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Preparative Separation of Enantiomers Using Hollow-Fiber Membrane Technology

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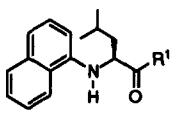
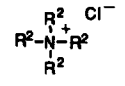
Abstract: Several chromatographically developed chiral selectors show promise for large scale separation of enantiomers using hollow-fiber membrane technology. Chiral selectors derived from *N*-(1-naphthyl)leucine have been used in a hollow-fiber membrane system (Sepracor) to separate the enantiomers of amino acid derivatives. Enantiomeric purities exceeding 95% have been obtained in a single pass through the system. For data collection, sample sizes were limited to gram quantities of racemate.

When bonded to silica, esters and amides of *N*-aryl amino acids afford chiral stationary phases (CSPs) useful for the separation of the enantiomers of a broad spectrum of compounds. For example, an *N*-(1-naphthyl)leucine-derived CSP shows separation factors of 12 to 60 for the enantiomers of various esters and amides of *N*-(3,5-dinitrobenzoyl)leucine.[1] While such high enantioselectivities exceed those needed for analytical or even preparative column chromatography, they make practical the resolution of racemates by batch adsorption[2] and by liquid-liquid partitioning systems.[3]

A variety of chiral agents have been used to explore the feasibility of the separation of enantiomers in liquid membrane devices with varying degrees of success.[4] Recently, the octadecyl ester of (*S*)-*N*-(1-naphthyl) leucine octadecyl ester (**1**) was shown to be an enantioselective transfer agent when incorporated in a simple supported liquid membrane system.[5] Using a hollow-fiber membrane system (Sepracor) and the dioctyl amide of (*S*)-*N*-(1-naphthyl)leucine (**2**) we have been able to separate the enantiomers of amino acid derivatives, achieving high enantiomeric purity. While gram quantities of racemate were used for data collection, it is clear that the present system could be used to resolve larger samples and that continuous (as opposed to batch) process scale separation of enantiomers is feasible by this approach.

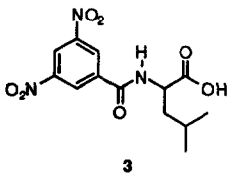


1 R^1 = $-O(CH_2)_{17}CH_3$
2 R^1 = $-N((CH_2)_7CH_3)_2$



R^2 = alkyl

Hexane



3

0.1 M Phosphate Buffer

Fatty esters and amides of (*S*)-*N*-(1-naphthyl)leucine (**1**, **2**) are soluble in hexane but insoluble in water. Conversely, *N*-(3,5-dinitrobenzoyl)leucine, **3**, is soluble in pH 7 buffer and not extracted into dilute hexane solutions of selectors **1** or **2**. However, addition of a hydrophobic phase transfer agent to the hexane-selector solution leads to enantioselective extraction of **3** into the hexane solution.

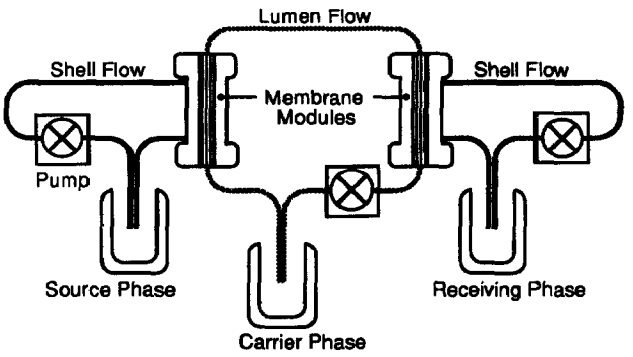


Figure 1. A diagram of the Sepracor MSX-750™ Membrane Solvent Extraction System.

A Sepracor MSX-750™ Membrane Solvent Extraction System fitted with two Model TS membrane modules was used in this study, Figure 1. Within a module, one liquid phase circulates through the hollow polyacrylonitrile fibers (310 μ O.D., 210 μ I.D.) while the second circulates over the *ca.* 0.75 m^2 surface area of the bundled fibers (shell). The system uses three independent circulating solvent loops. The water immiscible carrier phase flows in a closed loop from the center reservoir through the bore (lumen) of the fibers in both modules and back to the reservoir. The aqueous source and receiving phases circulate in separate closed loops, each through the shell of a module and back to the originating reservoir. The separation of the phases is maintained by regulating the relatively low pressures within the modules and the rates of flow. The magnetically-stirred, water-jacketed reservoirs were maintained at 18 °C.

In a typical run, 1.6 g of racemic **3** in 500 mL of 0.1 M phosphate buffer (the source phase) was circulated through the shell of one module while 500 mL of 0.1 M phosphate buffer (the receiving phase) was circulated through the shell of the other. The carrier phase, 500 mL of hexane 0.02 M in (*S*)-**2** and 0.001 M in tetrahexylammonium chloride, was circulated through the lumen of both modules. The (*S*)-enantiomer of **3** preferentially partitions from the (initially) racemic source phase into the carrier phase and subsequently partitions into the receiving phase. As the source phase is

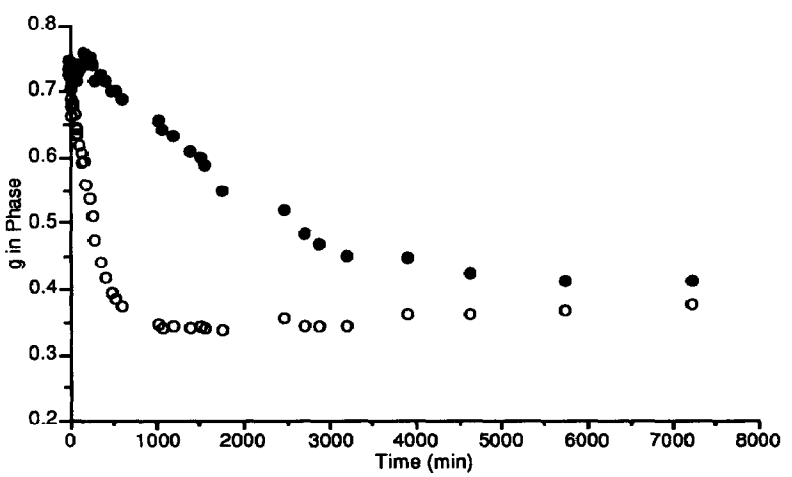


Figure 2. Enantioselective transport of *N*-(3,5-dinitrobenzoyl)leucine from the source phase. O = (*S*)-enantiomer, ● = (*R*)-enantiomer. The source phase originally contained 1.6 g of racemate in 500 mL of pH 7 buffer.

depleted of the more rapidly transported (*S*)-enantiomer, the rate and enantioselectivity of transport diminishes. The system eventually comes to equilibrium, the source and receiving phases having the same composition. Figures 2 and 3 show the concentration of each enantiomer in the source and receiving phases as a function of time.[6] Figure 4 shows the enantiomeric excess in the receiving phase as a function of time/extent of transport.

In this study, the rate of transport was intentionally slowed by the use of low concentrations of selector and ion-pairing reagent so as to facilitate data collection during the early portion of the run. Use of larger quantities of racemate extends the duration of the initial period of highly enantioselective transport. In addition to the presently used concentration gradient, temperature and/or pH gradients might be profitably employed to enhance selectivity, rate and extent of transport. For actual large scale operation, one would keep the source phase essentially saturated with racemate and employ a "double-barreled" arrangement in which a second hollow-fiber membrane unit using the other enantiomer of the selector also feeds from the source phase.[4b] As each enantiomer was transported from the source phase, the latter would remain essentially racemic and a high level of enantioselectivity for each enantiomer would be maintained so long as an adequate thermodynamic driving force for transport was maintained. In the event that a given selector-

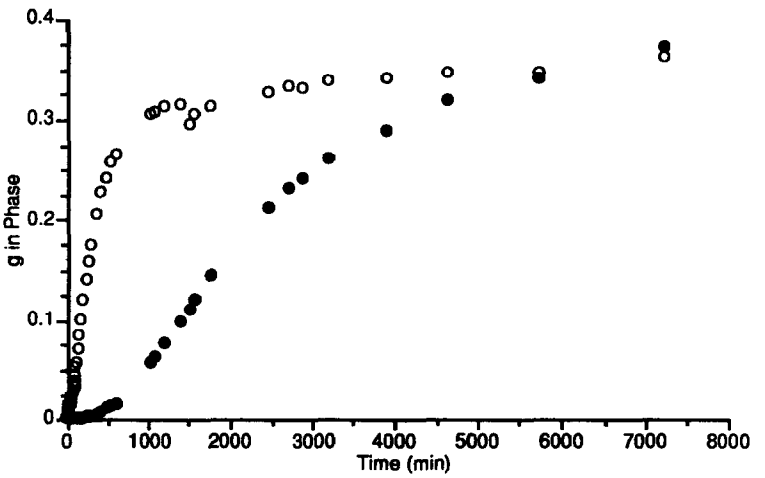


Figure 3. Enantioselective transport of *N*-(3,5-dinitrobenzoyl)leucine into the receiving phase. O = (*S*)-enantiomer, ● = (*R*)-enantiomer.

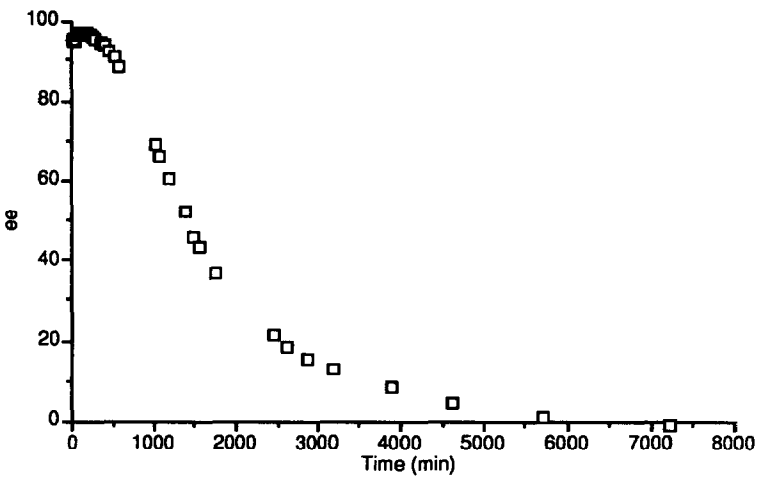


Figure 4. Enantiomeric excess of *N*-(3,5-dinitrobenzoyl)leucine in the receiving phase.

substrate combination afforded an undesirably low level of enantioselectivity, additional membrane units could be added (staging). Cussler and coworkers have used a hydroxyproline-derived chiral selector (typically employed in chiral ligand exchange chromatography) in a hollow-fiber membrane device.[7] Owing to selectivities (*d/l*) of less than 2.5, these workers used countercurrent flow of the two phases so as to cause each fiber to function as a low efficiency "chromatography" column. This enhances the extent of separation; complete separation of the enantiomers was reported. Since many enantiomers exhibit chromatographic separation factors in the range of 2 to 15 on various brush-type CSPs, one concludes that these compounds can be successfully resolved using a membrane method similar to that described but with the incorporation of the simple improvements discussed.[8]

Many of the engineering problems associated with hollow-fiber membrane systems have been solved. It is now a matter of developing appropriate chiral selectors to make possible the process-scale separations of commercially desired enantiomers by this technique.

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3. The enantiomers of various *N*-(3,5-dinitrobenzoyl) α-amino acid derivatives have been successfully separated by countercurrent chromatography. Chiral selector **1** was added to a hexane stationary phase, methanol-water serving as a mobile phase (J. Burns, unpublished data).
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6. Enantiomeric excesses were determined chromatographically using a column containing a CSP derived from (*R*)-*N*-(2-naphthyl)alanine of 33% enantiomeric excess and 3:1 methanol-water containing 0.025 M cetyltrimethylammonium bromide.
7. Ding, H. B.; Carr, P. W.; Cussler, E. L. *AIChE J.* **1992**, *38*, 1493-1498.
8. Though not presently described, similar experiments have been conducted with uncharged substrates. In such cases no phase transfer agent is required and methanol or acetonitrile was added to the aqueous phase to adjust substrate solubility.

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