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Continuous and Preparative Enantioseparation of Oxprenolol with Cellulose Tris(3,5-dimethylphenylcarbamate)-coated Belt

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Abstract: Enantiomer enrichment of oxprenolol up to 68 % enantiomeric excess was achieved by using a cellulose tris(3,5-dimethylphenylcarbamate) (CTPC)-coated rayon-belt. The *chiral belt* was successfully used for the first time in the continuous, rapid and preparative resolution of oxprenolol.

Recently, many efforts have been paid to developing new methods for large-scale, preparative separation of enantiomers. These involve membrane mediated separations using liquid membranes with a chiral mobile carrier[1] and solid chiral polymer membranes.[2] Among them, a hollow-fiber membrane system developed by Pirkle et al. is attractive from the continuous and preparative standpoint.[3] They used fatty esters and amides of (*S*)-leucine as chiral selectors for resolution of racemic amino acid derivatives.

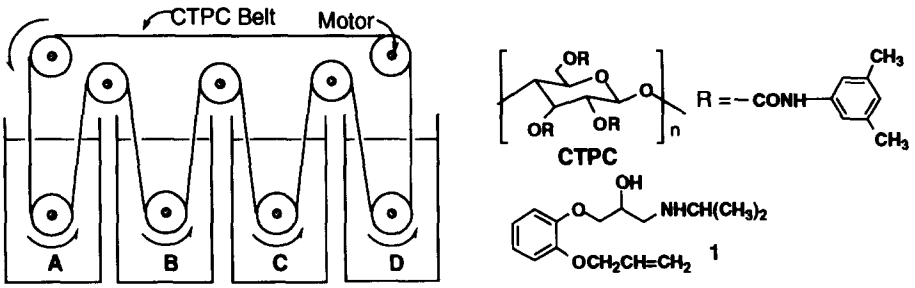

Fig. 1 An apparatus used in the resolution of (±)-**1** by *chiral belt*. A: **1** in hexane-2-propanol (Hex-2-PA) (9/1, 100 ml), B: Hex-2-PA, 95/5 (100 ml), C: Hex-2-PA, 7/3 (100 ml), D: hexane (100 ml).

Here, we report preparative, continuous and rapid resolution of oxprenolol (**1**), a β-adrenergic blocking agent (β-blocker), with cellulose tris(3,5-dimethylphenylcarbamate) (CTPC)-coated rayon-belt in organic media. CTPC has been widely used as a chiral stationary phase (CSP) for high-performance liquid chromatography (HPLC)[4] and is of great advantage for the easy preparation of a film or membrane. Therefore, the CTPC membrane can be used as the polymeric chiral selector for direct enantioseparation of some racemic compounds by a simple enantioselective adsorption[5] or permeation.[2d] These results promoted us to make a *chiral belt* consisting of CTPC-coated rayon for continuous, preparative separation of enantiomers of **1**.

CTPC was prepared according to the method previously reported.[4] The *chiral belt* was prepared by soaking a commercially available rayon ribbon (1.5 cm width, 120 cm length, 4.82 g) in a THF solution of CTPC (50 mg/ml), followed by drying in a desiccator under reduced pressure. The amount of CTPC coated on the rayon was *i.e.* 410 mg. An apparatus used for the enantioseparation is illustrated in Fig. 1. The CTPC belt (effective length, 111 cm) was fitted with the apparatus in a loop form and rotated at a constant speed of 33,

64, or 100 cm/h by a motor. The closed belt goes into a 100 ml of racemic solution of **1** (A: 0.5, 1.0, or 2.0 mg/ml) for enantioselective-adsorption, next into an enantioselective-desorption solvent (B), a desorption solvent (C: receiving phase), and then into a rinse solvent (D). Phase B is necessary not only for removing the solution of **1** attached on the surface of the belt, but also for an increase of the selectivity.[5]

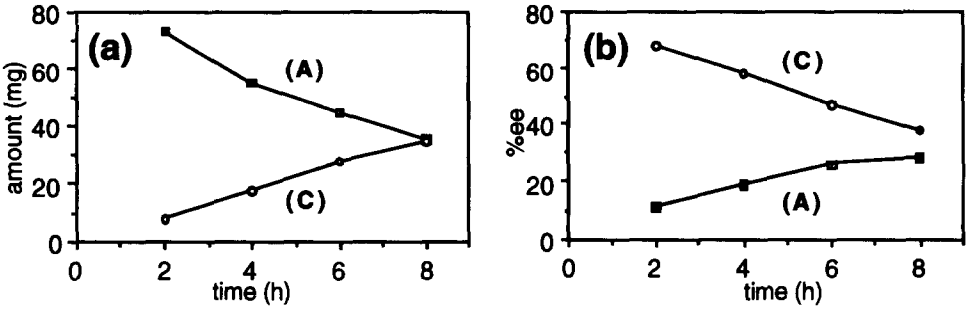

Fig. 2 Change in the amount (a) and ee (b) of **1** in the source (A) and receiving (C) phases; rotating rate, 64 cm/h; concentration of **1** in the source phase (A), 100 mg/100 ml.

Fig. 2 shows the amount (a) and ee (b)[6] in the source (A) and receiving (C) phases as a function of time at a constant speed 64 cm/h. The source phase (A) gradually became rich in (R)-isomer and reached up to 28 %ee after 8 h when about 65 % of **1** in the source phase was transported, while **1** in the receiving phase (C) was rich in (S)-isomer showing more effective activity than (*R*)-isomer, up to 68 %ee at the initial stage (after 2 h). As in most membrane-based systems, the selectivity (%ee in C) decreased with time. However, if the source phase can be kept as almost racemic, high level enantioselectivity will be maintained.

When the rotating rate was slower (33 cm/h), transport rate decreased, but the selectivity was similar. On the other hand, when the rotating rate was kept 100 cm/h, the selectivity became an slightly low level; the ee of **1** in the receiving phase (C) was 57 % at the initial stage. A high level of enantioselectivity (67 %ee at the initial stage) and high speed transport of **1** by a factor of 1.5 were achieved even when the concentration of **1** in the source phase (A) doubled (200 mg/100 ml). The present method can scale up without any difficulty and may be used for a large-scale separation.

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6. The amount and ee of **1** were estimated at regular time intervals by HPLC using CTPC as the chiral column with a hexane-2-propanol-diethylamine (80:20:0.1) mixture as the eluent: Okamoto, Y.; Kawashima, M.; Aburatani, R.; Hatada, K.; Nishiyama, T.; Masuda, M. *Chem. Lett.* **1986**, 1237.

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