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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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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TABLE 1. Influence of Various Concentrations of Acyl Derivatives of Benzo-18-crown-6 and Dibutyryldibenzo-18-crown-6 on the Passive Permeability of Rat Liver Mitochondria for Various Cations [A, Permeability of the Mitochondria in the Presence of the Cyclopolyether; A_o, in the Control]

Compund	Concentration, μM	A/A$_o$					
		H^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Ba^{2+}
1. Benzo-18-crown-6	10	1,2	1,2	1,1	1,3	1,1	1,2
	50	1,2	1,6	1,3	1,4	1,0	1,1
2. 4'-Acetylbenzo-18-crown-6	10	1,2	1,1	1,1	1,8	1,1	1,2
	50	1,1	1,4	1,3	2,3	1,0	1,3
3. 4'-Propionylbenzo-18-crown-6	10	1,3	1,3	1,6	2,2	1,1	1,3
	50	1,4	1,4	1,2	3,3	1,0	1,2
4. 4'-Butyrylbenzo-18-crown-6	10	1,2	1,3	1,3	1,4	1,2	1,3
	50	1,4	1,6	2,1	1,7	1,2	1,1
5. 4'-Valerylbenzo-18-crown-6	10	1,2	1,9	2,0	1,9	1,0	1,4
	50	1,3	2,4	2,7	3,6	1,2	1,1
6. 4',4"-Dibutyryldibenzo-18-crown-6, "trans" isomer	5	1,2	1,1	1,1	4,72	1,2	—
	10	4,1	1,1	1,6	8,2	2,0	
	50	8,5	1,2	2,3	27,0	3,9	—

the mitochondria, reducing the coefficient of respiratory control by 50% in a concentration of 1×10^{-4} M. In the case of compound 4, a similar effect is achieved at 5×10^{-4} M, and the other derivatives are ineffective even in a concentration of 1 mM. For comparison, Table 1 gives the effect of the "trans" isomer of dibutyryldibenzo-18-crown-6, which is 15-20 times more active than compounds 1-5 in relation to the induction of permeability for M^{2+}. This is possibly connected with the existence of definite steric requirements for the formation of cyclopolyether–cation complexes of the "sandwich structure" type which are satisfied to a higher degree by the diacyl derivatives of dibenzo-18-crown-6. It is also not excluded that the presence of only one substituted benzene ring in compounds 1-5 leads to changes in the electron density distribution on the oxygens of the "hole" of the macrocycle to an unstable fixation of the cation within it that is connected with this fact.

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