CATIONIC SPECIFICITY OF DOUBLE-LAYER PHOSPHOLIPID MEMBRANES MODIFIED WITH MACROCYCLIC POLYETHERS

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This paper gives the results of an investigation of the action of di-α-hydroxyethyl-2,3:11,12-dibenzo-18-crown-6 and di-sec-butyl-2,3:11,12-dibenzo-18-crown-6 (compounds 1 and 2, respectively) on the permeability and selectivity of double-layer membranes in a narrow range of concentrations of the ions investigated (10^{-2} M).

The synthetic bimolecular membranes were prepared from phospholipids isolated from ox-brain by the method of Muller et al. [1]. The compound under investigation in a concentration of 10^{-5} M was added on both sides of the membrane in a cell containing 25 mM tris-HCl solution, pH 7.5. The relative permeability coefficients were determined from the bi-ionic potential [2, 3]. Below we give the relative values of the permeability G_i/G_j and the relative permeability coefficients P_i/P_j for compounds (1) and (2). The coefficients have been determined for dicyclohexyl-18-crown-6 and di-t-butyl-dicyclohexyl-18-crown-6, and it has been established that the relative permeabilities and relative permeability coefficients depend on the concentrations of the ions under investigation in the solution, on the lipid composition of the double-layer membrane, and also on the values of the bi-ionic potentials [2, 3, 4]. Consequently, these indices are referred to a concentration of 10^{-2} M of the ions under investigation.

Below we give a comparison of the relative permeabilities and relative permeability coefficients for di-α-hydroxyethyl-2,3:11,12-dibenzo-18-crown-6 and di-sec-butyl-2,3:11,12-dibenzo-18-crown-6 (concentrations of the salts 10^{-2} M; concentrations of the polyethers, 10^{-5} M):

Ion	Compound 1		Compound 2	
	G_i/G_{Cs}	P_i/P_{Cs}	G_i/G_{Cs}	P_i/P_{Cs}
Cs	1	1	1	1
Rb	0,42	0,058	0,38	0.28
K	0,25	0,021	0,12	0,029
NH_4	0,042	0,0047	0,023	0,0061
CH_3NH_3	0,012	0,0014	0,014	0,0028
Na	0,082	0,0018	0 01	0,0005
Li	0,0021	0,0023	0,0023	0,0015

It can be seen from the figures given that the cationic specificity determined by the ratio of the permeabilities for compound 1 corresponds to the sequence: Cs > Rb > K > Na > NH_4 > CH_3NH_3 > Li, and the cationic specificity determined by the relative permeability coefficients for the same compound corresponds to the sequence: Cs > Rb > K > NH_4 > Li > Na > CH_3NH_3. Similarly, the cationic specificity determined by the ratio of the permeabilities for compound 2 corresponds to the sequence: Cs > Rb > K > NH_4 > CH_3NH_3 > Na > Li, and the cationic specificity determined by the relative permeability coefficient for the same compound corresponds to the sequence: Cs > Rb > K > NH_4 > CH_3NH_3 > Li > Na.

The results that we have obtained permit the conclusion that the cationic specificity of double-layer membranes modified with α-hydroxyethyl and butyl derivatives of dibenzo-18-crown-6 depends not only on the diameter of the macromolecule but also on the nature of the side chains.

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IONOPHORIC ACTIVITY OF ACYL AND ALKYL DERIVATIVES OF 2,3-BENZO-15-CROWN-5

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Benzo-15-crown-5 (according to the nomenclature suggested by Pedersen [1]) possesses the properties of potassium ionophores, which permits its use in the preparation of ion-selective electrodes and for modifying the permeability of biological membranes [2, 3]. The "hole" in this macrocyclic polyether has a diameter of 1.7-2.2 Å, which ensures complex-formation with Na^+ ions in a 1:1 stoichiometry and with larger cations in a 2:1 stoichiometry [2, 4]. The introduction of an alkyl group into the benzene ring of benzo-15-crown-5 increases its membrane activity, possibly by enhancing its lipophilicity [3]. A similar influence of substituents has been demonstrated in the case of dibenzo-18-crown-6 [5].

In the present paper we give the results of a comparison of the effect on the permeability of the mitochondrial membrane of derivatives of benzo-15-crown-5 containing acyl and alkyl groups in the benzene ring (compounds 2-6 and 7-10, respectively). The method of obtaining the rat liver mitochondria and of investigating oxidative phosphorylation and of the passive permeability of various cations has been described previously [6].

Analysis of the figures given in Table 1 showed that the alkyl derivatives as a whole possess a higher membrane activity than the acyl derivatives. An elongation of the carbon chain of the substituents also increases the membrane-active properties of the cyclopolyether (compounds 5 and 6, and 9 and 10), but it leads to a fall in ion selectivity. Thus, compounds 6 and 10 induce higher sodium permeability than potassium permeability; relatively high selec-

TABLE 1. Ionophoric Effects of Acyl and Alkyl Derivatives of Benzo-15-crown-5 on Rat Liver Mitochondria [A) change in the passive permeability of the mitochondria in the presence of the cyclopolyether, A_0) in the Control]

Benzo-15-crown-5 derivative	Concentration, μM	A/A_0					
		H^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Ba^{2+}
1. Benzo-15-crown-5	1000	1,8	1,2	2,7	4,0	1,3	1,2
	500	1,1	1,1	1,9	1,7	1,1	1,2
2. 4'-Acetyl	1000	0,4	0,7	1,4	2,9	1,3	2,2
	500	1,0	1,3	1,6	1,8	1,5	1,7
3. 4'-Propionyl	1000	1,0	0,5	1,6	1,2	1,1	1,0
	500	2,2	1,2	1,6	1,8	0,7	1,3
4. 4'-Butyryl	1000	0,2	0,3	2,5	0,1	0,7	0,01
	500	1,4	0,7	1,6	2,0	0,9	0,9
5. 4'-Valeryl	1000	1,0	1,9	6,7	3,0	1,3	1,3
	500	0,9	1,3	3,1	1,3	1,0	1,1
6. 4'-Hexanoyl	1000	8,7	16,0	10,0	3,6	7,8	2,2
	500	3,9	4,8	4,9	2,6	3,5	1,2
7. 4'-Ethyl	100	1,9	3,1	3,8	3,6	1,1	1,2
	50	1,3	1,1	3,0	1,8	1,0	1,1
8. 4'-Propyl	100	1,8	1,7	4,7	1,2	1,0	1,1
	50	1,3	1,0	3,0	1,1	1,0	1,0
9. 4'-Butyl	100	3,5	2,2	8,5	2,5	1,7	1,4
	50	1,8	1,9	4,2	2,1	1,1	1,2
10. 4'-Amyl	100	6,1	17,7	10,0	3,2	2,2	1,5
	50	3,9	5,6	5,7	2,6	1,4	1,3

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