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Enantioselective transport of amino acids as their potassium and sodium salts by optically active diaza-18-crown-6 ethers having arene sidearms

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Abstract—The enantioselective transport of amino acids as their sodium and potassium salts has been investigated by optically active diaza crown ethers. The reversed enantioselectivity of chiral crown ether **1** was observed.

1. Introduction

Amino acids are important bioactive substances. A study on transport selectivity and kinetics of amino acids through the liquid membrane would be helpful for separation and in understanding the transport process of amino acids through the cell membrane. Supramolecular systems for transporting biologically active agents (e.g., drug delivery, amino acids purification, etc.) have been singled out as one of the more promising for science and industry.[1–3] Selective membrane transport presents the basic functional features of supramolecular chemistry and is induced by the selective binding of substrate by the receptor in the membrane phase. So far, a lot of work has been carried out for designing and synthesizing new receptor molecules incorporating binaphthyl, sugars, tartaric acid,[4,5] steroids,[6] amino acids[7] etc. The chiral nature of crown ether, the rigidity of micro-environment of its cavity and the quality of the sidearm are all expected to play an important role in enantioselective induction. Aza crown ethers[8,9] with a sidearm attached to the nitrogen atom in the macrocyclic ring may enhance and regulate the cation binding properties as well as the lipophilicity. Lariat ethers or armed crown ethers, which have heteroatom containing podand arms, are known to have highly lipophilic character and a unique guest specificity via macro-ring-sidearm cooperativity. For some lariat ethers, the presence of a flexible sidearm with an electron donor site is well known to enhance the binding ability of the ligand by participation of this additional donor group in the complexation, providing a three dimensional cavity.

The first enantioselective transport of Z-amino acid (Z = benzyloxycarbonyl) and dipeptide K^+ carboxylates through a bulky chloroform membrane was reported by Gokel et al.[10]

Pietraszkiewicz et al. have also reported transport and liquid–liquid extraction of amino acids in their zwitterionic form, or as their potassium and sodium salts by using an 18-crown-6 incorporating a 2-naphthalene unit.[11] de Mendoza et al. reported the enantioselective transport of amino acids by guanidinium receptors.[12] We have previously[13] reported the enantioselective transport and liquid–liquid extraction of amino acids as their sodium and potassium salts by optically active crown ethers. Herein we have altered the aliphatic sidearms with aromatic crown ethers in order to investigate the effect of sidearms. Gokel et al.[14] has previously reported the importance of arene sidearms on the complexation of crown ether.

2. Results and discussion

Table 1 shows a set of transport experiments (Fig. 1) for phenylglycine, phenylalanine and tryptophan as their potassium and sodium salts, respectively. Sodium D-phenylglycinates, sodium D-phenylalaninates and sodium L-tryptophanates are better recognized than their

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potassium salts. Taking into account the transport experiments for macrocycle **1**, it is clear that the flux of the D-PhGlyNa is higher than for L-PhGlyNa (Fig. 2). This indicates that the D-enantiomer is more easily transported. In the case of the potassium salt, the situation is reversed. For PhAla, selectivity for D-enantiomer over its L-form is observed for the sodium salt, whereas the selectivity of L-enantiomer over its D-enantiomer is seen for the potassium salt. With tryptophan, the fluxes were higher for L-tryptophan in the case of sodium salt and D-tryptophan for potassium salt. The highest selectivity of a D-enantiomer over its L-enantiomer was observed in the case of potassium salt. For macrocycle **2**, the situation for PhGlyNa was reversed (Fig. 3). The selectivity of the L-enantiomer over its D-enantiomer was observed for each salt. For PhAla, the selectivity for the L-enantiomer over its D-form was observed for sodium salt. However, the selectivity was not observed for potassium salt. With tryptophan, the highest selectivity of a L-enantiomer over its D-enantiomer was observed in the case of sodium salt.

Table 1. Transport through liquid membrane data

Amino acid	$10^6 \times$Transport rates/mol h^{-1}		α_T	
	1	**2**	**1**	**2**
L-PhyGlyNa	0.50	1.10	1.10[b]	1.22[a]
D-PhyGlyNa	0.55	0.90		
L-PhyGlyK	0.99	1.15	1.98[a]	1.02[a]
D-PhyGlyK	0.50	1.13		
L-PhAlaNa	0.70	1.74	1.26[b]	1.76[a]
D-PhAlaNa	0.88	0.99		
L-PhAlaK	0.96	1.35	1.81[a]	1.00
D-PhAlaK	0.53	1.34		
L-TrpNa	0.51	0.60	1.24[a]	1.77[a]
D-TrpNa	0.41	0.34		
L-TrpK	0.32	0.35	2.12[b]	1.46[a]
D-TrpK	0.68	0.24		

Estimated error <12%.
[a] α_T: Ratio of fluxes (L/D).
[b] α_T: Ratio of fluxes (D/L).

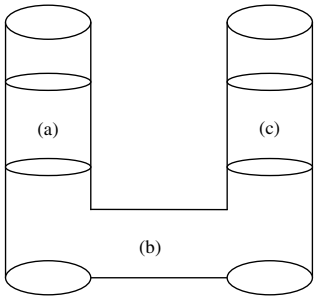


Figure 1. Transport apparatus and detailed experimental conditions: (a) feed phase (5 mL): amino acids 10^{-2} M and 10^{-2} M NaOH or KOH; (b) organic phase (10 mL): chloroform; carrier: **1** and **2** 10^{-3} M; (c) receiving phase (5 mL): pure water.

Taking into account the employed host systems, the observed enantioselectivity could be attributed to the different interaction modes of some functional groups of

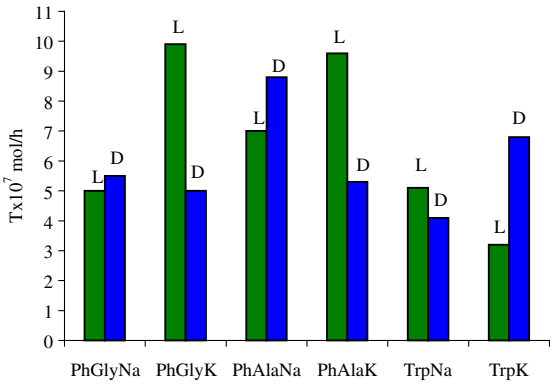


Figure 2. Bar plots of fluxes of amino acids as their sodium and potassium salts for **1**.

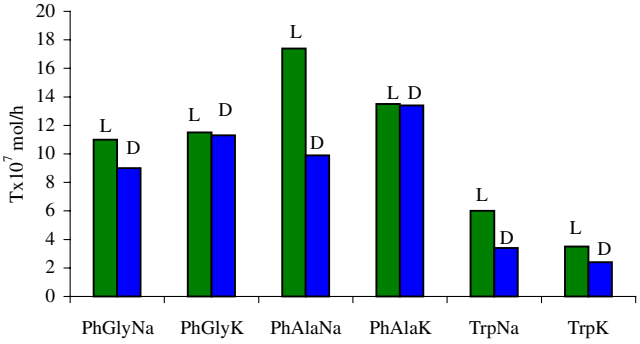


Figure 3. Bar plots of fluxes of amino acids as their sodium and potassium salts for **2**.

amino acids with the chiral barriers on sidearm of macrocycle. In general, the highest selectivity was observed in the case of tryptophanNa (L/D) in the case of macrocycle **2** (Fig. 5) and tryptophanK (D/L) in the case of macrocycle **1**. This could be the result of strong steric interactions of the indolic group relative to the phenyl one with chiral barriers on the sidearm. These results are consistent with our previous ones.[13] The most interesting result was that a reversed selectivity within the same amino acid enantiomer was observed for macrocycle **1** (Fig. 4). This indicated the influence of the cation involved. The effect of the cation involved in the transport is probably dependent on the structure of the crown ether employed. It is known that variations in Na^+/K^+ selectivity are primarily due to the degree of interaction of the pendant arm with Na^+ and K^+. Gokel et al. used lariat ether receptor systems to obtain clear evidence for cation-π interactions between Na^+ or K^+ and benzene, phenol and indole.[16–18] The complex of K^+ with lariat ether is the most remarkable owing to its previously reported apical-π interaction.[19] In our system, substituting the arene unit on the macro-ring may probable changed the conformation of the crown ether. The macro-ring-sidearm in our system probably led to the formation of apical-π interactions with K^+.

Ion pair[20] receptors to date have been based on hydrogen bonding, positively charged or Lewis acidic groups

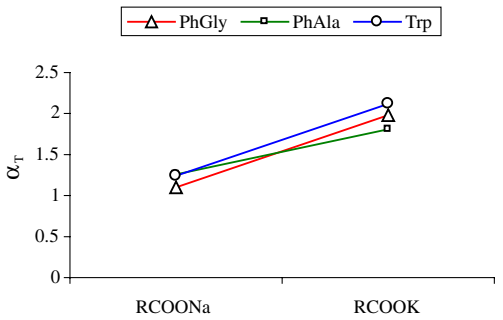


Figure 4. Enantiomeric differentiation of salts of amino acids during transport for **1**.

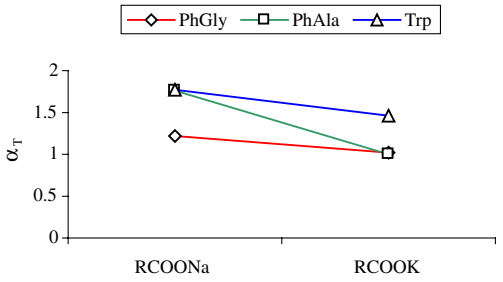


Figure 5. Enantiomeric differentiation of salts of amino acids during transport for **2**.

to coordinates the anion crown moieties to bind the cation. These types of host molecules often exhibit cooperative and allosteric effects, whereby the association of one ion alters the binding affinity of the counterion.[21] This cooperative behaviour can be positive or negative depending on whether the binding affinity is enhanced or reduced, respectively. Cooperative behaviour can result from several factors, such as through-bond or through-space electrostatic interactions between bound ions, or conformational changes induced by binding. In general the higher transport rates of macrocycle **2** can be explained in terms of cooperative behaviour (Table 1).

3. Experimental

3.1. General information

All chemicals were grade reagent unless otherwise specified. Melting points were determined with a GALLENKAMP Model apparatus with open capillaries. Infrared spectra were recorded on a MIDAC-FTIR Model 1700 spectrophotometer. The elemental analyses were obtained with CARLO-ERBA Model 1108 apparatus. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 high performance digital FT-NMR spectrometer, with tetramethylsilane as the internal standard for solutions in deuteriochloroform. J values are given in hertz. Optical rotations were recorded using an ATAGO DR Model 21949 polarimeter, and $[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1}. We have previously described the molecular recognition of some L-amino acids as their sodium and potassium salts by UV–vis titration method earlier.[15] Transport experiments were performed with amino acids sodium and potassium salts. Transport experiments were repeated three times for each run with the estimated error being <12%.

3.2. Transport experiments

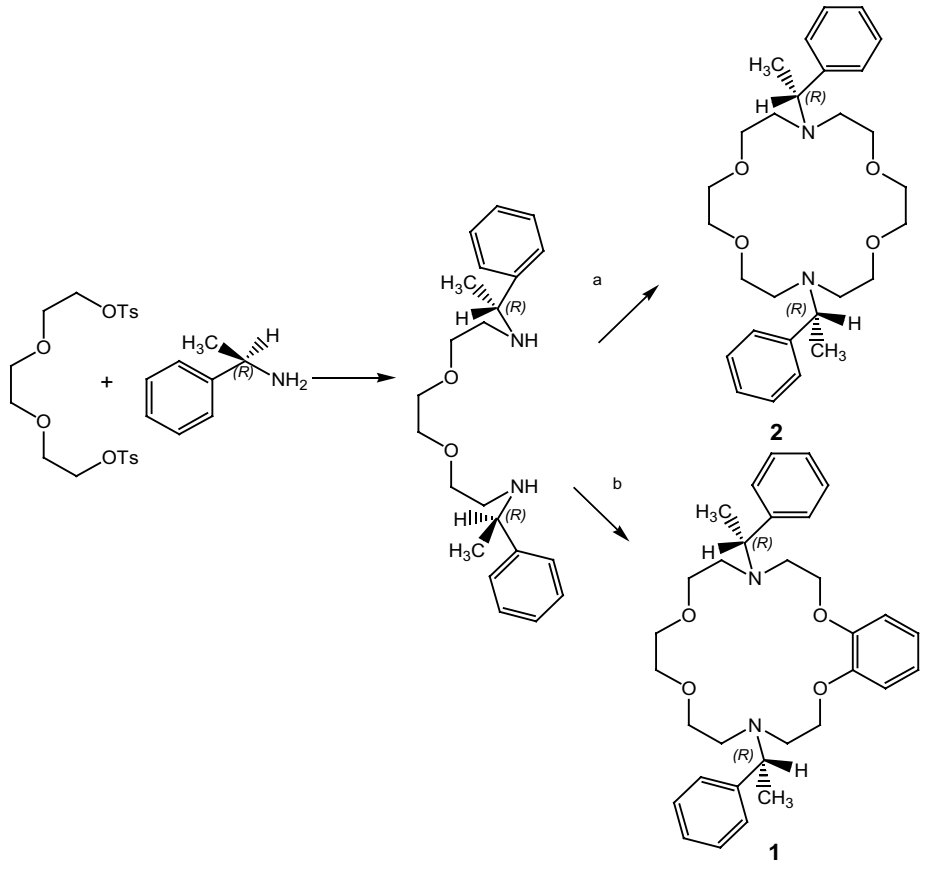
The transport experiments (Fig. 1) were run at 25 °C in a custom-made U-shaped glass apparatus of 25 mm diameter for 72 h. The bulk liquid membrane consisted of 10 mL of chloroform containing the crown ethers (Scheme 1) at a concentration of 10^{-3} M. The membrane was stirred magnetically at 200 rpm. The source phase (5 mL) contained the amino acid salt at a concentration of 10^{-2} M and at pH 10.5. The receiving phase was pure water. Blank tests indicated that transport of amino acids was negligible. The concentration of amino acids salts in the receiving phase and the water phase were assessed by UV. The initial transport rates measured for different amino acids salts are shown in Table 1.

3.3. *N*,*N*′-Di-(*R*)-(+)-1-phenylethyl-7,16-diaza-1,4,10,13-tetraoxa-2,3-benzo-cyclooctadec-2-ene 1

To a mixture of tripropylamine (14.3 g, 100 mmol) in xylene (500 mL), 1,2-bis-(2-*p*-tolylsulfonylethoxy)-benzene (5.06 g, 10 mmol) and 1,10-di-(*R*)-(+)-1-phenylethyl-4,7-dioxa-1,10-diazadecane[15] (3.56 g, 10 mmol) were added simultaneously. The mixture was stirred for 2 days at 120 °C. The mixture was then cooled to rt and the xylene evaporated. The concentrated crude product was washed with hot water, extracted with $CHCl_3$ (3×50 mL) and dried over Na_2SO_4. The chloroform was then evaporated and the residue purified by column chromatography (200 mesh Si-gel, ethyl acetate–petroleum ether–triethylamine 17:80:3) to afford **1** (2.80 g) in 54% yield as a yellow oil. $[\alpha]_D^{20} = +27.4$ (c 0.05, CH_2Cl_2), IR ν: 3068, 3029, 2974, 2926, 2872, 1597, 1496, 1441, 1371, 1348, 1325, 1261, 1215, 1112, 1053, 1029, 776, 745, 699; ^{1}H NMR δ: 1.17–1.19 (d, J 6.70, 6H, CH_3), 2.68–2.72 (m, 4H, $ArOCH_2CH_2N$), 2.84–2.87 (t, J 6.28, 4H, NCH_2), 3.31–3.37 (m, 8H, OCH_2, $ArOCH_2$), 3.66–3.68 (q, J 6.69, 2H, CHN), 3.76–3.81 (m, 4H, OCH_2CH_2O), 6.54–6.65 (m, 4H, Ar-H), 7.00–7.19 (m, 10H, Ar-H); ^{13}C NMR δ: 17.69, 50.35, 51.37, 61.70, 69.03, 71.06, 71.62, 113.63, 121.23, 127.21, 128.11, 128.61, 145.05, 149.35. Anal. Calcd for $C_{32}H_{42}N_2O_4$: C, 74.09; H, 8.16; N, 5.40. Found: C, 74.12; H, 8.12; N, 5.46.

3.4. *N*,*N*′-Di-(*R*)-(+)-1-phenylethyl-1,7,10,16-tetraoxa-4,13-diaza-cyclooctadecane 2

To a mixture of tripropylamine (14.3 g, 100 mmol) in xylene (500 mL), triethylene glycol ditosylate (4.58 g, 10 mmol) and 1,10-di-(*R*)-(+)-1-phenylethyl-4,7-dioxa-1,10-diazadecane[15] (3.56 g, 10 mmol) were added simultaneously. The mixture was stirred for 2 days at 120 °C.



Scheme 1. Reagents and conditions: (a) tripropyl amine (10 equiv), triethylene glycol ditosylate, xylene, 120 °C, 48 h; (b) tripropyl amine (10 equiv), 1,2-bis-(2-*p*-tolylsulfonylethoxy) benzene, xylene, 120 °C, 48 h.

The mixture was then cooled to rt and xylene evaporated. The concentrated crude product was washed with hot water to remove tripropylamine salt, extracted with $CHCl_3$ (3×50 mL) and dried over Na_2SO_4. The chloroform was then evaporated and the residue purified by column chromatography (200 mesh Si-gel, ethyl acetate–petroleum ether–triethylamine 17:80:3) to afford **2** (2.25 g) in 48% yield as a yellow oil. $[\alpha]_D^{20} = +19.2$ (*c* 0.05, CH_2Cl_2), IR *v*: 3091, 3053, 3029, 2972, 2931, 2869, 1605, 1478, 1455, 1376, 1352, 1298, 1201, 1121, 1067, 1034, 980, 911, 833, 770, 731, 708; ^{1}H NMR δ: 1.38–1.40 (d, *J* 6.76, 6H, CH_3), 2.78–2.86 (m, 8H, NCH_2), 3.56–3.61 (m, 16H, OCH_2CH_2O, OCH_2), 3.86–3.88 (q, *J* 6.72, 2H, NCH), 7.23–7.40 (m, 10H, Ar-H); ^{13}C NMR δ: 17.65, 51.24, 61.48, 71.15, 71.38, 127.09, 128.10, 128.48, 144.81. Anal. Calcd for $C_{28}H_{42}N_2O_4$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.38; H, 8.76; N, 5.87.

Acknowledgements

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