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Enantiomer Separation with Cellulose Tris(3,5-dimethylphenylcarbamate) Membrane. Enantioselective Adsorption and Desorption

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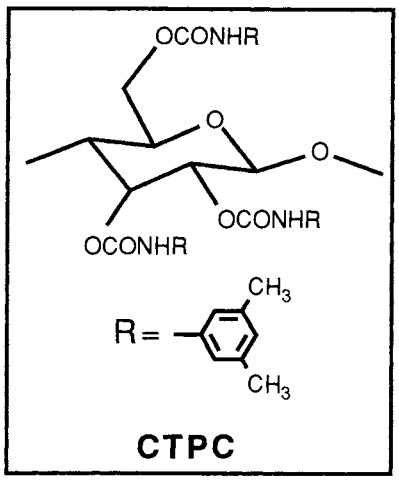
The enantioselective adsorption of some racemic compounds was investigated on cellulose tris(3,5-dimethylphenylcarbamate) membrane supported on a Teflon membrane filter. The highly enantioselective adsorption was observed for β-blockers such as oxprenolol. The enantiomeric excess of adsorbed oxprenolol reached up to 60%. The enantioselective desorption on the membrane was also studied.

In the past decade, many chiral stationary phases (CSPs) for high-performance liquid chromatography (HPLC) have been developed.[1] Among them, CSPs prepared from phenylcarbamate derivatives of polysaccharides have been attracting attention because they show characteristic and efficient chiral recognition abilities to wide range of racemic compounds.[2] Particularly, cellulose tris(3,5-dimethylphenyl-carbamate) (CTPC) is one of the most powerful CSPs when it is coated on silica gel.[3]



CTPC

In this study, we prepared CTPC membrane in order to develop a new chiral polymer device for enantiomer separation. The enantioselective adsorption of some racemic compounds on the membrane was investigated and the chiral resolving power of the membrane was compared with that of the CTPC used as a CSP for chiral HPLC. The observed results will serve to elucidate the mechanism of chiral recognition of CTPC.

Tröger's base(**1**), trans-stilbene oxide(**2**), 1-(9-anthryl)-2,2,2-trifluoroethanol(**3**), and β-adrenergic blocking agents (β-blockers) such as propranolol(**4**), alprenolol(**5**), and oxprenolol(**6**) were used as analytes. Most racemic compounds were commercially available or were prepared by the usual procedures. The CTPC was prepared according to the method previously reported.[3] The CTPC membrane was prepared by soaking a Teflon membrane filter (Advantec; 25 mm ϕ, 0.10 μm pore) into a THF solution of CTPC

(10 ml, 50 mg / ml), followed by drying under nitrogen. The amount of CTPC coated on a Teflon membrane was 11 - 14 mg.

The enantioselective adsorption was carried out in a sample bottle (10 ml) with a screw cap, in which 4 ml of hexane-2-propanol (Hex-2-PA) (9 / 1 v/v) solution of a racemic analyte (1 mg / ml) was placed. The CTPC membrane was sinked in the racemic solution at 30 °C for 90 min. Adsorption equilibrium was reached within 5 min and 30 min for analytes **3** and **6**, respectively. Then, the membrane was taken out and washed with Hex-2-PA (9/1) as quickly as possible to remove the racemic solution attached on the surface of the membrane. The analyte adsorbed on the membrane was almost completely desorbed by slightly heating and sonicating the membrane in 3 ml of Hex-2-PA (7/3 v/v). The amount and enantiomeric excess (ee) of the analyte adsorbed on the CTPC membrane was estimated by HPLC using a CSP consisting of CTPC coated on silica gel.

The results of enantioselective adsorption on the CTPC membrane are summarized in Table 1. The enantioselectivities were reproducible to about ±10% on repeated runs. The CTPC membrane showed chiral recognition ability for all racemates, particularly for β-blockers with high enantioselectivities. The (S)-(-)-isomers of β-blockers, which are much more effective as β-adrenergic agent (50-500 fold) than the (R)-(+)-isomers,[4] were preferentially adsorbed on the membrane. Oxprenolol rich in (S)-isomer up to 60 %ee was obtained by the single adsorption-desorption procedure. Since many optically active polymers have been prepared so far and their chiral recognition abilities were evaluated, this is, to the best our knowledge, the first successful example of enantioselective adsorption of racemic compounds in organic solvents by chiral polymer membrane.[5]

The enantioselectivities correspond to the separation factors (α) observed in the HPLC

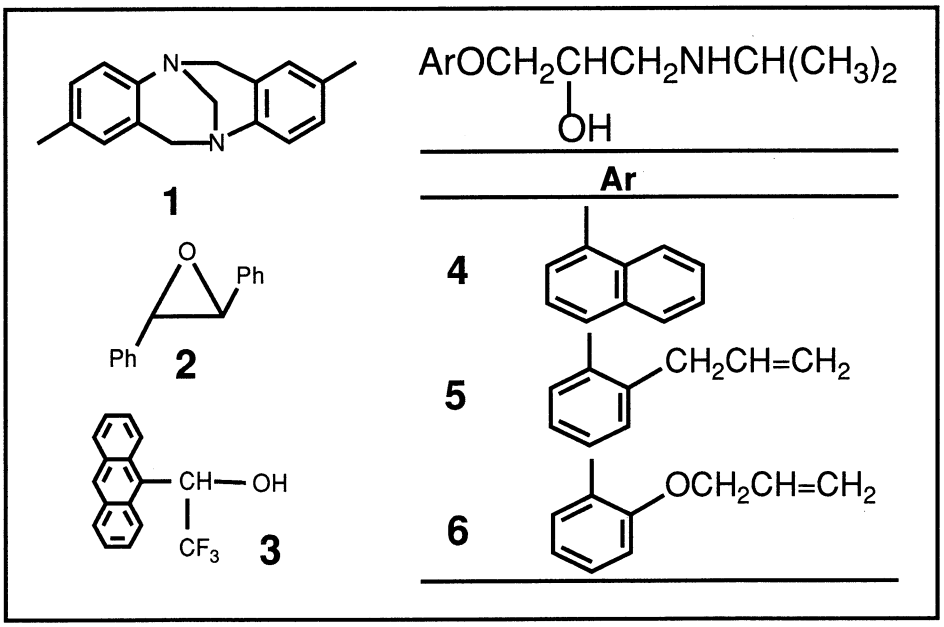


Table 1. Enantioselective Adsorption on the CTPC Membrane[a)]

		Analyte adsorbed		
Racemate	CTPC(mg)	mg(%)[b)]	ee(%)[c)]	α[d)]
1	13.7	0.10 (0.8)	9.3((-)-1S,3S)	1.32(-)
2	13.1	0.14 (1.1)	23.5((-)-1S,2S)	1.68(-)
3	13.6	0.29 (2.1)	39.8((+)-S)	2.59(+)
4	13.2	0.28 (2.1)	31.6((-)-S)	2.39(-)
5	14.3	0.14 (1.0)	38.3((-)-S)	3.87(-)
6	12.4	0.31 (2.5)	59.3((-)-S)	6.03(-)

a) Average of 3 - 5 independent runs. b) In parentheses is shown weight% to CTPC.
c) In parentheses are shown the sign of optical rotation and configuration of the enantiomer preferentially adsorbed on the CTPC membrane.
d) Separation factor in the optical resolution by HPLC using CTPC column.[3,6)] In parentheses is shown the sign of optical rotation of the 2nd-eluted enantiomer.

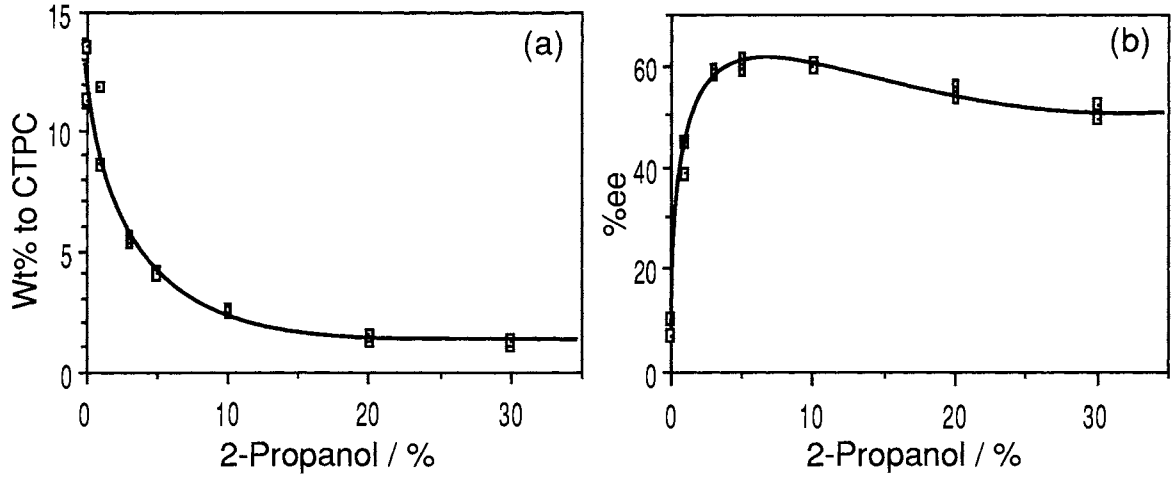


Fig. 1. Effect of 2-propanol on the amount (a) and %ee (b) of oxprenolol adsorbed on the CTPC membrane in the enantioselective adsorption.

separation of these analytes using CTPC as a CSP.[2,6)] The analytes which were better resolved on the CTPC column were adsorbed more enantioselectively on the membrane. The 2nd-eluted enantiomers on the CTPC column were adsorbed more strongly on the CTPC membrane than the first-eluted enantiomers. Besides THF, acetone and dioxane were used to prepare CTPC membrane. However, the difference in the enantioselectivity of oxprenolol on the membrane was not regarded as significant.

The enantioselectivity was greatly dependent on the content of 2-PA in hexane. The changes in %ee and the amount of oxprenolol adsorbed on the CTPC membrane were plotted against the content of 2-PA (Fig. 1). The increase in 2-PA content results in a decrease in the amount of oxprenolol adsorbed on the membrane. On the other hand, %ee of the oxprenolol increased with an increase in the content of 2-PA and reached a maximum value (~61 %ee) at around 5% 2-PA, and then gradually decreased. Same tendency was observed in case of analyte **3**. The maximum %ee was 42% at around 3% 2-PA. These results indicate that the enantiomers and 2-PA adsorb competitively on the membrane.

In the enantioselective adsorption experiments, the analytes adsorbed on the CTPC membrane were almost completely desorbed by using Hex-2-PA (7/3). However, we have found that the use of a less polar solvent such as Hex-2-PA (99/1 or 99.5/0.5) brings about enantioselective desorption which allows to enrich one enantiomer in good recovery.

The CTPC membrane, on which oxprenolol had been adsorbed in 60±5 %ee previously, was sinked in 5ml of Hex-2-PA (99/1 or 99.5/0.5) at 30 °C for about 1 h. Oxprenolol slightly rich in (S)-isomer by 20±10 %ee was first desorbed, and the remaining oxprenolol (80±5 %ee) on the membrane was obtained in 65±5% recovery. In a similar manner, the (+)-isomer-rich analyte **3** (65 %ee) was obtained in 50% recovery, starting from 34 %ee **3** by the enantioselective desorption.

In conclusion, the CTPC membrane possesses highly enantioselective adsorbing power, particularly to β-blockers. These findings suggest that the present system will be applicable to a new device for enantiomer separation system, *i.e.*, enantioselective permeation process. In this direction, further study is now in progress.

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