenolol in the experiment using hexane-2-propanol (7 : 3) as an extraction solvent. After 30 h, when 38% of the oxprenolol in the source phase was transported, the remaining oxprenolol was (R)-rich up to 23% ee. The results are summarized in Table I. This may be the first successful enantiomer enrichment of a neutral racemic compound using a solid chiral polymer membrane in an organic solvent system. The permeation rates of (−)-(S)- and (+)-(R)-oxprenolols during the first five permeation–extraction procedures were 0.13 and 0.05 mg h^{-1}, respectively, and their flux rates were 1.6×10^{-3} and 0.64×10^{-3} mol h^{-1} m^{-2}, respectively. The permeation rate of (S)-isomer was one-fifth of that observed in the liquid–liquid permeation experiment.

The enantioselectivity and the permeation rate were affected by the content of 2-propanol in the extraction solvent and also by the permeation time. Tables II and III show the effects of content of 2-propanol or permeation time on the % ee, permeation rate, and relative permeation rate of (S)-isomer to that of the liquid–liquid permeation. These data were obtained as the average value of oxprenolol recovered by the first five permeation–extraction procedures. For comparison, the results obtained by the liquid–liquid permeation experiment are also shown.

When hexane-2-propanol (8 : 2) was used as the extraction solvent, the % ee of permeated oxprenolol and the permeation rate showed maximum values (Table II). The less polar solvent, hexane-2-propanol (9 : 1), was not appropriate to extract (S)-isomer adsorbed on the membrane, and therefore, the % ee and the permeation rate lowered. On the other hand, the % ee and permeation rate also decreased with an increase in the content of 2-propanol. It has been reported that 2-propanol greatly affected the % ee and amount of oxprenolol adsorbed enantioselectively on the CTPC membrane.[13] In these cases, 2-propanol which was adsorbed on the membrane during the extraction procedures may probably prevent the enantiomers from the effective enantioselective adsorption.

When the permeation time was 30 min, the % ee of the oxprenolol was as high as that for 60 min. At a shorter time, 15 min, the % ee lowered to 43%, probably because adsorption did not reach equilibrium within 15 min.[13] In this permeation–extraction procedure, adsorption probably reached equilibrium

Table II Effect of 2-Propanol in the Extraction Solvent on Enantioseparation of Oxprenolol[a]

	Permeated Oxprenolol				
Hexane : 2-propanol	%ee	V_S (mg h^{-1})[b]	V_R (mg h^{-1})[c]	V_S/V_R	Relative Rate[d]
9 : 1	39	0.091	0.040	2.3	1/8.2
8 : 2	48	0.140	0.050	2.8	1/5.4
7 : 3	43	0.134	0.053	2.5	1/5.6
6 : 4	41	0.130	0.054	2.4	1/5.8
Liquid–liquid[e]	~ 0	~ 0.75	~ 0.75	~ 1	1

[a] Average of the initial five permeation–extraction procedures.
[b] Permeation rate of (S)-isomer.
[c] Permeation rate of (R)-isomer.
[d] Relative permeation rate of (S)-isomer to that in liquid–liquid permeation.
[e] Liquid–liquid permeation.

Table III Effect of Permeation Time on Enantioseparation of Oxprenolol[a]

Permeation Time (min)	Permeated Oxprenolol				
	%ee	V_S (mg h^{-1})[b]	V_R (mg h^{-1})[c]	V_S/V_R	Relative Rate[d]
60	48	0.134	0.053	2.5	1/5.6
30	47	0.201	0.073	2.8	1/3.7
15	43	0.286	0.115	2.5	1/2.6
Liquid–liquid[e]	~ 0	~ 0.75	~ 0.75	~ 1	1

[a] Average of the initial five permeation–extraction procedures.
[b] Permeation rate of (S)-isomer.
[c] Permeation rate of (R)-isomer.
[d] Relative permeation rate of (S)-isomer to that in liquid–liquid permeation.
[e] Liquid–liquid permeation (see text).

within 30 min. The permeation rate increased as the permeation time was decreased. The permeation rate of (S)-isomer at the permeation time of 15 min was 1/2.6 of that of the liquid–liquid permeation (Table III).

In conclusion, in the liquid–liquid permeation of oxprenolol through the CTPC membrane in hexane-2-propanol, enantioselectivity was very low because of swelling of the membrane. However, the enantiomeric enrichment through the membrane was enabled by the permeation–extraction process. The oxprenolol obtained through the membrane was rich in (S)-isomer up to about 50% ee at initial stage and (R)-enrichment of a source phase (23% ee) was achieved. The procedure developed in this study may be applicable to a large scale, automatic, and continuous separation of enantiomers.

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