Enantioselective Membranes

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Chiral Polymers of Intrinsic Microporosity: Selective Membrane Permeation of Enantiomers

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Abstract: *Following its resolution by diastereomeric complexation, 5,5′,6,6′-tetrahydroxy-3,3,3′,3′-tetramethyl-1,1′-spirobisindane (TTSBI) was used to synthesize a chiral ladder polymer, (+)-**PIM-CN**. (+)-**PIM-COOH** was also synthesized by the acid hydrolysis of (+)-**PIM-CN**. Following characterization, both (+)-**PIM-CN** and (+)-**PIM-COOH** were solvent cast directly into semipermeable membranes and evaluated for their ability to enable the selective permeation of a range of racemates, including mandelic acid (Man), Fmoc-phenylalanine, 1,1′-bi-2-naphthol (binol), and TTSBI. High ee values were observed for a number of analytes, and both materials exhibited high permeation rates. A selective diffusion–permeation mechanism was consistent with the results obtained with these materials. Their high permeability, processability, and ease of chemical modification offer considerable potential for liquid-phase membrane separations and related separation applications.*

The need for enantiomerically pure compounds creates incentive for the development of new strategies for the resolution of racemic mixtures.[1] Chromatographic methods, particularly gas–liquid and solid–liquid chromatography, have been the standard analytical approach for enantiomer separation.[2] High-performance liquid chromatography (HPLC) and diastereomeric crystallization remain the most important methods for the large-scale separation of enantiomers. However, most current resolution methods have some limitations. For example, diastereomeric crystallization often requires the resolution of reagents that are effective only for a specific system;[3,4] enzyme-mediated kinetic resolution faces decreased catalytic activity over time;[5,6] and chromatographic methods present the disadvantage of being discontinuous and expensive. Although the development of simulated moving bed chromatography (SMB) and supercritical-fluid chromatography (SFC) allows for continuous operation on a preparative scale,[7–10] specialized equipment, optimization studies for each substrate, and the cost of stationary phases detracts somewhat from the broad application of these methods.[11]

Membrane-mediated enantiomer separation offers an alternative technology.[12] Low energy consumption, high processing capacity, and continuous operation suggest membrane processes have the potential to satisfy many of the criteria for large-scale enantiomer enrichment. Dense enantioselective membranes can be divided into two classes: diffusion-selective membranes and sorption-selective membranes.[13,14] Diffusion-selective membranes are usually nonporous, and their proportionality of permeability and permeation selectivity is inverse, which can limit their application.[13] Sorption-selective membranes, on the other hand, generally require a porous support and chiral selectors.[14,15] Nonselective permeation is difficult to avoid with these materials.[14] Materials that are intrinsically chiral and have high porority can show both high permeability and high selectivity. However, the combination of these desirable features is rare. Furthermore, an ideal enantioselective membrane should be relatively straightforward to synthesize, possess satisfactory mechanical properties, and be processable for direct casting as a membrane.

One promising class of materials are polymers of intrinsic microporosity (PIMs).[16,17] The scaffold of a typical PIM contains a spiro center, which provides a site of contortion and inhibits bond rotation of the rigid fused rings. The combination of both features obstructs the efficient packing of polymer chains in the solid state, thus giving rise to microporosity in the material. Porosity originates solely from the molecular structure, which is independent of processing history.[16,17] These materials have attracted considerable attention as media for gas separation, gas storage, and the adsorption of volatile organic compounds, and as supports for heterogeneous catalysis.[18–20] All PIMs reported to date have been achiral, and all reported studies of materials incorporating 5,5′,6,6′-tetrahydroxy-3,3,3′,3′-tetramethyl-1,1′-spirobisindane (TTSBI(**1**)) have utilized the racemic form. Research on applications of this material for liquid-phase selective permeation has not been reported. Racemic **1** has also been used as a building block for siliconate tetraanionic molecular squares[21–24] and tetraanionic organoborate squares, as well as for the synthesis of racemic PIMs.[24]

Herein we report the resolution of **1** and the synthesis of two chiral polymers of intrinsic microporosity derived from this chiral monomer: chiral, fluorescent ladder polymers (+)-**PIM-CN** (Figure 1) and (+)-**PIM-COOH**. The organic soluble polymers were directly cast as porous membranes and were found to be effective in enabling the selective permeation of a range of enantiomers.

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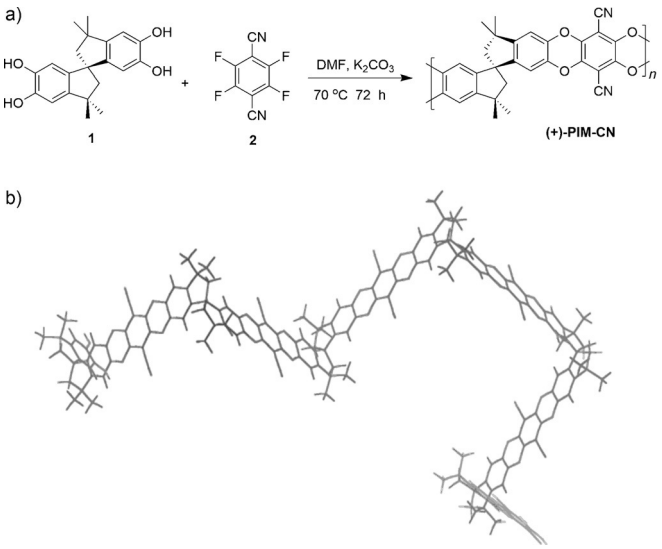


Figure 1. a) Condensation polymerization of (+)-**1** with **2**. b) A computer-modeled structure (Spartan, PM-3) of a random 5-mer. DMF = *N*,*N*-dimethylformamide.

The synthesis of a chiral PIM requires enantiomerically pure **1**. A number of approaches were explored, and the formation of diastereomeric complexes with (8*S*,9*R*)-(−)-*N*-benzylcinchonidinium chloride (**3**; see Scheme S1 in the Supporting Information) proved to be most successful.[25] Acetone was found to be the most effective solvent of those screened (see Table S1 in the Supporting Information). When racemic **1** was heated with **3** at reflux as a solution in acetone, a solid diastereomeric complex was obtained. ^{1}H NMR spectroscopic analysis and elemental analysis revealed that the precipitate contained the spirobisindane and the alkaloid in a 1:2 ratio (see Figure S1 and Table S2). Decomposition of the complex with 1N HCl gave (+)-**1** ($[\alpha]^{25}_{589nm} = +40.1°$, THF) in 70% overall yield (based on one enantiomer). HPLC on a chiral stationary phase established the spirobisindane to be enantiomerically pure (see Figure S3).

The condensation of enantiomerically pure (+)-**1** with 2,3,5,6-tetrafluorophthalonitrile (**2**) in DMF with excess K_2CO_3, according to a previously reported procedure for *rac*-**1**[18] resulted in the formation of (+)-**PIM-CN** in 96% yield (Figure 1a). (+)-**PIM-CN** had a specific rotation of $[\alpha]^{25}_{589nm} = +389.6°$ in THF. The polymer, a bright-yellow fluorescent solid, was characterized by gel permeation chromatography (GPC) and had a number-average molar mass, M_n, of 62239 g mol^{-1} and a weight-average molar mass, M_w, of 72778 g mol^{-1}, with a polydispersity (PDI) of M_w/M_n = 1.2. (+)-**PIM-CN** was an intrinsically porous polymer with a surface area of 740 m^2 g^{-1} and an average pore diameter (4V/A by BET) of 3.5 nm (see Table S3 and Figure S10).

The specific rotation of (+)-**PIM-CN** was approximately 10 times higher than that of the individual monomer **1**. Furthermore, the CD spectrum of (+)-**PIM-CN** (Figure 2) in THF showed a bisignate Cotton effect with a zero crossing at 240 nm. Although a random structure of the polymer is most probable, for chiral polymers without helicity, the specific rotation is usually similar to that of the chiral monomer.

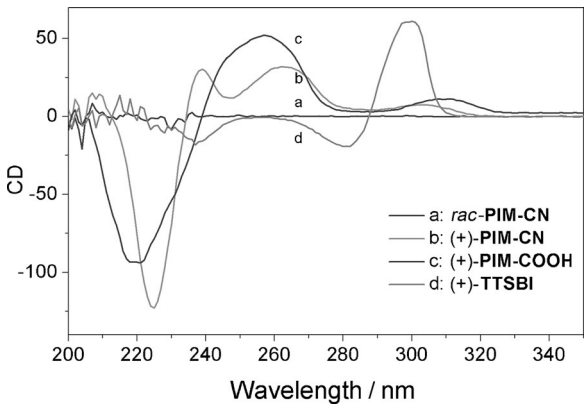


Figure 2. CD spectra of *rac*-PIM-CN (a), (+)-PIM-CN (b), (+)-PIM-COOH (c), and (+)-TTSBI (d).

Bisignate Cotton effects arise from exciton coupling of chiral ordered chromophores,[29,30] thus suggesting that some segments of the polymer chain have higher-ordered structure.[31,32]

(+)-**PIM-CN** can be cast as a free-standing porous thin film. The (+)-**PIM-CN** membrane was cast from THF solutions onto flat-bottomed watch glasses (inside diameter: 2 cm; see the Supporting Information). The membranes were fitted to a U-tube apparatus (average membrane thickness: 300 μm), and the concentration-driven permeation (CP) of racemates was evaluated (see Figure S11). The permeation rate (P (in g m m^{-2} h^{-1})) was estimated from the slope of a plot of normalized quantity Q (in g m m^{-2}) versus permeation time t (in h). Q is defined by the equation $Q = qL/A$, in which q is the quantity of permeated solute, and L and A are the thickness and effective area of the membrane, respectively.[33] The *ee* values were determined by HPLC analysis on chiral stationary phases.

Figure 3 shows the CP of a solution of (*R*,*S*)-mandelic acid (Man, 2 mg mL^{-1}) in methanol with (+)-**PIM-CN**. (*R*)-Man permeates the membrane preferentially, with an *ee* value of 31.4% at 8 h (Figure 3b). The permeation rate (P) was 0.07×10^{-3} g m m^{-2} h^{-1} (Table 1). We also investigated the permeation of (*R*,*S*)-binol. The *ee* value of material that had permeated through the (+)-**PIM-CN** membrane after 3 h was 53% (Figure 4b). Notably, the selective permeation of

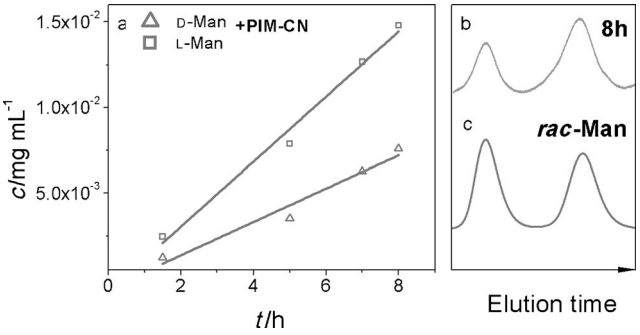


Figure 3. a) Enantioselective permeation of (*R*,*S*)-mandelic acid through (+)-**PIM-CN**. b) HPLC chromatogram of the receiver side at 8 h after the start of permeation. c) HPLC chromatogram of racemic Man. (For HPLC separation conditions, see Table S4).

Table 1: Permeation rate of racemates through (+)-**PIM-CN** and (+)-**PIM-COOH** membranes.

Chiral selector	Racemate	$10^3 P$ [g m m^{-2} h]	*ee* [%]	α[a]
(+)-**PIM-CN**	Man	0.07	32	1.92
(+)-**PIM-CN**	binol	0.019	53[b]	3.3[b]
(+)-**PIM-CN**	TTSBI	1.65	87[b]	14.4[b]
(+)-**PIM-COOH**	Fmoc-Phe	0.073	75	7

[a] Selectivity factor. [b] The selectivity and *ee* value were determined at an early stage of permeation (after 3 h for binol and 1 h for TTSBI).

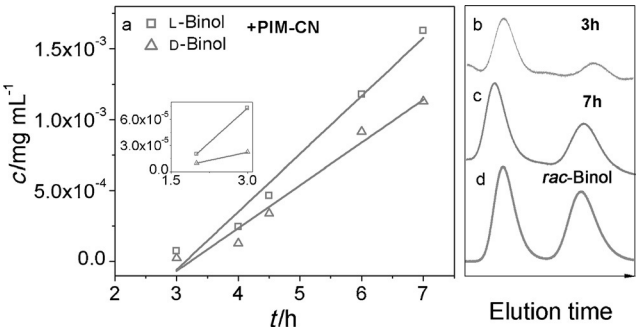
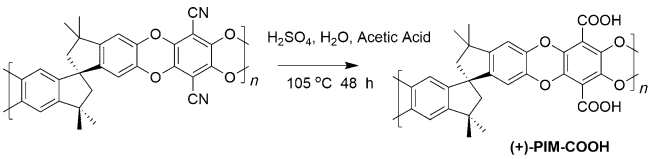


Figure 4. Enantioselective permeation of (*R*,*S*)-binol through (+)-**PIM-CN**. The inset shows the results at an early stage of permeation. b,c) HPLC chromatogram of the receiver side at 3 and 7 h, respectively, after the start of permeation. d) HPLC chromatogram of racemic binol.

spirobisindane (±)-TTSBI was also observed with (+)-**PIM-CN**: After 1 h, the *ee* value was 87% (see Figure S12). Thus, (+)-**PIM-CN** membranes have the potential to produce starting material for the replication of chiral membranes. Significantly, the permeation rates of the (+)-PIM membranes are higher than or comparable to those of previously reported nonporous solid (−)-OMPS/PMMA silicone chiral membranes[34] and a chiral, highly porous metal–organic framework (MOF) membrane[35] (Table 1; see also Table S8). We suggest that the significantly higher permeation is due to the intrinsic porosity of (+)-PIM polymers, thus emphasizing the significance of this class of enantiomerically pure materials for chiral resolution. Unlike chiral membranes based on polysaccharides[36] or chiral MOFs (CMOFs),[35,37,38] which often require the development of coating techniques on porous substrates, the solution processability of high-molecular weight (+)-PIMs facilitates the direct fabrication of porous, mechanically robust membranes with highly selective permeability.

Some insight into the origin of the highly selective permeation of Man, binol, and TTSBI by (+)-**PIM-CN** was obtained by measuring the adsorption of racemates by this material. Interestingly, within the analytical precision of the experiment, the adsorption of these compounds was not selective (see Table S5). We conclude that permeation through the (+)-**PIM-CN** membrane is based on a selective diffusion–permeation mechanism.[33]

(+)-**PIM-CN** can be chemically modified to expand the possible range of separation targets. To demonstrate this possibility, we prepared a carboxylated derivative by subjecting (+)-**PIM-CN** to acid hydrolysis to produce (+)-**PIM-COOH** (Scheme 1).[26] ^{1}H NMR, ^{13}C NMR, and IR spectroscopy (see Figures S6–S8) showed that hydrolysis proceeded to over 90% conversion into carboxylic acid groups without appreciable loss of molecular weight ($M_n = 67\,578$ g mol^{-1} and $M_w = 123\,760$; some broadening of the PDI occurred, to 1.8). According to the GPC results, the hydrolysis of (+)-**PIM-CN** with a strong acid was not destructive to the polymer backbone.[27,28] The modified material (+)-**PIM-CN** had a specific rotation of $[\alpha]^{25}_{589\,nm} = +378.3°$ in THF and exhibited a CD spectrum very similar to that of (+)-**PIM-CN**. (+)-**PIM-COOH** showed reduced solubility in solvents such as chloroform, dichloromethane, and DMSO, but greater solubility in THF. Whereas (+)-**PIM-CN** was fluorescent yellow, the solid (+)-**PIM-COOH** was dark-brown in color. Furthermore, as compared to (+)-**PIM-CN**, (+)-**PIM-COOH** films were slightly more brittle, probably as a result of interchain interactions between the carboxylic acid groups.[27,28] A decrease in the water contact angle of (+)-**PIM-CN** as compared to that of (+)-**PIM-COOH** from 100° to 30° suggests that the (+)-**PIM-COOH** membrane is considerably more hydrophilic, a property that could be advantageous for the permeation of more-polar analytes (see Figure S9).



Scheme 1. Hydrolysis of (+)-**PIM-CN** to (+)-**PIM-COOH**.

The carboxylate derivative (+)-**PIM-COOH** was also evaluated for enantioselective permeation. Although insufficient examples have been explored to generate guidelines for choosing the most suitable membrane for separation, the (+)-**PIM-COOH** membrane provided superior selective permeation of N-(9-fluorenylmethoxycarbonyl)phenylalanine (Fmoc-Phe) racemates as compared to (+)-**PIM-CN**. During the initial 1 h, 75% *ee* was observed (Table 1 and Figure 5b). The increased hydrogen-bonding interactions of (+)-**PIM-COOH** may contribute to the difference in performance.

Regarding the mechanism of permeation, we observed selective adsorption (68% *ee*) and permeation (75% *ee*) of (*S*)-Fmoc-Phe with (+)-**PIM-COOH** (see Figure S12; Figure 5d). That is, the isomer selectively absorbed and permeated was identical. In contrast to (+)-**PIM-CN**, selective sorption occurs within (+)-**PIM-COOH**; however, since the selectively absorbed enantiomer is also selectively permeated, the mechanism of the (+)-**PIM-COOH** material may still be classified as selective diffusion.[13,14]

Solid membranes through which enantiomers are selectively permeated on the basis of selective diffusion typically exhibit maximum enantioselectivity during the initial stage of permeation; selectivity generally decreases with time owing to competing nonselective diffusion of the more weakly binding enantiomer.[39] The (+)-PIM membranes in this study also exhibited a decrease in enantioselectivity as a function of time (see Figure S13). Besides a mechanism-based contribu-

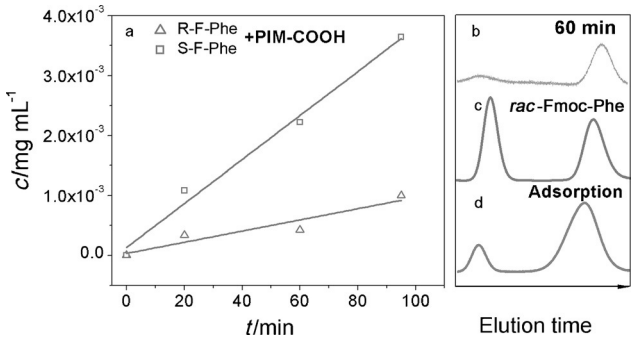


Figure 5. a) Enantioselective permeation of (*R*,*S*)-Fmoc-Phe through (+)-**PIM-COOH**. b) HPLC chromatogram of the receiver side at 1 h. c) HPLC chromatogram of racemic Fmoc-Phe. d) Selective adsorption of Fmoc-Phe over (+)-**PIM-COOH**.

tion, an additional factor is thought to be slight swelling of the membrane in methanol. Membranes soaked in methanol increase in volume by approximately 15% in 8 h. Enhanced nonselective diffusion can occur in the expanded pores of the polymer and contribute to a time-dependent increase in nonselective diffusion. Efforts are currently being made to stabilize these linear polymers by cross-linking.

In conclusion, we have prepared and characterized the first examples of chiral (+)-PIM materials. The polymers are soluble in organic solvents and can be cast as solid films with very high internal surface areas. When used as semipermeable membranes, the materials show both high and enantioselective permeability for a range of racemic compounds. The selectivity is highest during the initial stages of permeation. The unique properties of chiral (+)-PIM materials, exceptional porosity and solution processability, offer the potential to break the traditional barrier of an inverse proportionality of permeability and permeation selectivity. Analysis of uptake and permeation selectivity suggests a selective diffusion–permeation mechanism for (+)-**PIM-CN** and (+)-**PIM-COOH**. The intrinsic porosity of (+)-PIM polymers and the capacity for the introduction of functional groups on the polymers can be used to optimize solvent durability and loading capacity. This approach will provide the opportunity to expand the range of possible analytes and the ability to modulate permeation rates and selectivity. Further research on the scope of these chiral materials for the enantioselective permeation of racemates and applications in related separation techniques is now in progress.

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