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Chiral separation membranes from modified polysulfone having myrtenal-derived terpenoid side groups ☆

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Abstract

Novel polymeric materials, having a chiral environment, were obtained by the reaction of lithiated polysulfone with chiral terpenoid myrtenal. The resulting polymers gave self-standing durable membranes. Molecularly imprinted membranes were prepared from the novel myrtenal-containing polysulfones by the presence of print molecules during the membrane preparation process. The D-isomer imprinted membrane showed D-isomer adsorption and diffusivity selectivity, and vice versa. As a result, the D-isomer imprinted membrane transported the D-isomer in preference to the L-isomer, and vice versa. The control non-imprinted membrane also showed permselectivity toward racemic glutamic acid mixtures. The expression of permselectivity for the molecularly imprinted membranes was synergistically due to adsorption and diffusivity selectivity.

Keywords: Chiral separation; Membrane; Molecular imprinting; Myrtenal; Optical resolution; Polysulfone; Permselectivity; Adsorption selectivity; Diffusivity selectivity

1. Introduction

Chirality plays an important role in biological processes [1]. To this end, the resolution of racemates has attracted much attention in the pharmaceutical industry, food preparation, agricultural chemicals, perfume production, and so forth. The principal pathways to obtain pure enantiomers have been asymmetric synthesis and the resolution of racemates. In spite of the advances in asymmetric synthesis of pure enantiomers [2–4], the resolution of racemates is still the main method for the production of pure enantiomers in industry. A pair of enantiomers is separated by several methods, such as diastereomer crystallization, preferential crystallization, chemically kinetic resolution, enzymatic kinetic resolution, chromatography, and membranes. Among chiral separation technologies, membrane processes are perceived as economically and ecologically competitive to other conventional chiral separation methods. Membrane separation technology can be

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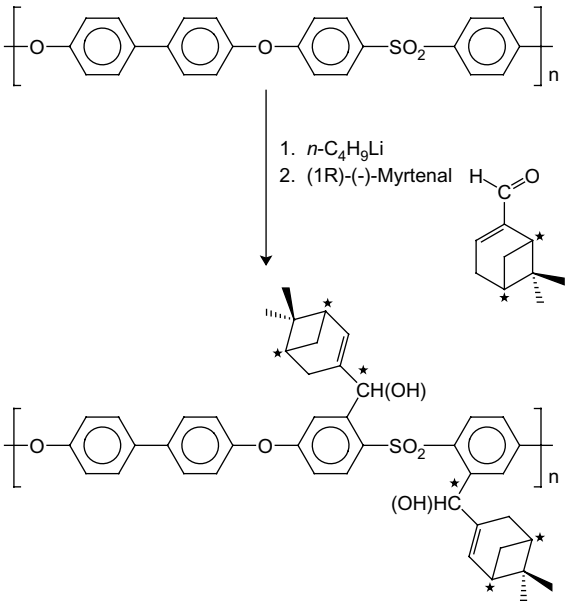
done continuously under mild conditions and process scale-up is relatively easy. Chiral separation with membranes can be divided into liquid and solid membranes. In the former membrane systems, optical resolution was carried out by bulk [5,6], supported [7–9], and emulsion liquid membranes [10]. Optical resolution was also investigated by solid (polymeric) membranes [11–61]. It is well known that with the exception of optical activity, chiral enantiomers give identical physicochemical properties. Thus, physical stereoselectivity is an important factor for chiral recognition and chiral separation. All synthetic membranes for optical resolution already reported [5–61] possess such chiral environments in them.

In the present study, novel polymeric materials with chiral environment were obtained by the reaction of lithiated polysulfone with the chiral terpenoid myrtenal. The chiral separation ability of the molecularly imprinted membranes from resulting novel polymeric materials was investigated.



Scheme 1. Reaction scheme for preparing modified polysulfone having myrtenal-derived terpenoid side groups.

2. Experimental

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 (1R)-(−)-myrtenal 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 (DMF) was purified by the usual method [62]. *N*-α-Benzyloxycarbonyl-D-glutamic acid (Z-D-Glu), *N*-α-benzyloxycarbonyl-L-glutamic acid (Z-L-Glu), D-glutamic acid (D-Glu), L-glutamic acid (L-Glu), sodium azide, copper sulfate, and ethanol were used without purification. Distilled water was employed.

2.2. Polymer synthesis

Radel® R5000 PPSf was dried at 120 °C prior to use. Lithiation reactions were performed under an inert atmosphere of dry argon in glassware that had been dried overnight at 120 °C. The reaction vessel was a three-neck glass flask equipped with a high torque mechanical paddle stirrer, gas inlet, and septum.

Modified PPSf polymers were prepared according to Scheme 1 with three different nominal degree of substitutions (DSs) (0.5, 1.0, and 2.0) by reacting (1R)-(−)-myrtenal with lithiated PPSf having DS 0.5, 1.0, and 2.0. A typical procedure for the synthesis of myrtenal polymer derivatives is described here. PPSf (15.0 g, 37.5 mmol) powder was dissolved with THF (750 cm^3 for DS 0.5 and 1.0, 1000 cm^3 for DS 2.0), cooled to −50 °C with a dry-ice ethanol bath and lithiated using 10.0 mol dm^{-3} *n*-butyllithium (*n*-BuLi) in a procedure described elsewhere [63–65]. A 10% excess *n*-BuLi was used to account for traces of water in the polymer, solvent, and reagents. For example, 82.5 mmol *n*-BuLi was used in the preparation of the DS 2.0 polymer derivatives. The electrophile, myrtenal, was syringed quickly (1 s) into the reaction flask to quench the lithiated polymer by reaction with the aldehyde group. The molar ratio of electrophile to polymer lithiated sites was typically 3:1 (e.g. for DS 2.0, 6 mol of electrophile for 1 mol of PPSf). The reaction mixture turned into a white slurry within a few seconds after the addition of the electrophile. Mechanical stirring had to be rapidly increased due to the large increase in viscosity, but then was lowered almost to a minimum after only a few minutes, because the viscosity of the mixture was reduced. Failure to increase the stirring speed after the addition of the electrophile resulted in cross-linked material.

The temperature of the cooling bath was gradually warmed up to −15 °C over a period of one hour and maintained at that temperature for an additional 30 min at that temperature. The reaction mixture was precipitated into approximately 3 dm^3 of ethanol 95%, stirred for 1 h and filtered. The polymer precipitate was white, but the liquid phase rapidly turned yellow–orange as a result of side reactions due to the presence of excess reagents. Higher DS polymer derivatives were hydrophilic due to the increased number of –OH functional groups on the polymer chains originating from the conversion of the aldehyde electrophile reagent to –OH groups by lithiated PPSf. It was observed that the high DS polymer precipitate had a tendency to aggregate during the recovery step probably as a result of that factor combined with the larger quantity of THF used in the preparation of high DS polymer derivatives. In order to facilitate the recovery of higher DS polymers, we suggest replacing ethanol by 2-propanol as the non-solvent for precipitation and also increasing its quantity. The white powders were stirred for several hours in three separate lots of fresh ethanol for complete removal of reagents and by-products, filtered and dried at 65 °C in a vacuum oven (yields >90%).

2.3. Nuclear magnetic resonance (NMR) spectroscopy

The myrtenal polymer derivatives were characterized by NMR spectroscopy using a Varian Unity Inova spectrometer at a resonance frequency of 399.961 MHz for ^1H and 100.579 MHz for ^{13}C. For each analysis, ~5–10 wt% solutions were prepared from $CDCl_3$ for low DS polymers (PPSf-050 and PPSf-093) while the polar solvent DMSO-d_6 was used for the higher DS polymer (PPSf-188). It should be noted that the OH signals in the two lower DS polymers appear at high field compared with the high DS polymer because of the difference in solvent environment and its interaction with the OH group. The actual DSs of the PPSf derivatives measured by NMR were 0.50, 0.93, and 1.88, respectively. TMS was used as the internal standard. The DS of modified polymers was readily determined using ^1H NMR by comparing the intensity of distinct signals as will be described later.

2.4. Preparation of molecularly imprinted polymers

Each polymeric membrane in the present study was prepared from DMF solution, containing the imprinting components. Modified polysulfone having myrtenal moiety acts not only as a functional polymer bearing hydrogen binding sites for amino acid recognition, but also as a membrane matrix like molecularly imprinted cellulose acetate [30,37], carboxylated polysulfone [35], or poly(hexamethylene terephthalamide/isophthalamide) [42] membrane. In the present study, PPSf-093, of which DS being 0.93, was used as a candidate polymer for molecularly imprinted membrane. *N*-α-Benzoyloxycarbonyl-D-glutamic acid (Z-D-Glu) or *N*-α-benzoyloxycarbonyl-L-glutamic acid (Z-L-Glu) were adopted as print molecules. Mole ratio of 0.50 for print molecule to unit mole of PPSf–093 in the membrane preparation process was studied. A 0.1883 g of PPSf-093 and 0.0489 g of print molecule, Z-D-Glu or Z-L-Glu, were dissolved in 3.0 cm^3 of DMF. The DMF solution thus prepared was poured into a 8.9 cm diameter flat laboratory dish, and the solvent was allowed to evaporate at 50 °C for 24 h. After drying, the print molecule was extracted from the resultant membrane by a large volume of 50 vol.% aqueous ethanol solution until the print molecule was hardly detectable in aqueous ethanol by UV analysis. In the present study, most of added print molecule was leached out from the membrane. Thickness of the membrane thus obtained was 22–25 μm.

The control membrane was prepared from PPSf-093 without a print molecule. Thickness of the control membrane was 23 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 °C with stirring, and with a constant applied voltage of 3.5 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 were determined on a high performance liquid chromatography (HPLC) instrument (JASCO PU 1580) equipped with a UV detector (JASCO UV 1570) and a CHIRALPAK MA(+) column (50×4.6 mm i.d., Daicel Chemical Ind., Ltd.) with aqueous copper sulfate solution as an eluent.

The flux, J_i or J_j (mol cm^{-2} h^{-1}) is defined as

$$J = Q/At$$

where Q (mol) is the amount of permeated Glu, A (cm^2) is the effective membrane area and t (h) is the time.

The permselectivity (separation factor) $\alpha_{i/j}$ is defined as the ratio J_i/J_j divided by the concentration ratio [i-Glu]/[j-Glu].

$$\alpha_{i/j} = (J_i/J_j)/([i\text{-Glu}]/[j\text{-Glu}])$$

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 °C. 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

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

where (i-Glu) and (j-Glu) are the amount of enantiomer of Glu adsorbed in the membrane and [i-Glu] and [j-Glu] denote the concentrations in the solution after equilibrium had been reached, respectively.

3. Results and discussion

3.1. Characterization of myrtenal polymer derivatives

Fig. 1 shows three stacked spectra of PPSf modified by addition of (1R)-(−)-myrtenal, DS 0.50,

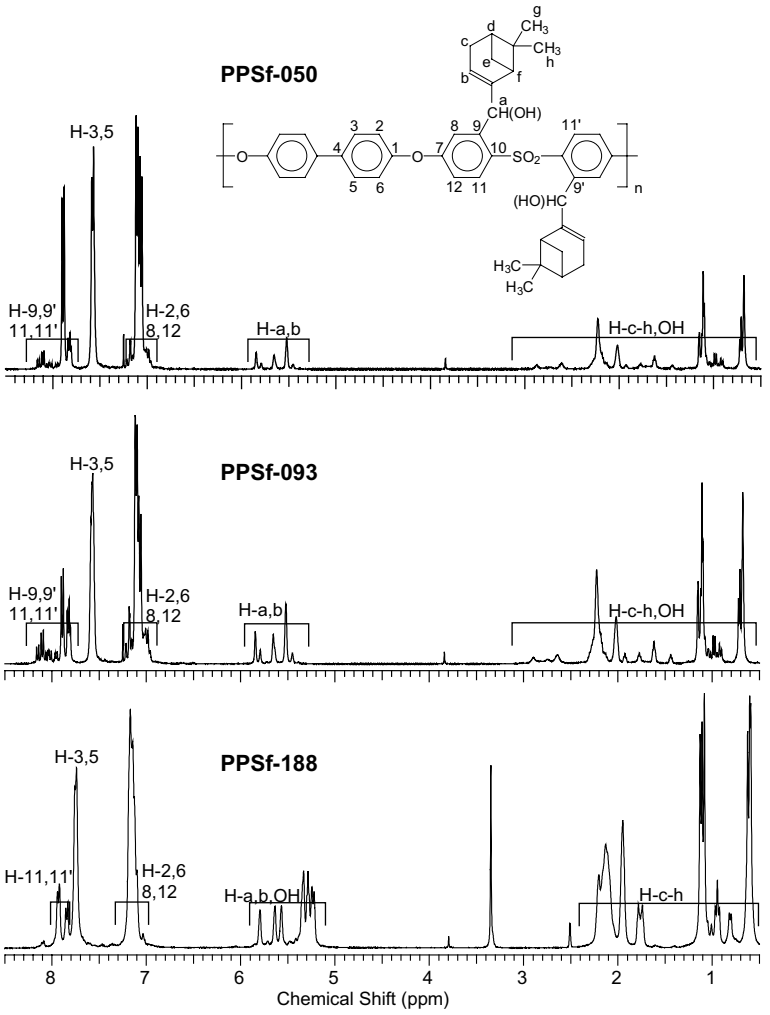


Fig. 1. NMR spectra of PPSf modified by addition of (1R)-(−)-myrtenal, DS 0.50 (PPSf-050), 0.93 (PPSf-093), and 1.88 (PPSf-188).

0.93, and 1.88 along with signal assignment. The spectra can be divided into three predominant regions: The aromatic region, showing hydrogen atom signals from the polymer backbone phenylene ring, the aliphatic region with signals originating from the CH, CH_2, and CH_3 groups of myrtenal and the third region, located in between the two others, shows signals from deshielded hydrogen atoms also from the myrtenal 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-093) 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 (7.4–7.7 ppm) of the polymer backbone. The same reasoning was applied for the higher DS (PPSf-188), except that the intensity of H-a,b and –O*H* (5.0 – 6.0 ppm) was compared with H-3,5. The experimental calculated DSs of myrtenal modified polymers are summarized in Table 1.

3.2. Chiral separation

Cellulose acetate [30,37], carboxylated polysulfone [35], and poly(hexamethylene terephthalamide/isophthalamide) [42] were previously converted into chiral recognition membranes by an alternative molecular imprinting adopting *N*-α-benzoyloxycarbonyl-D-glutamic acid (Z-D-Glu) or D-α-benzoyloxycarbonyl-L-glutamic acid (Z-L-Glu) as a print molecule. To this end, the present modified polysulfone PPSf-093 was converted into chiral recognition membranes 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 the ratio of the mole number of the print molecule to that of myrtenal moiety, was fixed at 0.50. Fig. 2 shows time–transport curves of enantioselective electrodialysis of racemic glutamic acids through three types of membranes, such as Z-D-Glu imprinted (a), control non-imprinted (b), and Z-L-Glu (c) imprinted membranes. The control non-imprinted membrane transported the L-isomer of Glu in preference to the D-isomer (Fig. 2(b)). Against this, the D-Glu was permeated in preference to the L-Glu through the Z-D-Glu imprinted membrane (Fig. 2(a)). As for the L-Glu imprinted membrane (Fig. 2(c)), the L-isomer was selectively permeated as anticipated from other results, and the permselectivity toward the L-isomer was higher than that for the control non-imprinted membrane. Those results suggest that the print molecule Z-D-Glu and Z-L-Glu worked as print molecules in the membrane preparation processes.

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-093	1.00	0.93
PPSf-188	2.00	1.88

In order to elucidate the factors governing permselectivity of those membranes, adsorption selectivity toward racemic Glu mixtures was studied. The amount 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 ($(Glu)_M$/mol)

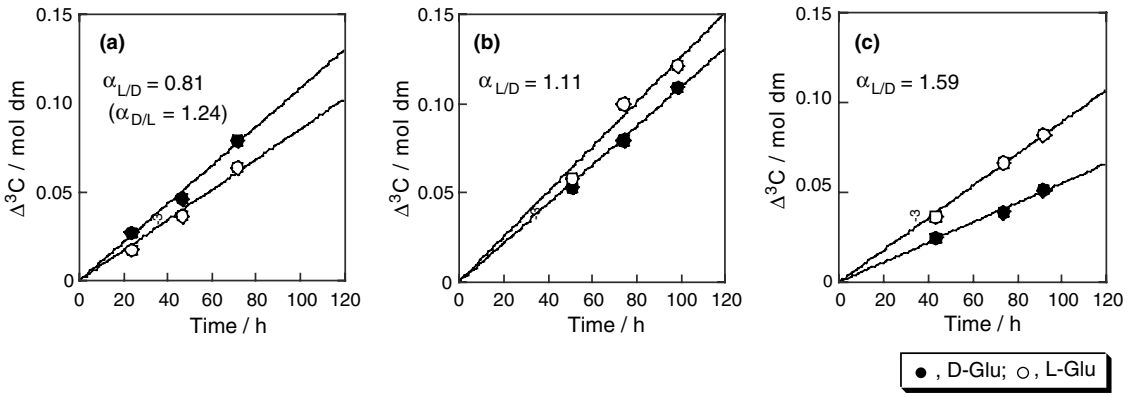


Fig. 2. Time–transport curves of D-Glu and L-Glu through the imprinted and the control non-imprinted membranes by electrodialysis at $\Delta E = 3.5$ V. (a), Z-D-Glu imprinted membrane, (Z-D-Glu)/(PPSf-093) = 0.5. (b), control non-imprinted membrane. (c), Z-L-Glu imprinted membrane, (Z-L-Glu)/(PPSf-093) = 0.5.

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

Membrane	Substrate	$10^7(\mathrm{Glu})_M$/mol	$10^2(\mathrm{Glu})_M$/(Polym.)	$S_{A(L/D)}$
Z-D-Glu imprinted membranes	D-Glu	9.48	4.01	0.87[a]
	L-Glu	8.36	3.62	
Control non-imprinted membrane	D-Glu	7.67	4.07	1.15
	L-Glu	8.69	4.60	
Z-L-Glu imprinted membrane	D-Glu	5.60	2.39	1.22
	L-Glu	6.77	2.88	

[a] $S_{A(D/L)} = 1.15$.

but also relative to constitutional repeating unit of the polymer ($(\mathrm{Glu})_M$/(Polym.)). As expected from previous studies [30,35,37,42,66], the Z-D-Glu imprinted membrane showed adsorption selectivity toward the D-isomer, and vice versa. Contrary to the anticipated result, the control non-imprinted membrane showed a slight adsorption selectivity toward L-Glu, even though it was prepared without the print molecule. The observed phenomenon that the L-isomer was preferentially incorporated into the control non-imprinted membrane led to the conclusion that there might be the chiral recognition site toward L-Glu in the control non-imprinted membrane. Although we cannot specify the chiral recognition site toward L-Glu at the moment, the most plausible interaction sites toward L-Glu in the membrane must be around hydroxy and sulfone groups rather than others. During the modification reaction of the polymer, the lithiated sites of PPSf react exclusively with the aldehyde group in myrtenal 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 the reaction to occur on either side of aldehyde (above or below) leading to racemic mixture (50:50) of *R* and *S* isomers. Steric hindrance around the reaction site, arising from the differences in the molecular ring bridges, 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 resulting isomer ratio. The adsorption result for the control non-imprinted membrane strongly suggests that the attack on the aldehyde groups did not occur from both sides evenly. Due to this, adsorption selectivity toward L-Glu was expressed in the control non-imprinted membrane. The presence of Z-L-Glu during the membrane preparation process enhanced the adsorption selectivity toward the L-isomer as can be seen in Table 2. Even though the control non-imprinted membrane essentially bear the recognition sites toward L-Glu, Z-D-Glu worked well as a print molecule in the membrane preparation process, the Z-D-Glu imprinted membrane showed D-Glu adsorption selectivity.

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

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

The estimated diffusivity selectivity and other results are summarized in Table 3. The Z-D-Glu imprinted membrane showed diffusivity selectivity toward the D-isomer, and vice versa. The diffusivity selectivity toward the control non-imprinted membrane was slightly preferable to D-Glu. From this, diffusivity

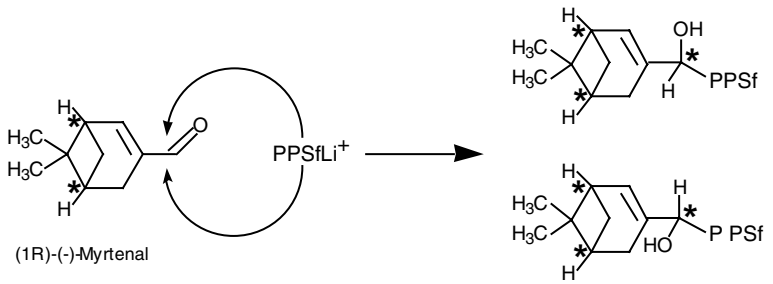


Fig. 3. Possible reaction path for the attack on the aldehyde group. The asterisk (*) shows a chiral center.

Table 3
Results of enantioselective electrodialysis of racemic Glu's through the imprinted and the control non-imprinted PPSf membranes

Membrane	$\alpha_{L/D}$	$S_{A(L/D)}$	$S_{D(L/D)}$
Z-D-Glu imprinted membrane	0.81[a]	0.87[b]	0.93[c]
Control non-imprinted membrane	1.11	1.15	0.97
Z-L-Glu imprinted membrane	1.59	1.22	1.30

[a] $\alpha_{D/L} = 1.24$.
[b] $S_{A(D/L)} = 1.15$.
[c] $S_{D(D/L)} = 1.08$.

selectivity might be also expressed by the presence of the print molecule during the membrane preparation process and the chirality of the myrtenal pendant side group of the modified polymer hardly contributed to the diffusivity selectivity. It is often observed that there is a retarded permeation of preferentially adsorbed permeant due to the relatively strong interaction between the preferentially incorporated enantiomer and the membrane [15,18,20,23,24,29,39,40,55]. In the present study, however, it can be said from Table 3 that chiral separation of the molecularly imprinted membranes were synergistically dependent on both adsorption and diffusivity selectivity and that of the control non-imprinted membrane was mainly determined by the adsorption selectivity.

4. Conclusions

Novel polymeric materials, having a chiral environment, were obtained by the reaction of lithiated polysulfone with myrtenal. Those polymers gave self-standing durable membranes. Molecularly imprinted membranes were prepared from the novel polysulfones with myrtenal by the presence of print molecules during the membrane preparation process. The D-isomer imprinted membrane showed D-isomer preferable adsorption and diffusivity selectivity, and vice versa. As a result, the D-isomer imprinted membrane transported the D-isomer in preference to the L-isomer, and vice versa. The Z-D-Glu imprinted membrane transported D-Glu from racemic Glu's mixture with permselectivity of 1.24. L-Glu was permeated in preference to D-Glu with permselectivity of 1.59 through the Z-L-Glu imprinted membrane. The control non-imprinted membrane also showed permselectivity and the L-isomer was selectively transported with that of 1.11. The expression of permselectivity for the molecularly imprinted membranes was synergistically due to adsorption and diffusivity selectivity.

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