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

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UDC 547.693.5.04

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_o) in the Control]

Benzo-15-crown-5 derivative	Concentration, μM	A/A_o					
		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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0009-3130/79/1502-0213$07.50

tivity with respect to K^+ is observed for compounds 1, 5, and 9, and with respect to bivalent cations for compound 6. On the whole, the alkyl derivatives of benzo-15-crown-5 cause the complete uncoupling of oxidative phosphorilation in concentration of 5-10 μM, while compounds 1-6 have little effect in this concentration. Among the acyl derivatives, compound 6 is the most effective uncoupling agent for oxidative phorylation, which correlates with its action on the permeability of the mitochondria (Table 1).

The lower K^+/Na^+ selectivity of the benzo-15-crown-5 in mitochondria as compared with model systems [2, 3] is apparently explained by the physicochemical structural features of their membranes (surface charge, dielectric constant, packing density of the lipids and proteins, etc.). In view of this, it must be mentioned that the K^+/H^+ selectivity of potassium electrodes based on benzo-15-crown-5 depends very significantly on the membrane system used [2].

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INVESTIGATION OF THE MEMBRANE-ACTIVE PROPERTIES OF ACYL DERIVATIVES OF 2,3-BENZO-18-CROWN-6

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UDC 547.639.5.04

Macrocyclic polyethers or crown compounds are known as functional analogs of natural ionophores with wide possibilities of use [1]. We have shown previously [2] that the introduction of acyl, alkyl, or α-hydroxyalkyl groups into the benzene rings of 2,3:11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene (or dibenzo-18-crown-6 in the nomenclature suggested by Pedersen [3]) substantially affects both the effective concentration capable of modifying the permeability of biological and artificial membranes and also the ionic selectivity of these compounds.

One of the steps of the structural-functional analysis of the ionophoric properties of the substituted cyclopolyethers is a comparison of the membrane activities of benzo- and dibenzo-18-crown-6's and also of their derivatives. In the present paper we describe the action of acylated benzo-18-crown-6's (compounds 1-5, Table 1) on the permeability of the membranes of mitochondria and the process of oxidative phosphorylation that they bring about. The conditions for the isolation of rat liver mitochondria and for measuring oxidative phosphorylation and the passive permeability of the mitochondrial membranes have been described previously [4].

As follows from the figures given in Table 1, compounds 3 and 5 in concentrations of 1×10^{-5} M possess a relatively high membrane activity which increases the passive permeability of the mitochondria for magnesium ions more than threefold. Cyclopolyether 5 also induces substantial transmissibility for K^+ and Na^+, i.e., the membrane effects of this complexone are not very specific in relation to the complexed cation. Compound 5 is also the most effective among derivatives of this group in relation to oxidative phosphorylation by

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Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 243-244, March-April, 1979. Original article submitted January 18, 1979.

0009-3130/79/1502-0214$07.50