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Chiral Separation of Racemic Amino Acids through Membranes derived from Modified Polysulfone Having Perillaldehyde Moiety as a Side Group

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Novel polymeric materials, having chiral environment, were obtained by the reaction of lithiated polysulfone with the chiral terpenoid perillaldehyde. The resulting polymers gave self-standing durable membranes that showed chiral separation ability by electrodialysis. In the present study, optical resolution of racemic glutamic acids was demonstrated. The dominant factor governing chiral separation ability was determined to be diffusivity selectivity from the results of permeation and adsorption selectivity.

Key words : chiral separation / optical resolution / perillaldehyde / polysulfone / pemselectivity / adsorption selectivity / diffusivity selectivity

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1. Introduction

Among separation technologies, membrane processes are perceived to be economically and ecologically competitive to conventional separation methods. Membrane separation technology can be done continuously under mild conditions and process scale-up is relatively easy. In addition, energy consumption is generally low[1)]. In the production of enantiopure compounds, membrane technology is expected to be promising alternative to conventional chiral resolution methods, such as diastereomer crystallization, preferential crystallization, kinetic resolution, and chromatography. Chiral separation with membranes can be divided into liquid and solid membranes. In the class of liquid membrane, optical resolution was carried out by bulk[2)], supported[3)], and emulsion liquid membranes[4)]. Optical resolution was also studied by solid (polymeric) membranes[5～24)], which are considered to be more durable than liquid membranes. As is well known, excepting optical activity, optically active chiral enantiomers have identical physicochemical properties. Thus, physical stereoselectivity is an important factor for the recognition and separation of optically active compounds. All synthetic membranes for optical resolution already reported[7～24)] possess such chiral microenvironments in them. In the present study, novel polymeric materials, having chiral environment, were obtained by the reaction of lithiated polysulfone with the chiral terpenoid perillaldehyde. The chiral separation ability of the resulting membranes was investigated.

2. Experimental Section

2.1 Materials

Radel® R5000 polyphenylsulfone (Solvay Advanced Polymers) (PPSf) was used as the parent thermoplastic polymer for post-modification. *n*-Butyllithium (10.0 mol dm^{-3} in hexane) and (1S)-(-)-perillaldehyde were obtained from Aldrich Chemical Co. and were used as received. Reagent grade tetrahydrofuran (THF) was freshly distilled over lithium aluminum hydride and under argon. N,N-Dimethylformamide

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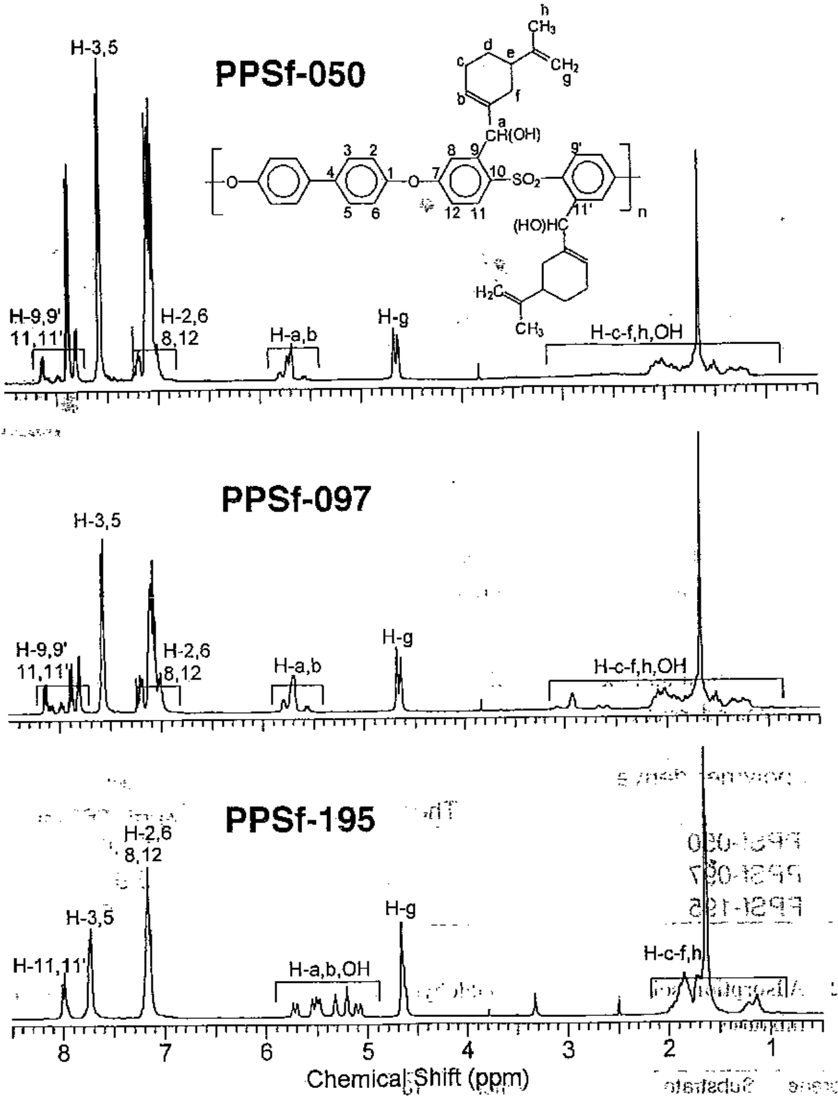

Fig. 1 ^{1}H NMR spectra of PPSf modified by addition of (1S)-(-)-perillaldehyde, DS 0.50 (PPSf-050), 0.97 (PPSf-097), and 1.95 (PPSf-195).

each analysis, ~5 to 10 wt% solutions were prepared from $CDCl_3$ for low DS polymers (PPSf-050 and PPSf-097) while the polar solvent DMSO-d_6 was used for the higher DS polymer (PPSf-195). The actual DSs of the PPSf derivatives measured by NMR were 0.50, 0.97, and 1.95. TMS was used as the internal standard. The DS of modified polymers was readily determined using ^{1}H NMR by comparing the intensity of distinct signals as will be described later.

2.4 Membrane Preparation

Membranes were prepared from DMF solution (60.0 g dm^{-3}). 3.0 cm^3 of polymer solution was poured into a flat laboratory dish (8.9-cm diameter) and the solvent was allowed to evaporate at 50 ℃ for 24 h. The thickness of the membranes was 22 - 29 μm.

2.5 Enantioselective Electrodialysis

A 50 vol.% aqueous ethanol solution of racemic Glu was placed in both chambers of the permeation cell. The concentration of racemic Glu was fixed to be 1.0 × 10^{-3} mol dm^{-3}. The electrodialysis was carried out at 40 ℃ with stirring, and with a constant applied voltage of 1.0 V between platinum black electrode (10 mm square ; distance between the electrodes, 65 mm). Aliquots were drawn from the permeate side at each sampling time. The amounts of D-Glu and L-Glu that permeated through the membrane (J_D, J_L) were determined on a high performance liquid chromatography (HPLC) instrument (JASCO PU 1580) equipped

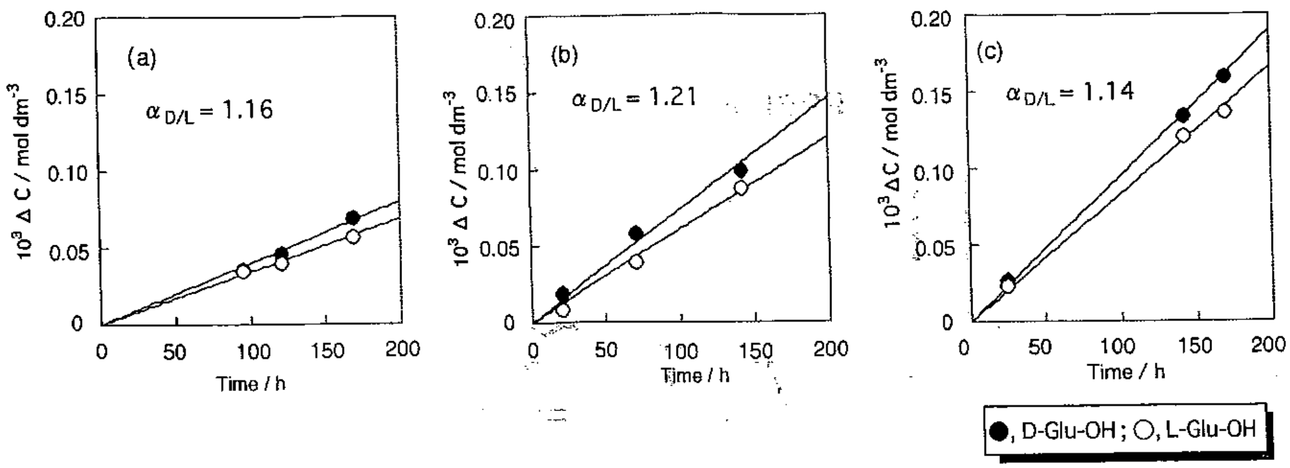

Fig. 2 Time-Transport curves of D-Glu and L-Glu by electrodialysis at Δ E = 1.0 V through the control non-imprinted PPSf membranes.
(a) PPSf-050 control non-imprinted PPSf membrane (b) PPSf-097 control non-imprinted PPSf membrane
(c) PPSf-195 control non-imprinted PPSf membrane

Table 1 Theoretical and experimental DSs obtained from ^{1}H NMR calculations for PPSf polymer derivatives

PPSf polymer derivative	DSs of modified polymers	
	Theoretical	Experimental
PPSf-050	0.50	0.50
PPSf-097	1.00	0.97
PPSf-195	2.00	1.95

Table 2 Adsorption selectivity of perillaldehyde polymer membranes toward racemic Glu mixtures

Membrane	Substrate	10^6(Glu)$_M$ / mol	10^2(Glu)$_M$ / (Polym.)	$S_{A(D/L)}$	$S_{A(L/D)}$
PPSf-050	D-Glu	1.22	5.24	0.96	1.04
	L-Glu	1.26	5.41		
PPSf-097	D-Glu	1.20	4.15	0.91	1.09
	L-Glu	1.29	4.49		
PPSf-195	D-Glu	1.15	5.21	0.92	1.09
	L-Glu	1.24	5.63		

with a UV detector (JASCO UV 1570) and a CHIRAL-PAK MA (+) column (50 × 4.6 mm i.d., Daicel Chemical Ind., Ltd.) with aqueous copper sulfate solution as an eluent.

The pemselectivity (separation factor) $\alpha_{D/L}$ is defined as the ratio J_D / J_L divided by the concentration ratio [D-Glu] / [L-Glu].

$$\alpha_{D/L} = (J_D / J_L) \ / \ ([\text{D-Glu}] / [\text{L-Glu}])$$

2.6. Adsorption Selectivity

The membranes were immersed in a 1.0 × 10^{-3} mol dm^{-3} racemic Glu solution in 50 vol. % aqueous ethanol and the mixture was allowed to equilibrate at 40℃. A 0.02 wt.% sodium azide was added as a fungicide. The amount of Glu in the supernatant subtracted from the amount initially in the solution gave the amount of Glu adsorbed by the membrane. Quantitative analyses were done as above.

Adsorption selectivity $S_{A(i/j)}$ is defined as

$$S_{A(i/j)} = ((\text{i-Glu}) \ / \ (\text{j-Glu})) \ / \ ([\text{i-Glu}] \ / \ [\text{j-Glu}])$$

where (i-Glu) and [j-Glu] are the amount of enantiomer of Glu adsorbed in the membrane and the concentration in the solution after equilibrium had been

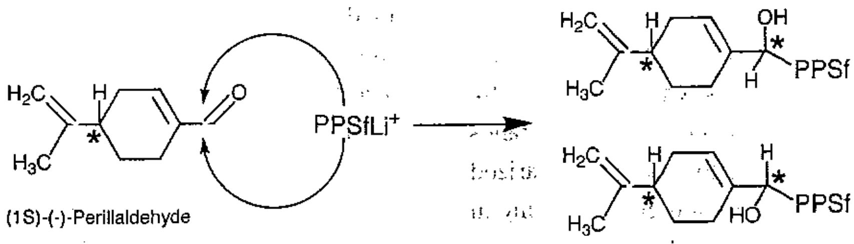

Fig. 3 Possible reaction path for the attack on the aldehyde group. The asterisk (∗) shows a chiral center.

Table 3 Summary of chiral separation of perillaldehyde membranes

Membrane	$\alpha_{D/L}$	$S_{A(D/L)}$	$S_{D(D/L)}$
PPSf-050	1.16	0.96	1.21
PPSf-097	1.21	0.91	1.33
PPSf-195	1.14	0.92	1.24

reached, respectively.

3. Results and Discussion

3.1 Characterization of Perillaldehyde Polymer Derivatives

Fig. 1 illustrates three stacked spectra of PPSf modified by addition of (1S)-(-)-perillaldehyde, DS 0.50, 0.97, and 1.95 along with signal assignment. The spectra can be divided into three predominant regions. The aromatic region shows proton signals from the polymer backbone phenylene ring. The aliphatic region shows signals originating from the CH, CH_2 and CH_3 groups of perillaldehyde. The third region, located in between the two previous regions, shows signals from deshielded hydrogen atoms also from the perillaldehyde group. Signal assignment was done for three types of derivatives as described in Fig. 1. The DS of the lower substitution derivative (PPSf-050 and PPSf-097) was directly calculated by comparing the intensity of the H-a,b signals (5.0-6.0 ppm) with the distinct 4H intensity of the aromatic H-3,5 (7.65-7.85 ppm) of the polymer backbone. The same reasoning was applied for the higher DS (PPSf-195), except that the intensity of H-a,b and -OH (5.0-6.0 ppm) was compared with H-3,5. The experimental calculated DSs of perillaldehyde modified polymers are summarized in Table 1.

3.2 Chiral Separation

Carboxylated polysulfones[15], cellulose acetate[16], and poly(hexamethylene terephthalamide/isophthalamide) (6T/6I = 31.6/68.4, mol/mol)[18] were previously converted into chiral recognition membranes by an alternative molecular imprinting adopting N-α-benzyloxycarbonyl-D-glutamic acid (Z-D-Glu) or N-α-benzyloxycarbonyl-L-glutamic acid (Z-L-Glu) as a print molecule. To this end, the authors first tried to convert the present modified polysulfones into chiral recognition materials by applying an alternative molecular imprinting with Z-D-Glu or Z-L-Glu as a print molecule. In the present study, the molecular imprinting ratio, which is defined as the ratio of the mole number of the print molecule to that of perillaldehyde moiety, was fixed at 0.5. Against our expectation, the present perillaldehyde polymer DS 0.97 was not converted into a chiral recognition material. In the present study, an alternative molecular imprinting was applied to the present polymer (PPSf-097) at one fixed molecular imprinting condition of 0.5. Molecular imprinting efficiency is dependent on various factors, such as a molecular imprinting ratio, combination of a print molecule adopted, nature of a given candidate polymer and so forth. Preliminary experiments showed that 9-ethyladenine is expected to work as a print molecule toward the present perillaldehyde polymers and these results will be reported shortly.

Fig. 2 shows time-transport curves of enantioselective electrodialysis of racemic glutamic acids through three types of non-imprinted perillaldehyde polymer membranes. The D-isomer of Glu was permeated in preference to the L-isomer through those membranes.

In order to elucidate the factors governing permselectivity of those membranes, adsorption selectivity toward racemic Glu mixtures was studied. The amounts of racemic Glu's adsorbed in the membranes and adsorption selectivities for them are summarized in Table 2. The adsorbed Glu's are given not only in absolute amounts ($(\mathrm{Glu})_M$ / mol) but also relative to constitutional repeating unit of the polymer ($(\mathrm{Glu})_M$ / (Polym.)). All three types of membranes showed adsorption selectivity toward L-Glu. The observed phenomena that the L-isomer was preferentially incorporated into those membranes led to the conclusion that there might be chiral recogniton sites toward the L-Glu in the membranes. We cannot specify the chiral recognition site toward the L-Glu at the moment. The most plausible interaction sites toward the L-Glu in membrane must be around hydroxy and sulfone groups rather than others. From this it can be said as follows: the lithiated sites of PPSf react exclusively with the aldehyde group in perillaldehyde as shown in Fig. 3. The attack on the aldehyde groups generates a new chiral center PPSf-C*H (OH) -R as the sp^2 carbon of the aldehyde becomes sp^3 with four different substituents. One would expect reaction to occur on either side of aldehyde (above or below) leading into a racemic mixture (50 : 50) of R and S isomers. Steric hindrance around the reaction site however may alter this ratio by favoring attack on one side over the other. However, we consider that it could be very difficult to determine the isomer ratio. The adsorption results lead us to the conclusion that the attack on the aldehyde groups did not occur from both sides evenly. Due to this, adsorption selectivity toward L-Glu was expressed, and as a result, chiral separation was obtained.

Using permselectivity ($\alpha_{D/L}$) and adsorption selectivity ($S_{A(D/L)}$), diffusivity selectivity ($S_{D(D/L)}$) was obtained by the following equation :

$$S_{D(D/L)} = \alpha_{D/L} / S_{A(D/L)}$$

The estimated diffusivity selectivity and other results are summarized in Table 3. Diffusivity selectivity for each membrane was greater than unity, implying the D-isomer diffused in and through the membranes faster than the L-isomer. We speculate that diffusivity selectivity might be expressed by the chirality of perillaldehyde group, which is the pendant side group of the modified polymers. From Table 3, chiral separation of the present membranes was dependent on diffusivity selectivity.

Enantioselective permeation of racemic glutamic acids has previously been studied by several other types of membranes, such as the Boc-L-Trp imprinted tetrapeptide derivative DIDE membrane[11, 14], the Z-D-Glu or Z-L-Glu imprinted carboxylated polysulfone[15], cellulose acetate[16], and polyamide[17] membranes, and egg shell membrane[20]. Those membranes generally gave higher permselectivity than the present membranes based on chiral perillaldehyde. Possible reasons for the lesser permselectivity are that the molecular imprinting site is less effective, or that the lithiated sites of PPSf reacted with the aldehyde group in perillaldehyde from both sides evenly as shown in Fig. 3.

4. Conclusions

Novel polymeric materials, having a chiral environment, were obtained by the reaction of lithiated polysulfone with perillaldehyde. Those polymers gave self-standing durable membranes, which showed chiral separation ability by electrodialysis. In the present study, optical resolution of racemic glutamic acids was demonstrated. Permselectivity toward D-Glu from racemic Glu's mixtures ranged from 1.14 to 1.21. The dominant factor governing chiral separation ability was determined to be diffusivity selectivity from results of permeation and adsorption selectivity.

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