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Extraction of Chiral Ammonium Cations and Transport through Supported Liquid Membranes Mediated by 1,2,4-Triazole-containing Podands and Macrocycles

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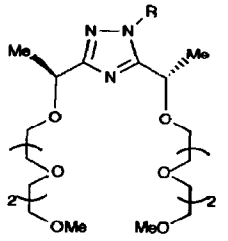
Abstract: Extraction of chiral primary alkylammonium salts was achieved in the presence of 1,2,4-triazole-containing macrocycles and podands with moderate enantioselectivities. Although preferential transport of (*R*)-1-naphthylethylammonium salts was always observed, significant differences in both rates and selectivities were found when bulk ($CHCl_3$-CCl_4) or supported (microporous polypropylene film) membranes were employed. The preparation of new proton-ionizable chiral bistriazolo-18-crown-6 macrocycles **3c,d** is described.

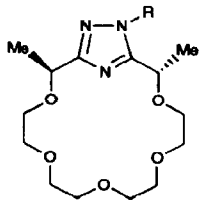
Macrocycle-mediated cation transport has been extensively studied using bulk liquid membrane systems.[1,2] A major drawback of this methodology is the large amount of carrier solution required with respect to the interfacial area. Incorporation of macrocyclic carriers into polymer-supported liquid membranes overcomes this disadvantage.[3,4] In such systems, use of very hydrophobic carriers is required to prevent leakage into the surrounding source and/or receiving phases.

Previously, we reported the protonated amine transport and chiral recognition by 1,2,4-triazole-containing carriers **1**[5] and **2**[6,7] using a bulk liquid membrane system. Both series exhibited good transport rates for 1-naphthylethylammonium ($HNEA^+$) and methyl phenylglycinate salts, as well as moderate selectivities for *R* and *S* enantiomers, respectively. Since carrier preorganization has more influence on chiral recognition than on transport efficiency, we have also recently described the synthesis of other lipophilic carriers like **3a** and **3b**[8] (PMB = *p*-methoxybenzyl) endowed with four chiral centers in a more rigid framework, in the hope they could induce a higher discrimination between enantiomeric alkylammonium cations.



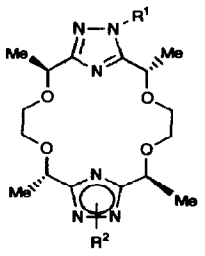
1

a R = H
b R = $C_{12}H_{25}$
c R = $CH_2COCholesteryl$



2

a R = H
b R = $C_{12}H_{25}$
c R = $CH_2COCholesteryl$



3

a $R^1 = R^2 = PMB$
b $R^1 = PMB$, $R^2 = C_{12}H_{25}$
c $R^1 = R^2 = H$
d $R^1 = H$, $R^2 = C_{12}H_{25}$

In this letter we report on the preparation of novel proton-ionizable chiral bistriazolo-18-crown-6 **3c** and **3d**, as well as the mediated transport of $HNEA^+$ using a supported liquid membrane system by means of carriers **1b**, **2b** and **3d**, and enantioselective extraction of racemic ammonium salts of naphthyl- and phenylethylamine, phenylglycine and phenylalanine methyl esters, among others, by the same receptors. Only a few examples of enantioselective transport of amino acid salts mediated by chiral crown ethers have been described so far.[9]

The synthesis of lipophilic bistriazole crowns **3a** and **3b** as mixtures of regioisomers has already been described.[8] The cleavage of the protective PMB group(s) would lead to the corresponding proton-ionizable heteromacrocycles **3c** and **3d**. However, use of typical cleavage conditions for this and related groups,[10] such as heating in acidic media,[11] catalytic hydrogenation[12] or transfer hydride,[13] proved unsuccessful. This difficulty was overcomed by using cerium ammonium nitrate (CAN).[14] Thus, oxidation of macrocycle **3a** with a five-fold excess of CAN in aqueous acetonitrile afforded the unsubstituted bistriazolo-18-crown-6 **3c** in a 43% yield.[15,16] This compound is an interesting example of proton-ionizable chiral heteromacrocycle having four chiral centers of the same configuration with D_4 symmetry.[17] Similarly, the lipophilic derivative **3d**[15] was obtained in a 60% yield from the mono-PMB derivative **3b**.[16]

Enantioselective transport experiments of $HNEA^+$ mediated by lipophilic carriers **1b**, **2b** and **3d** were performed using a supported liquid membrane which consisted of a thin microporous polypropylene film (Celgard 2502) (Figure 1). The pores of the polymeric material were filled at room temperature with a solution of the carrier in phenylhexane under vacuum to facilitate immobilization. The lower solubility of **3c** in apolar solvents prevented its use as a carrier by this method.

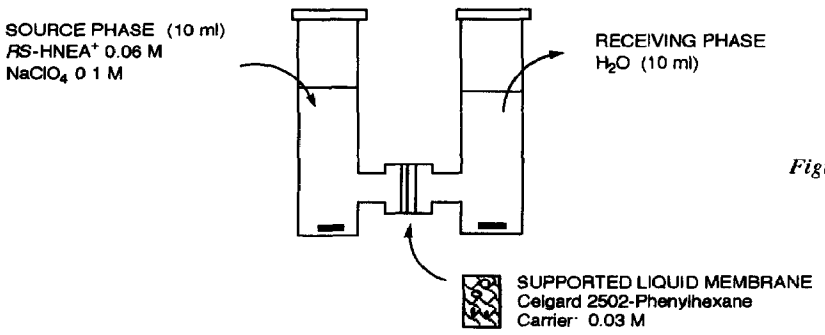


Figure 1

Ligands **1b**, **2b** and **3d** exhibited good transport rates for $HNEA^+$ (Table 1). Moreover, the acyclic receptor **1b** was found to be much more efficient than the macrocyclic carriers **2b** and **3d** which showed closely related transport rates. Since the lipophility of all three carriers is similar, these results could be explained considering the faster dynamic complexation and decomplexation rates expected for **1b**, typical of flexible acyclic ionophores. Such processes are especially relevant in biological membranes. Our polymeric liquid systems ressemble the biological membranes better than the bulk ones, because of their thickness and hydrophobicity. Curiously, relative transport rates of $HNEA^+$ with carriers **1b** and **2b** were reversed using a bulk membrane system[5] (Table 1). All carriers were found enantioselective for the *R* enantiomer of $HNEA^+$. The best results (26 % *e.e.*) were obtained with macrocycle **2b**. The lower selectivity (12 % *e.e.*) found for **3d**

is rather surprising, despite its decreased flexibility. Probably, the rigid framework of the compound (CPK model) prevents an optimal three-dimensional arrangement of the donor sites in the macrocyclic host cavity.

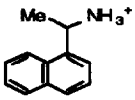
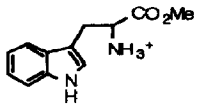
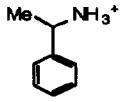
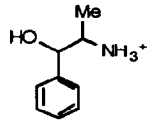
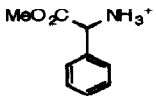
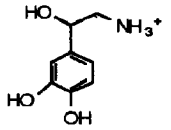
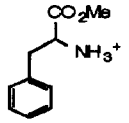
Table 1. Comparative transport rates of (*RS*)-HNEA$^+$ across a bulk[5] and a supported liquid membrane

Carrier	*Bulk* [a] (enantioselectivity)[c]	*Supported* [b] (enantioselectivity)[c,d]
1b	100 (12)	170 (6)
2b	277 (9)	18 (26)
3d	–	22 (12)

[a] Transport rates (x 10^7 mol.h^{-1}) across a $CHCl_3$:CCl_4 phase;[5] [b] Transport rates (x 10^9 mol.h^{-1}.cm^{-2}) across a polypropylene film determined by plots of concentration *vs.* time using UV absorptions at λ = 280 nm; [c] Corresponding to the (*R*)-HNEA$^+$ enantiomer; [d] Chiral recognition was determined by integration of the resolved peaks in HPLC of the diastereomeric HNEA$^+$ Mosher derivatives present in the receiving phase after 24 h.

Some extractions of diverse primary ammonium cations.were carried out with receptors **1b**, **2b**, and **3d**. The experiments were carried out shaking 2.0 ml of an aqueous solution of the corresponding racemic alkylammonium chloride (3 x 10^{-2} M) and $NaClO_4$ (5 x 10^{-2} M) with an equal volume of a 10^{-2} M solution of the receptor in chloroform. Table 2 lists the extraction percentages and the enantioselectivities.

Table 2. Enantioselective extraction of primary alkylammonium salts

Receptor	1b		2b		3d		Receptor	2b		3b	
Ammonium ion	% [a]	*e.e.*	% [a]	*e.e.*	% [a]	*e.e.*	*Ammonium ion*	% [a]	*e.e.*	% [a]	*e.e.*
	25	7[b,d]	90	32[b,d,e]	17	11[b,d]		40	16[c,e]	< 5	- g
		-	45	17[b,e]	< 5	- g		10	- g	< 5	- g
	5	13[c,f]	50	26[c,e,f]	5	- g		< 5	- g	< 5	- g
		-	45	15[c,e]	7	- g					

[a] Estimated error, *ca.* 10 %; [b] Corresponding to the (*R*)-enantiomer; [c] Corresponding to the (*S*)-enantiomer; [d] Determined by HPLC of Mosher derivatives of the transported ions; [e] Determined directly by ^{1}H-HMR; [f] Determined by CG-MS of the Mosher derivatives of the transported ions; [g] In the cases where extraction values were < 10 % the *e.e.* were not determined

The best extraction rates and enantioselectivities were obtained for macrocycle **2b**, in particular for $HNEA^+$. Values for the acyclic receptor **1b** were found to be lower. The bistriazolo receptor **3d** showed also low ability to extract ammonium ions. The poor results obtained for neurotransmitters such as norefedrine and noradrenaline could be probably due to the high hydrophilic nature of these cations.

In conclusion, the good transport rates, extraction ability and moderate enantioselectivities shown by some of the compounds studied here make this class of triazole-containing receptors interesting targets for ammonium transport through supported liquid membranes. This is the case, for example, of the easily accessible receptors **1b** and **2b**. Structural modifications directed to increase their chiral barrier are currently investigated.

Experimental Procedure for the Preparation of 3c,d: To a stirred solution of the corresponding N-*p*-methoxybenzyltriazole **3a** or **3b** (0.5 mmol) in acetonitrile (6 mL) at 0 °C, CAN (2.5 mmol for each PMB group) in H_2O (1 mL) was added. After 30 min. at 0-5 °C, the reaction mixture was left overnight at r.t. In the case of **3d** H_2O (30 mL) was added and the solution extracted with ethyl acetate (3 x 50 mL). The organic phase was successively washed with aq. sat. sodium hydrogen carbonate (40 mL), 40 % aq. sodium hydrogen sulfite (40 mL), aq. sat. sodium hydrogen carbonate (40 mL), and brine (40 mL) and then dried and the solvent evaporated. The oily residue was purified by column chromatography on silica gel (methylene chloride: methanol, 15:1); compound **3d**[15] was isolated as an oil; Yield: 60 %. In the case of **3c** the reaction mixture was diluted with H_2O (25 mL) and washed with ethyl acetate (2 x 35 mL). The aqueous phase was neutralized with sat. aq. sodium hydrogen carbonate and then 40 % aq. sodium hydrogen sulfite was added (15 mL). The suspension was centrifugated and filtered, and the solid washed with water (2 x 25 mL). The aqueous filtrates were evaporated to dryness. The residue was triturated with acetonitrile (80 mL) and the suspension filtered through celite. The solvent was removed and the oily residue solidified on treatment with ethyl ether. Compound **3c**[15] was isolated as a hygroscopic solid; mp. 105-7 °C; Yield: 43 %.

References and Notes

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15. **3c**: $[\alpha]_D$= - 15 ° (c = 0.5, MeOH); ^{1}H-NMR (MeOD): δ = 4.72 (q, CH), 3.8-3.4 (m, OCH_2), 1.51 (d, CH_3); ^{13}C-NMR (MeOD): δ = 162.6 (br, C-triazole), 72.1, 69.6 (CH, CH_2), 19.8 (CH_3); MS (high resolution, FAB)= *m/z* calculated for $C_{16}H_{27}N_6O_4$: 367.2094; Found: 367.2090. **3d**: $[\alpha]_D$ = - 26.3° (*c* = 0.88, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ = 4.88 (q, CH),4.8 (m, CH), 4.67 (q, CH), 4.2 (m, NCH_2), 3.9-3.4 (m, OCH_2), 1.9 (m, CH_2), 1.6 (m, CH_3), 1.26 (s, CH_2), 0.88 (t, CH_3); ^{13}C-NMR ($CDCl_3$): δ = 163.5, 156.4 (br, C-triazole), 72.0, 71.1, 70.5, 69.9, 69.0, 68.7 (CH, OCH_2), 48.7 (NCH_2), 31.8, 29.9, 29.3, 29.2, 29.0, 26.6, 22.6 (CH_2), 20.6, 20.4, 19.8 (CH_3), 14.0 (CH_3); Elemental analysis calculated for $C_{28}H_{50}N_6O_4$: C, 62.89; H, 9.42; N, 15.71. Found: C, 63.29; H, 9.68; N, 15.83.
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