67. Enantiomer-Selectivity for Phenylethylammonium Ion of Membranes Based on a Chiral Macrocyclic Polyether

by **Walter Bussmann, Jean-Marie Lehn*, Urs Oesch, Pierre Plumeré*** and **Wilhelm Simon**

Eidgenössische Technische Hochschule, Laboratorium für Organische Chemie, Universitätstrasse 16, CH-8092 Zürich

* Laboratoire de Chimie Organique Physique, Université *Louis Pasteur*, 4, rue Blaise Pascal, F-67070 Strasbourg

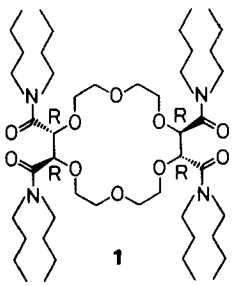
(18.II.81)

Summary

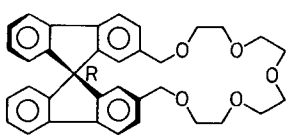
A chiral macrocyclic crown ether exhibits an enantiomer-selectivity of 2.6 for α-phenylethylammonium ion when incorporated in solvent polymeric membranes. The sequence of selectivity of these membranes clearly differs from that of lipophilicity for the different biogenic ammonium ions studied, indicating a significant structural contribution.

Chiral macrocyclic polyethers which bind chiral ammonium ions with high enantiomer-selectivity and behave as ionophores have been described [1–3]. The enantiomer-selectivity of such ligands can easily be determined quantitatively by using an electrochemical procedure described earlier [4] [5]. Here we report on such studies using the ion carrier **1** *(Scheme)* [6] in solvent polymeric membranes and phenylethylammonium ions as substrates in aqueous solutions contacting the membrane.

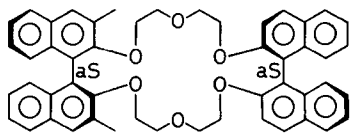
Scheme



1



2



3

The selectivities $K^{Pot}_{PEA,J}$ presented in *Figure 1* indicate the preference of the ions J relative to the (±)-α-phenylethylammonium ion by the membrane. In contrast to other ionophores described (see **2** and **3** in *Fig. 1*), **1** induces a rather high selectivity for PEA^+ over ephedronium (EPH^+) and pseudo-ephedronium

0018-019X/81/3/0657-05$01.00/0

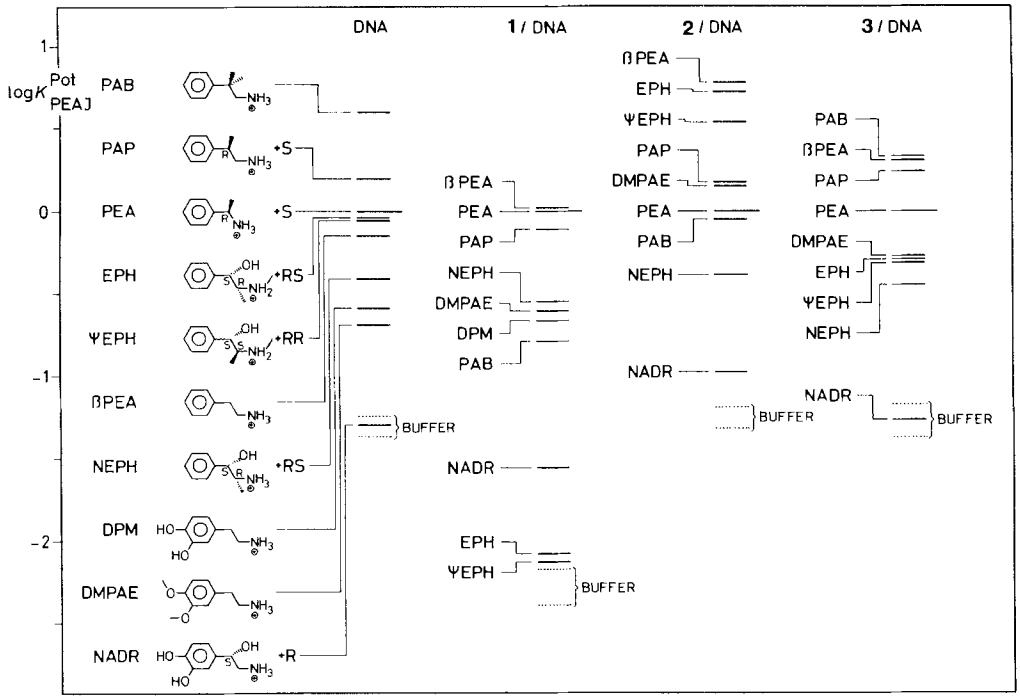


Fig. 1. *Selectivity factors* ($\log K^{Pot}_{PEAJ}$) *for lipophilic cations* $J^{\oplus}$ *relative to α-phenylethylammonium ion* ($PEA^{\oplus}$) *of membranes without ionophore* (DNA: dinonyl adipate) *and of membranes with ionophore* **1** *to* **3**

Table 1. *Selectivity factors,* $\log K^{Pot}_{PEAJ}$, *for membranes without ionophore* (DNA) *as well as for membranes with ligands* **1**, **2**, *and* **3** (0.1 M solutions)

Ion J	DNA	1/DNA	2/DNA	3/DNA
PEA^+	0.0	0.0	0.0	0.0
H^+	1.37	−1.77	0.46	1.26
K^+	−1.36	−0.53	−1.68	−0.83
NH_4^+	−1.44	−1.80	−1.66	−1.13
Na^+	−1.54	−1.44	−2.03	−1.26
Li^+	−1.58	−2.91	−2.10	−1.33
Ca^{2+}	−2.19	−3.21	−2.57	−2.00
Mg^{2+}	−2.23	−3.28	−2.59	−2.03

(ψEPH^+) ions as well as over alkali and alkaline-earth-metal cations (see also *Table 1*). An exception is K^+, which is rejected only by a factor of about 3.

The correlation of the lipophilicity of the non-protonated substrates with the observed selectivity *(Fig. 2)* indicates that membranes without ionophore or with **3** exhibit an extraction behaviour which is dominated by the lipophilicity. Here the lipophilicity is expressed by the logarithm of the partition coefficient ($\log P_{oct}$) of the species studied between water and octanol [7]. This behaviour is very much in contrast to that of **2**, and especially to that of **1**, where the most lipophilic

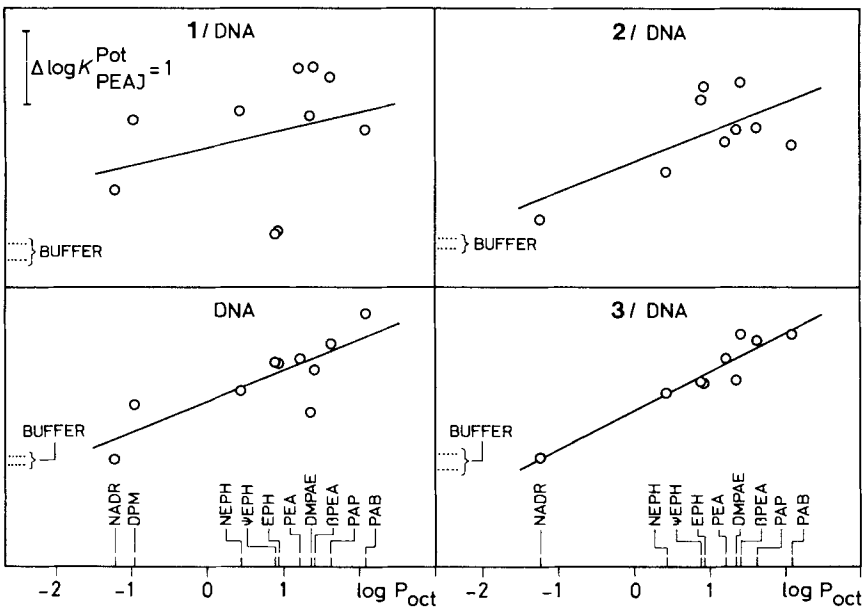


Fig. 2. *Change of the selectivity factor* $\log K^{Pot}_{PEAJ}$ *with increasing lipophilicity of the substrate*

Table 2. *Enantiomer-selectivity of ligand* **1** *expressed as a potential difference* $\Delta\Delta E$ *and the corresponding selectivity factor* $K_{(+)}/K_{(-)}$ [5]

Cation (0.1 M)	Enantiomer-Selectivity	
	$\Delta\Delta E = \Delta E_{(+)} - \Delta E_{(-)}$ [mV]	$K_{(+)}/K_{(-)}$ (see [5])
PEA^+	25.1 ± 0.1[a])	2.65 ± 0.01
EPH^+	2.3 ± 2.0[b])	1.09 ± 0.09
ψEPH^+	4.2 ± 2.0[b])	1.18 ± 0.09
PGM^+	4.4 ± 1.9	1.19 ± 0.09

[a]) Standard deviation (5 degrees of freedom). [b]) Bridge electrolyte: 1 M lithium acetate.

substrate species are not the most preferred ones. This indicates that the selectivity displayed by ionophore **1** includes a marked structural contribution. Since PEA^+ is a primary ammonium cation, and EPH^+ as well as ψEPH^+ are secondary ammonium ions, this effect may be related to the very marked discrimination in favour of $R-NH_3^+$ *vs.* $R-NH_2^+-CH_3$-binding displayed by the tetracarboxylate receptor molecule corresponding to **1** (CO_2^- groups replacing the four $CONBu_2$ groups) (see *Fig. 3* in [8]). This can be understood as a result of the ability of the NH_3^+ site to anchor into the macrocycle, whereas binding of $NH_2^+CH_3$ is hindered both by the loss a $NH^+\cdots O$ H-bond and by the steric bulk. A similar effect has been observed for the transport of various pharmacologically active ammonium ions through a chloroform phase by dicyclohexyl-18-crown-6 [9].

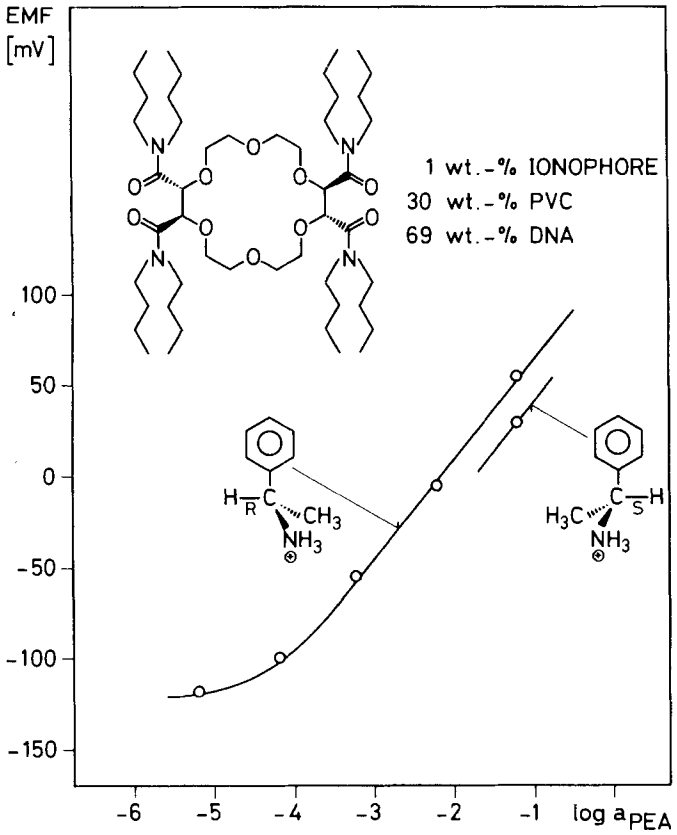


Fig. 3. *Enantiomer-selective electrode response to phenylethylammonium ions* ($PEA^{\oplus}$) *of a cell assembly with a solvent polymeric membrane based on* **1**

Solvent polymeric membranes containing **1**, in fact, exhibit a response to α-phenylethylammonium ions when they are used in ion selective electrode cell assemblies *(Fig. 3)*. The slope of the electrode response is 57.9 mV ± 1 mV (standard deviation; theoretical: 58.2 mV) in the range of 10^{-1} to 10^{-3} M with a detection limit of $\leq 10^{-4}$ M. As indicated in *Figure 3*, membranes with **1** show a remarkable preference of (*R*)- over (*S*)-phenylethylammonium ions (see *Table 2*). This preference by a factor of 2.6 is, so far, the highest enantiomer selectivity observed potentiometrically for α-phenylethylammonium ions [5]. It is considerably higher than the value reported recently for a similar crown ether and apparently of opposite sign [10].

This work was partly supported by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung*. One of us (W.B.) thanks ORION RESEARCH for a grant.

Experimental Part

Membranes. The solvent polymeric membranes were prepared according to a procedure described in [11] [12] using 1 wt.-% ligand, 30 wt.-% polyvinyl chloride (PVC, SDP hochmolekular, *Lonza AG*, CH-3930 Visp) and 69 wt.-% bis(1-butyl-pentyl)-adipate (DNA).

EMF.-Measurements. (For details see [5] [11].) They were performed at $20 \pm 1°$ using cell assemblies of the type Hg; Hg_2Cl_2, KCl (satd.)/sample solution (buffered)/solvent polymeric membrane//0.1 M β-phenylethylamine (buffered), AgCl; Ag. The sample solution and the internal filling solution of the ion selective electrode contained 0.5 M [tris(hydroxymethyl)]methylamin (TRIS) (*puriss. p.a., Fluka AG*, CH-9470 Buchs), adjusted to pH 7.0 with hydrochloric or phosphoric acid.

Selectivity. The selectivity factors, $\log K^{Pot}_{PEA,J}$, were obtained by the separate solution method (SSM, 0.03 M *(Fig. 1)* or 0.1 M buffered ammonium chloride and 0.1 M buffered metal-chloride solutions *(Table 1)* as described earlier [13] (see also [5]).

Ionophores. The ligands **2** [3] and **3** [1] were kindly provided by Prof. Dr. *V. Prelog* and Prof. Dr. *D.J. Cram.*

Reagents. Doubly quartz distilled water was used throughout. Metal chlorides of the highest purity available (*pro analysi, Merck*, Darmstadt, BRD) and the hydrochlorides of the following amines were used: (+)-(*R*)-, (−)-(*S*)-, racemic α-phenylethylamine (PEA), racemic noradrenaline (NADR), dopamine (DPM) and (−)-(*R*)-, racemic phenylglycine methylester (PGM) from *Fluka AG*, CH-9470 Buchs. The hydrochlorides of PEA and PGM were prepared as described earlier [11] [14]. (+)-(1*S*,2*R*)-, (−)-(1*R*,2*S*)-, racemic ephedrine (EPH) and (+)-(1*S*,2*S*)-, (−)-(1*R*,2*R*)-, racemic pseudo-ephedrine (ψEPH) (from *Sigma*, Chemical Company, St. Louis, Miss. 63178, USA); racemic norephedrine (NEPH) (from *Eastman*, Organic Chemicals, Rochester, N.Y. 14650, USA); β-phenylethylamine (βPEA) (from *ICN/K&K Laboratories*, New York, N.Y. 11803, USA); racemic amphetamine (PAP), phenylisobutylamine (PAB) and 2-(3,4-dimethoxyphenyl)ethylamine (DMPAE), see [9].

Preparation of Bis(1-butyl-pentyl)-adipate (DNA). Adipic acid dichloride (0.1 mol-equiv.) *(Fluka, purum)* dissolved in benzene was added dropwise to a solution of 5-nonanol (0.2 mol-equiv.) *(Fluka, purum)* in benzene and pyridine at room temperature. The reaction mixture was stirred for 20 h. The solvent was evaporated and the residue taken in water, neutralized with dil. HCl-solution, extracted with ether and washed with dil. NaOH-solution and water. The crude product was further purified by distillation (0.1 Torr, 85°). The ^{1}H-NMR., IR. and mass spectra (MS.) are in agreement with the expected structure. The elemental analysis led to the following results:

$C_{24}H_{46}O_4$ (398.63) Calc. C 72.31 H 11.63% Found C 72.37 H 11.53%

REFERENCES

[1] *D.J. Cram & J.M. Cram*, Science *183*, 803 (1974); *S.C. Peacock & D.J. Cram*, J. Chem. Soc. Chem. Commun. *1976*, 282.

[2] *W.D. Curtis, D.A. Laidler, J.F. Stoddart & G.H. Jones*, J. Chem. Soc. Chem. Commun. *1975*, 835.

[3] *V. Prelog & D. Bedeković*, Helv. Chim. Acta *62*, 2285 (1979).

[4] *A.P. Thoma, Z. Cimerman, U. Fiedler, D. Bedeković, M. Güggi, P. Jordan, K. May, E. Pretsch, V. Prelog & W. Simon*, Chimia *29*, 344 (1975).

[5] *A.P. Thoma, A. Viviani-Nauer, K.H. Schellenberg, D. Bedeković, E. Pretsch, V. Prelog & W. Simon*, Helv. Chim. Acta *62*, 2303 (1979).

[6] *J.-P. Behr, J.-M. Girodeau, R.C. Hayward, J.-M. Lehn & J.-P. Sauvage*, Helv. Chim. Acta *63*, 2096 (1980).

[7] *C. Hansch & A. Leo*, 'Substituent Constants for Correlation Analysis in Chemistry and Biology', John Wiley & Sons Inc., New York, Chichester, Brisbane, Toronto 1979.

[8] *J.-M. Lehn*, Pure Appl. Chem. *50*, 871 (1978).

[9] *E. Bacon, L. Jung & J.-M. Lehn*, J. Chem. Res. (S) *1980*, 136.

[10] *Y. Yasaka, T. Yamamoto, K. Kimura & T. Shono*, Chemistry Lett. *1980*, 769.

[11] *A. Viviani-Nauer*, Diss. ETHZ Nr. 6573, 1980.

[12] *G.J. Moody, R.B. Oke & J.D.R. Thomas*, Analyst *95*, 910 (1970).

[13] *A.P. Thoma, E. Pretsch, G. Horvai & W. Simon*, in 'Biochemistry of Membrane Transport' (G. Semenza & E. Carafoli (Ed.)), Springer Verlag, Berlin, Heidelberg, New York 1977, p. 116.

[14] *D. Bedeković*, Diss. ETHZ Nr. 5777 (1976).