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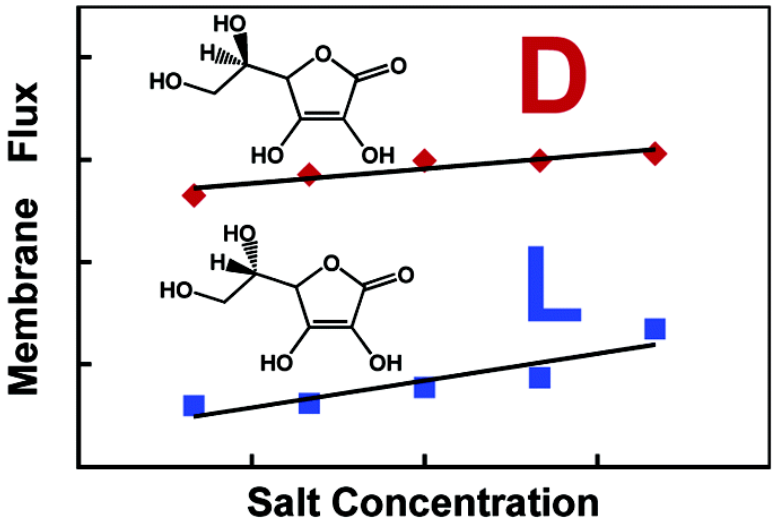

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Optically Active Polyelectrolyte Multilayers as Membranes for Chiral Separations

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Driven by the pharmaceutical industry's need for single enantiomer drugs,[1] techniques are urgently sought for preparative-scale separations of chiral forms of the same compound for molecules that cannot be synthesized in chirally pure form. Chromatographic methods, such as HPLC and SFC,[2] are generally slow and labor intensive, requiring specialized engineering approaches, such as simulated moving beds,[1] for acceptable throughput. Membrane separations, in comparison, offer significant advantages in simplicity and throughput.[3]

Recently, ultrathin polymeric membranes have been prepared using the polyelectrolyte "multilayer" (PEMU) approach, where constituent charged polymers are adsorbed on a sequential basis to form a rugged, uniform, continuous film.[4] These PEMUs have demonstrated exceptional efficiency, in terms of flux and selectivity, in the membrane separation of both gaseous[5] and solution species.[6] Here, we present preliminary results which show that using optically active PEMUs for chiral membrane separations permits very high enantiomer permeation rates with encouraging selectivity.

Our study included PEMUs made from polypeptides, such as L- and D-poly(lysine), PL, poly(glutamic acid), PGA, poly(*N*-(*S*)-2-methylbutyl-4-vinyl pyridininum iodide), PN(*S*)4VP, a synthetic alkylated polypyridine, and poly(styrene sulfonate), PSS. Multilayers were constructed on rotating disk electrodes, which permitted precise flux measurements of electroactive probes.[7,8] As chiral probes, we employed L- or D-ascorbic acid (the former is Vitamin C), 3-3(3,4-dihydroxyphenyl)-L/D-alanine (DOPA), and a chiral viologen (a geometric isomer, rather than enantiomer). An additional experimental variable was the concentration of salt in the supporting electrolyte, which has been shown to control the flux and selectivity of PEMUs when they are used for membrane separations of solution species.[6c,8,9]

An example of the differential transport rate, indicated directly by the current, of L- and D-ascorbic acid through a 90 nm PGA/PL multilayer, is shown in Figure 1 and compared to the bare electrode (which shows no selectivity). The bare electrode currents may be used to subtract precisely the series resistance to mass transport caused by diffusion through a layer of stagnant liquid next to the membrane (this resistance depends on the stirring rate) to yield a membrane-limited current.[8] Flux data from a variety of probe/multilayer combinations are summarized in Table 1.

A number of significant observations may be gleaned from Table 1. First, optically active multilayers produce chiral separations. Second, a multilayer made from two optically active polyelectrolytes, such as P*D*GA and P*D*L, was more selective for D-ascorbic acid than was a multilayer comprising only one optically active polyelectrolyte.

It was also observed (Table 1) that reversing the chirality of polyelectrolytes within the multilayer inverted the selectivity for L- over D-isomers (compare P*L*GA-P*L*L and P*D*GA-P*D*L). Combination of the L-form of one polyelectrolyte and the D-form of its oppositely charged partner effectively "neutralized" the chiral selectivity. Finally, for the sake of completeness, no selectivity for any of the chiral probes was observed when multilayers were made only from optically inactive polyelectrolytes.

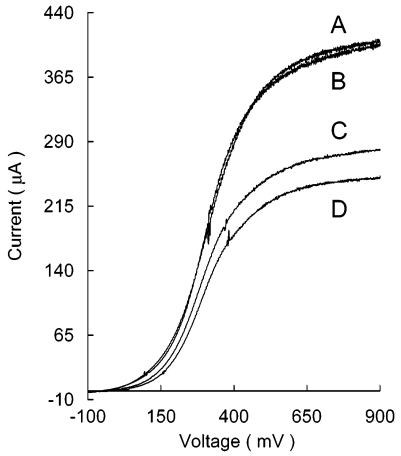

Figure 1. Linear scan voltammograms on a rotating disk electrode; uncoated for D-ascorbic acid (A); uncoated for L-ascorbic (B); coated for D-ascorbic with a P*D*GA/P*D*L multilayer of thickness 90 nm (C); coated for L-ascorbic with a P*D*GA/P*D*L multilayer of thickness 90 nm (D). 1 mM ascorbic, 2.0 M NaCl in 10 mM phosphate buffer (pH 7.4). Electrode was 8 mm diameter platinum, temperature 22 °C, and rotation rate 1000 rpm.

Table 1. Percent Selectivities for Different Membranes and Chiral Probes Used at Different Salt Concentrations

membrane	probe	%S[c] (0.1 M NaCl)	%S (0.5 M NaCl)	%S (2.0 M NaCl)
PN(S)4VPI-PSS[a]	AA[d]	18.9 D/L	10.2 D/L	*f*
	viologen	28.6 O/N[e]	26.0 O/N	17.2 O/N
PN4VPI-PSS[b]	AA	0.2 D/L	0.1 D/L	*f*
	viologen	0.4 O/N	0.2 O/N	0.2 O/N
P*L*GA-P*L*L	AA	28.1 D/L	25.0 D/L	17.8 L/D
	DOPA	14.1 L/D	13.3 L/D	11.4 D/L
P*D*GA-P*D*L	AA	28.9 D/L	25.2 D/L	18.7 D/L
	DOPA	13.8 D/L	13.2 D/L	11.7 D/L
P*D*GA-P*L*L	AA	0.4 D/L	0.2 D/L	0.2 D/L
	DOPA	0.3 D/L	0.4 D/L	0.1 D/L
P*L*GA-P*D*L	AA	0.3 D/L	0.1 D/L	0.4 D/L
	DOPA	0.1 D/L	0.1 D/L	0.2 D/L

[a] Optically active quaternized P4VP. [b] Nonoptically active P4VP. [c] % flux selectivity. [d] Ascorbic acid. [e] Ratio of optically active probe over nonoptically active probe. [f] Current was too high to obtain meaningful flux.

Optically active polymeric membranes, including some made from modified polypeptides, have been reported in the literature.[10] For example, membranes modified with ca. 1 μm thick poly(amino acid)-bearing amphiphilic side chains show permeation rate ratios > 8.0 for α-amino acid enantiomers.[10a] A self-supporting membrane, prepared by solvent casting, has been used to separate racemic mixtures of amino acids, hydroxy acids, and alcohols with 12−54 enantiomeric excess (% ee).[10b] A recent report[10c] on poly(vinylidene fluoride) membranes grafted with polypeptides repre-

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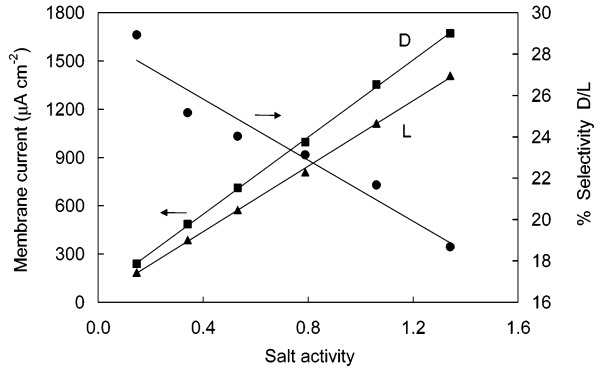

Figure 2. Left *y*-axis shows membrane current density for two enantiomeric forms of ascorbic acid. PEMU was 16 alternating layers of P*D*L and P*D*GA. Right *y*-axis shows the % selectivities of D- over L-ascorbic acid as a function of supporting salt concentration. Solution included 10 mM phosphate (pH 7.4). Voltage = 900 mV.

sents a frequent approach to making chiral membranes via vapor deposition. In contrast, PEMUs have the advantage that they may be constructed with very uniform, ultrathin, pinhole-free morphology under ambient (water-based) processing conditions.

Typical fluxes for PEMU membranes were very high, due, in part, to their thin dimensions. However, even when permeabilities (which normalize out thickness) are compared, the PEMU membranes exhibit enhanced flux as compared to reported chiral membranes.[10h] For example, the permeability coefficient (P_c) for the PEMU membranes described herein was in the range (278−1944) × 10^{-10} cm^2 s^{-1} as compared to values in the range (0.028−1103) × 10^{-10} cm^2 s^{-1} for previously reported chiral membranes which demonstrated comparable enantioselectivities.[10c,e,f]

PEMU membranes offer unusual control in selectivity and flux, achieved by regulating the salt concentration.[8] Salt swelling induces reversible "doping" of ion exchange/transport sites within PEMU membranes. For singly charged ions, such as ascorbic acid (pK_a = 4.17) at the pH employed in this study, the ion transport rate is linearly proportional to the salt activity,[8] as demonstrated in Figure 2. Higher flux comes at the expense of selectivity (also shown in Figure 2), but the loss of selectivity is not severe. In any case, the tuning of flux with salt allows rational tradeoffs with selectivity. The selectivity trend is also represented in Table 1 for the other optically active probes. In the case of multiply charged ions, such as the viologens, transport is a strongly nonlinear function of salt concentration.[8] To assess the mechanism of selectivity, it is instructive to consider the relationship between a steady-state flux, *J*, across a membrane of thickness, *t*, where the concentration of species is fixed on one side and zero on the other side of the membrane and solutions are "well-stirred":[11]

$$J = \frac{\bar{D}\bar{C}}{t} \tag{1}$$

where $\bar{D}$ is the diffusion coefficient of the species in the membrane, and $\bar{C}$ is the membrane concentration. Percent selectivities are defined by

$$\%S_{D/L} = \frac{\bar{D}_D\bar{C}_D}{\bar{D}_L\bar{C}_L} - 1 \tag{2}$$

where the "L" and "D" subscripts refer to the respective isomer. From eq 2, flux selectivity may arise from differences in $\bar{D}$, $\bar{C}$, or both. A difference in $\bar{C}$ implies a difference in the partition coefficient, a thermodynamic parameter, between isomers. However, a species that is strongly bound may also move more slowly (smaller $\bar{D}$, a kinetic effect). Higashi et al.[10g] have examined the nature of chiral interaction and recognition in polypeptide membranes deposited by Langmuir−Blodgett techniques. The P*L*GA films studied exhibited favorable enantioselective binding affinity for D-isomers, allowing the L-isomer to permeate more quickly.[10f] Lee and Frank[10c] pointed out that hydrogen bonding interactions between chiral probe and side groups embedded within the membranes may be critical in controlling membrane/probe interactions. The issue of hydrophobic interactions in chiral recognition and selectivity was also raised.

In the present work, partitioning of L- and D-ascorbic acid into chiral multilayers was determined directly using in situ FTIR in the attenuated total internal reflectance mode (ATR). ATR crystals coated with multilayers allowed for the measurement of the vibrational spectra of probes entering the multilayer from solutions passing over the crystal.[8] Equilibrium concentrations of L- and D-isomers inside a P*D*GA-P*D*L multilayer, compared to a precision of ±2%, showed a 4% difference (L over D). Because the difference was barely discernible using FTIR, an electrochromatographic separation (CEC)[2c,12] of optical isomers was employed using PGA/PL coated capillaries. Baseline resolution of isomers yielded a selectivity factor of 1.05 (see Supporting Information).

These results, for the systems studied, emphasize that membrane selectivity is for *flux*, a dynamic parameter, and does not represent substantial differences in partitioning. In other words, it is possible to obtain much greater selectivity than expected simply on the basis of partitioning. A difference in $\bar{D}$ between isomers implies a difference in the rate of hopping,[8] stemming from a possible difference in activation energies.

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Note Added after ASAP: Version published on Web 5/1/2003 did not include author's corrections. Version published on Web 5/7/2003 and print version are correct.

Supporting Information Available: Experimental methods, and structures of the polyelectrolytes and probe molecules (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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