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Thermodynamics of complexation and membrane activity of crown ethers

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THERMODYNAMICS OF COMPLEXATION AND MEMBRANE ACTIVITY OF CROWN ETHERS

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Abstract

The use of thermodynamic characteristics in the analysis of data on complexation makes it possible to give the obtained data a definite physical and chemical interpretation. Our studies allow us to evaluate the complex forming abilities of compounds similar in structure to the molecules studied, and will help to analyze the "structure-function". They can replenish the database on the physical and chemical properties of crown ethers, and enable the prediction of only "constructed compounds".

We have developed a reliable set of procedures for conductometric analysis of complex forming, membrane active and thermodynamic properties of sulfo derivatives-DB18C6, diacyl derivatives-DB18C6, 4',4''(5'')-dimethylaminoethanol-DB18C6 and bis-o-methoxyphenoxy-diethyl ethers.

Keywords: *crown ether, ionophore, complexon, channel former, thermodynamic characteristics.*

Introduction

All known biological effects of crown ethers, one way or another, are associated with their properties to form complexes with ions or molecules that have polar groups, and also induce trans membrane transfer of ions (manifesting ionophore, channel former) or to mediate it indirectly. Natural ionophores inducing more or less selective membrane permeability for ions were significantly supplemented by crown ethers and their analogues with similar properties [3, 6, 8, 11, 12].

After first publications of Pedersen, related to crown ethers' synthesis and study [18, 19] a great number of compounds of this class were created with unique characteristics, different names and configurations. The unusual properties of crown ethers and possible areas of their use are revealed. One of the noteworthy properties of crown ethers and their analogues (in addition to the ability to form "guest-host"

complexes with high selectivity) is the manifestation of ionophore and channel formation activity. Indeed, by the present time among the crown ethers and their analogs, selective ionophores and channel-forming structures have been discovered capable of transmembrane transport of ions and exhibit biological activity.

Macrocyclic polyethers or crown ethers are compounds that, on the one hand, are well studied by chemists and can be synthesized with various modifications of the molecule; on the other, they are embedded in the membranes and induce ion transport on them.

The crown ethers and their analogues described so far differ both in complexation properties and in membrane action. A detailed study of the dependence of the effect of crown ethers on membranes on their molecular structure serves as a prerequisite for revealing patterns between structure and membrane activity, substantiating the directed synthesis of crown ethers with predetermined properties. Such studies are an inevitable stage in the search for ways of directed synthesis of substances inducing in the membranes permeability of a given type.

The influence of the nature of the substituents on the charge distribution in the crown ethers macrocycle was studied in a number of concrete examples in the works of Varnek [26, 27].

As is well known, along with the size of the macrocyclic cavity of the crown ether, the nature and length of the side radicals, the role of the structural parameters of the crown ether molecule affecting its membrane properties is played by the number of substituents in the benzene rings of the macrocycle [24].

In connection with the importance of the above problems, the purpose of this article was to study the complexation, membrane active and thermodynamic properties of crown ethers.

1 Materials and methods

Curves of conductometric titration were obtained [11] with a 5 fold repetition ($n = 5$). These data were subjected to statistical processing using a software package of statistical analysis on a computer with the calculation of the standard deviation (S), the Student's criterion (t), the variance of the normal distribution (δ) according to the formula:

$$\delta = t^* \Delta S_s$$

where δ is the variance of the normal distribution;

t is the Student's ratio;

ΔS_s – root-mean-square deviation [21].

For statistically significant changes, a confidence level of $P < 0.05$ was assumed. Fig. 1 shows the dependence of the change in the free Gibbs energy upon complexation of sulfo derivatives-DB18C6 with K^+ , Na^+ and Ca^{2+} ions.

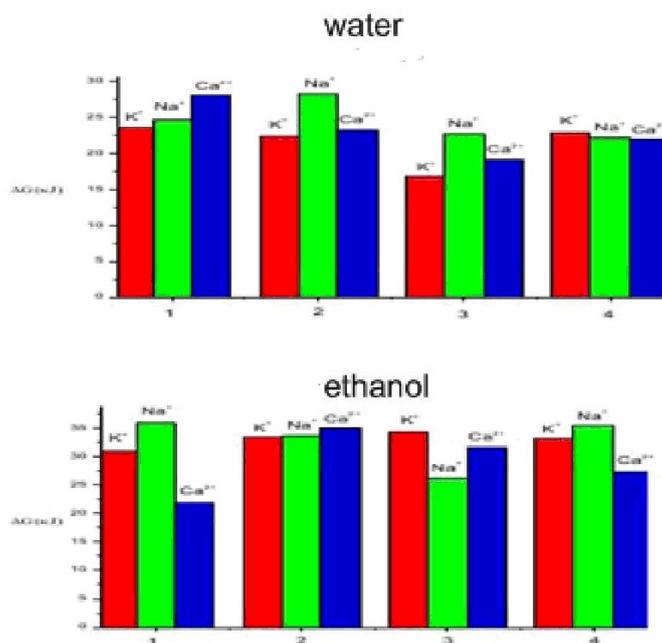


Fig. 1. Change in the free Gibbs energy during complexation of sulfo derivatives-DB18C6 with K^+ , Na^+ and Ca^{2+} ions. 1) 4'-t-butyl-4''(5'')-DB18C6-sulfonic acid, 2) 4'-acetyl-4''(5'')-DB18C6-sulfonic acid, 3) 4'-DB18C6-sulfonic acid, 4) 4',4''(5'')-DB18C6-disulfonic acid.

It is obvious that the free energy of complex formation in a solution is determined by the following expression:

$$\Delta F_{comp.} = -RT^* \ln K$$

$$\Delta F_{comp.} = \Delta F_{ML} - \Delta F_M^s + \Delta F_{ML}^s - \Delta F_L^s = \Delta F_{ML} - \Delta F_M^s + \Delta(\Delta F^s)_L^{ML},$$

where ΔF_{ML} the interaction energy of the molecules of the complexation with ions in the gas phase, ΔF_M^s is the free-ion solvation energy, and the term $\Delta(\Delta F^s)_L^{ML}$ reflects the difference in solvation energies of complexes and free molecules [2].

Gibbs free energy indicates the tendency of binding of crown ions by metals. Its negative value means the spontaneous formation of complexes with the ions K^+ , Na^+ and Ca^{2+} . The higher the value of ΔG in absolute value, the higher the tendency to form complexes. As can be seen from the Table 1, the range of ΔG for complexation in an aqueous medium is ~ 11 kJ and ~ 14 kJ in ethanol solution. This means that with respect to some ions the process of self-arbitrary formation of complexes is selective. But, unambiguously it follows that the process of binding of crown ethers with metal ions by molecules is preferable in ethyl alcohol, rather than in water. This, apparently, is connected, first of all, with the conformation of molecules of crown ethers, determined by the external environment.

Biologically important K^+/Na^+ -selectivity of complexation is established for 4'-DB18C6-sulfonic acid in ethanol (K^+/Na^+ selectivity in ethanol = 4.2).

It was shown that the sulfo derivatives-DB18C6 are amphiphilic to varying degrees, and the affinity for the nonpolar phase decreases in the series: 4'-tert-butyl-4''(5'')-DB18C6-sulfonic acid, 4'-acetyl-4''(5'')-DB18C6-sulfonic acid, 4'-DB18C6-sulfonic acid, 4',4''(5'')-DB18C6-disulfonic acid. It was also found that the affinity of these compounds for the nonpolar phase is higher in the aqueous phase of potassium chloride [23]. The largest channelformer activity among them for K^+ ions is 4'-t-butyl-4''(5'') - DB18C6-sulphonic acid.

The highest Ca^{2+} selectivity is observed in ethanol for 4'-acetyl-4''(5'')-DB18C6-sulfonic acid, and in water for 4'-t-butyl-4''(5'')-DB18C6-sulfonic acid, and a monotonous increase in this selectivity is observed in the water.

Table 1

The thermodynamic parameters of the side substituents diacyl derivatives-DB18C6

Substide	C(cal/MK)	S(cal/MK)	H(kcal/MK)	GG(kcal/MK)
diacyl derivatives DB18C6				
$C_6H_5COCH_3$	14.54	89.12	-20.76	0.43
$C_6H_5COC_2H_5$	20.74	98.72	-25.96	2.06
$C_6H_5COC_3H_7$	26.24	108.14	-30.91	4.03
$C_6H_5COC_4H_9$	31.74	117.55	-35.86	5.96
$C_6H_5COC_6H_{13}$	42.74	136.39	-45.75	9.89
$C_6H_5COC_7H_{15}$	48.24	145.81	-50.71	11.83
$C_6H_5COC_8H_{17}$	53.74	155.23	55.65	12.51

2 Results

An analysis of the results shows that, in practically all experiments, complexation with respect to K^+ , Na^+ and Ca^{2+} ions in ethanol is higher than in water, and differs by one or more orders. An exception is the complexation with Ca^{2+} ions in ethanol for 4'-third-butyl-4''(5'')-DB18C6-sulfonic acid, where it is less than in water by more than 10 times.

Thus, it is obvious that the stability of the 4'-acetyl-4''(5'')-DB18C6-sulfonic acid complex with Ca^{2+} ions differs from the stability of the complexes of the other sulfo derivatives studied. As noted above, the stability constant can be represented as a measure of the calorific value and the change in the entropy of the complexation reaction, because the stability of the complex increases with increasing calorific value and entropy of the process. Apparently, this is precisely what happens in the case of the complexation of 4'-acetyl-4''(5'')-DB18C6-sulfoxide lot with Ca^{2+} ions in ethanol.

If we consider the structural formula of 4'-acetyl-4''(5'')-DB18C6-sulfonic acid, it can be seen that the sulfo group from the acceptor substituent can be converted to the donor substituent, which leads to an increase in the reactivity of the second benzene nucleus. Conditions are created for the transition of the benzoic structure to a quinoid structure, as a result of which a complete positive charge appears on the catecholic oxygen and, as a consequence, the formation of a "trinuous structure" of the macro ring (Fig. 2) [25].

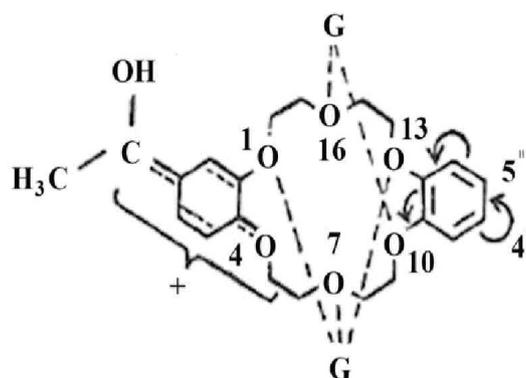


Fig. 2. The quinoid structure of 4'-acetyl-4''(5'')-DB18C6-sulfonic acid. The remaining 5 oxygenates of a macrocycle have two pairs of free electrons, which are capable of binding to Ca^{2+} ions.

We observed similar effects earlier in the study of the complexformation of diacyl derivatives-DB18C6 [13]. Thus, the formation of a quinoid structure (Fig.2) leads to significant conformational changes in the structure of the acetyl-4''(5'') - DB18C6-sulfonic acid molecule in complex formation in ethanol. This again confirms the increase in the contribution of the entropy term to the complexation reaction in comparison with other investigated sulfo derivatives-DB18C6.

Earlier, we showed that, on the whole, there is a good correlation of the stability constant of complexes with the thermodynamic parameters of complex formation [11, 14], but the greatest correlation coefficient is observed for changing the enthalpy values of the substituent radicals. With increasing length of substituents in the benzene rings of dialkyl and diacyl derivatives-DB18C6, the stability constant of complexes with Ca^{2+} ions changes monotonically. Moreover, for dialkyl derivatives-DB18C6 it is linear, then for both diacyl derivatives-DB18C6 it has a quadratic character. Table 1 shows the thermodynamic parameters of the side substituents of the macrocycle for diacyl derivatives-DB18C6. The complexing ability varies depending on the change in the interaction energy between the cation and the donor oxygen atoms of the macrocycle, since the substituents on the side benzene rings have an unquestionable effect on the charge distribution in the ring, and hence on the electrostatic interactions of the cation with the ligand. The process of solvation of the initial reagents and complexes also contributes to their contribution. This explains the apparent dependence of complex formation in solution on the change in enthalpy, the thermodynamic function, which most fully reflects the processes of solvation of the initial reagents and the resulting complexes, as well as the binding energy with the donor atoms of the macrocycle.

Using sulfonic derivatives-DB18C6 as an example, it can be seen that the conformational changes in the crown ether molecule can not be neglected, depending on the nature of the substituents. Apparently, it is just such conformational changes in the crown ether molecule during complexation that can increase the entropy contribution to the thermodynamic process.

The influence of the nature of the substituents on the charge distribution in the crown ethers macrocycle was studied in a number of concrete examples in the works

of Warneck [26, 27]. Benzene rings in DB18C6 somewhat reduce the charge on the oxygen atoms connected with them. The analogous effect is exerted by electron-donating substituents (Cl^- , NO_3^-). Alkyl substituents have practically no effect on the charge distribution in the macrocyclic ring. For hydrocarbon chains, a conformational variety is characteristic, the optimal conformation of hydrocarbon radicals, in which carbon atoms (starting with the propyl radical) are in the trans position, when the hydrocarbon radical does not create steric hindrance to the ion. When the alkyl chain is "bent" to the macrocycle, the stress energy increases, which indicates the absence of steric hindrance from the alkyl radicals during complexation. At the same time, alkyl chains can rotate along the C-C bond without essential energy costs and be oriented both on one side with benzene rings (in-orientation) and in the opposite (out-orientation) direction.

We studied the complexation of the 18-membered crown ethers on the nature of the introduced side substituents. In particular, some N-substituted diamino-DB18C6, dibutyl derivatives-DB18C6 and diacyl derivatives-DB18C6. The quantitative characteristics of the complexation of these compounds with the potassium ion in ethanol were evaluated (Table 2). It is shown that all derivatives having N-containing substituents in the side benzene rings form stable complexes with potassium ions in solution. The maximum value of the stability constant of the complex was obtained for bisacetamide-DB18C6, the same compound exhibits the greatest membrane activity. The stoichiometry of the complexes of all the investigated N-substituted DB18C6 with potassium ions is 1: 1 and 2: 1 crown ether: cation.

When studying the complexation of the homologous series of diacyl derivatives-DB18C6, we were unable to fix the formation of complexes of these compounds with alkali metals in the experimental conditions used by us (the concentration of crown ethers was on the order of 10^{-4} M) by the conductometric method. But all the compounds of this homologous series from 4',4''-diacetyl- to 4',4''(5'')-dioctanoyl-DB18C6 have been effectively bound by calcium ions.

Table 2

Quantitative characteristics of the complexation of N-substituted DB18C6 with potassium ion in ethanol

Crown ethers	radical formula	lgK	λ_0^{M+L}	$r_s, \text{\AA}$
4', (5'') diamino-DB18C6	-NH ₂	7,05	7,46	10,05
4',(5'') bis (acetamide)-	-NH-CO-CH ₃	7,60	7,60	9,87
4',(5'') bis (nitrofur- furolicideneamine)-	-N-CH-O-NO	6,38	7,59	9,87
4',(5'') bis (cyana- mildeneamine)-	-N=CH ₂ - CH ₂ =CH ₃	6,82	7,60	9,87

Acyl groups, being electron acceptors, reduce the electron density of the macrocycle, which accordingly decreases the complexing ability with monovalent cations. The complex with calcium, apparently, is formed due to the participation in the complexation of carbonyl oxygen.

A similar role in the complexation of side-knots was observed by other authors [20] for the complexes Rb^+ and Cs^+ with 4-nitro-B18C6. From the data given earlier, it can be seen that as the concentration of crown ether increases, the electrical conductivity of the solution decreases and then goes to the plateau. Apparently, at these concentrations of the cyclopolyether the maximum binding of Ca^{2+} ions is achieved. The parameters of complex formation of diacyl derivatives-DB18C6 and Ca^{2+} ions were calculated from the titration curves in the region of maximum cation binding (Table 3).

As the length of the hydrocarbon chain of the acyl substituents increases, an increase in the stability constant of the forming complexes is observed; the maximum stability constant is reached in the calcium complex-dipropionyl-DB18C6. A further increase in the length of the hydrocarbon radical leads to a gradual decrease in the stability of the complexes, which is probably due to the appearance of conformational obstacles to cation binding.

Table 3

Quantitative characteristics of the complexation of diacyl derivatives-DB18C6 with $CaCl_2$ in ethanol at 25°C

Crown ethers	lgK	λ_0^{M+L}	$r_s, \text{Å}$
4',4''-diacetyl-DB18C6	6.83	11.8	6.4
4',4''(5'')-dipropionyl- DB18C6	6.89	10.3	7.3
4',4''(5'')-dibutyryl- DB18C6	6.87	11.4	6.6
4',4''(5'')-divaleryl- DB18C6	6.74	11.9	6.3
4',4''(5'')-digeksanoyl- DB18C6	6.31	12.0	6.1
4',4''(5'')-digeptanoyl- DB18C6	5.72	11.7	6.5
4',4''(5'')-dioktanoyl- DB18C6	5.36	10.0	7.5

Diacyl derivatives-DB18C6, which have a ketone group in lateral substituents, are inducers of permeability of artificial and biological membranes for divalent cations; and the pronounced Ca^{2+}/Mg^{2+} selectivity of these crown ethers is observed. The ability to transport single-valence ions for diacyl derivatives-DB18C6 is practically not eliminated, although all of them have a noticeable protonophoric activity. Comparing the experimental data on the membrane activity and complexation ability of the studied diacyl derivatives-DB18C6, we note that the most efficient membrane -otropic compounds form stable complexes with Ca^{2+} ions in the solution, and the logarithms of the stability constants of these complexes are 6.87 and 6.74 for 4',4''(5'')-dibutyryl- and 4',4''(5'')-divaleryl- DB18C6, respectively.

Complex formation of various secbutyl substituted-DB18C6 with single and divalent metal ions in ethanol was studied using the method of conductometric titration. The butyl derivatives-DB18C6 are able to change the conductivity of bilayer membranes and mitochondrial membranes for alkali and alkaline-earth cation ions [24]. With these metal cations, the investigated secbutyl derivatives-DB18C6 form complexes of 1:1 composition, the stability constants of the complexes are higher with

alkali metal ions, especially with Rb^+ and Cs^+ ions. The equilibrium constants of the complexation reactions with the Mg^{2+} and Ca^{2+} ions differ insignificantly among themselves (Table 5).

The monosubstituted-DB18C6 (4'-secbutyl-DB18C6) possesses the maximum complexing ability for monovalent cations. It is possible that the presence of only one lateral substituent has little effect on the conformation of the molecule and does not create serious steric hindrances to the capture of cations by a macrocyclic cavity. Obviously, the ability to form stable complexes of crown ethers with metal ions in solution is, although necessary, but by no means the only condition for the manifestation of membrane activity by crown ethers. Thus, for the sec-butyl-substituted-DB18C6, the stability constants of complexes with monovalent metal ions are significantly higher than those of Mg^{2+} or Ca^{2+} ions, nevertheless these compounds induce a pronounced Mg^{2+} -conductivity of the membranes. Additionally, dibutylbutyl-DB18C6 exhibits some membrane activity for monovalent ions, including H^+ , but this is a common property inherent in all ionophors of divalent cations.

Of particular interest is the fact that crown ethers differing in the mechanism of membrane action differ markedly in complexing properties. We studied the complex formation of these compounds with different metal ions (Table 4). Analyzing the experimental data and comparing the quantitative characteristics of the complexation of 4'4''(5'')-dimethylaminoethanol-DB18C6 and the bis-o-methoxyphenoxy-diethyl ether (channel-formers) with those for 4',4''-diacetyl-DB18C6 (Ca^{2+} -complexon) and dialeryl-DB18C6 the most efficient Ca^{2+} -ionophore, it can be noted that the stability constants of the channel-former complexes with Ca^{2+} ions are (1-1.5) orders of magnitude lower than for Ca^{2+} -ionophores-diacetyl derivatives-DB18C6 (Table 5).

Analysis of the experiments on the complexation of various derivatives of 18-membered crown ethers allows us to conclude that the introduction of substituents of various types in the side benzene rings has an effect not only on the stability of the complexes that form, but also on the selectivity and stoichiometry of complex-formation.

As was shown above, crown ethers possess complexon, ionophore and channel-shaped properties [17, 24, 25]. Sulfonated derivatives-DB18C6 induce the formation of single ionic conduction channels in bilayers mainly for potassium ions.

Investigation of the dependence of crown ethers on biological and artificial membranes on their molecular structure, revealing the regularities between the structure of crown ethers and their membrane activity is an inevitable stage in the directed synthesis of new crown ethers with predetermined properties. Such studies allow searching for ways of direct synthesis of molecules inducing permeability of a given type in the membrane, in particular, new crown ethers for their use in experimental biology, medicine, analytical chemistry, agriculture and other branches of science and technology.

Table 4

The stability constants of complexes (lgK) of secbutyl derivatives of DB18C6 at 25°C

Crown ethers	lgK				
	K ⁺	Rb ⁺	Cs ⁺	Mg ²⁺	Ca ²⁺
4'-secbutyl-DB18C6	5.51	7.13	7.46	5.30	4.89
4',5''-disecbutyl-DB18C6	5.63	6.28	6.60	5.29	4.32
4',4''(5''')-disecbutyl-DB18C6	5.05	5.61	5.70	5.06	4.70

Table 5

Comparative characteristics of complexation properties of crown ethers, differing in the mechanism of membrane action

Crown ethers	lgK		
	K ⁺	Mg ²⁺	K ⁺
bis-o-methoxyphenoxy-diethyl ether	5.10	5.03	5.05
4',4''(5''')-dimethylaminoethanol-DB18C6	5.45	4.12	4.53
4',4''(5''')-diacetyl-DB18C6	6.83	3.78	-
4',4''(5''')-dibutyryl-DB18C6	6.74	4.27	-
4'- secbutyl-DB18C6	4.89	5.30	5.51
4',5''-disecbutyl-DB18C6	4.69	5.29	5.63

Ion selectivity of membranes depends not only on the ratio of the stability constants of the complexes, but also on the interphase coefficients of the distribution (extraction) of complex cations.

Thus, complex forming abilities of crown ethers, which differ in the mechanisms of membrane action, are investigated and compared. Complexing properties of sulfo-products-DB18C6 with single and divalent metal ions by conductometry were studied. The results obtained were compared with the complexing characteristics of Ca²⁺-complexons: 4',4''-diacetyl-DB18C6, 4',4''(5''')-dioctanoyl-DB18C6; Ca²⁺-ionophores of the same series: 4',4''(5''') -dibutyryl-DB18C6 and 4',4''(5''')-divaleryl-DB18C6, as well as Ca²⁺-channel formers: bis-o-methoxyphenoxy-diethyl ether and 4',4''(5''')-dimethylaminoethanol-DB18C6.

Quantitative characteristics of the complex formation of sulfo derivatives-DB18C6 with K⁺, Na⁺, Ca²⁺ ions in water and in ethanol were estimated. It is shown that these compounds are unable to form sufficiently stable complexes with ions of these salts. The maximum values of the stability constant of the complex were obtained for 4'-acetyl-4''(5''')-DB18C6-sulfonic acid in water and 4'4''(5''')-DB18C6-disulfonic acid in ethanol.

In molecules containing the side benzene rings, virtually any functional groups are easily introduced. Thus, the construction of a "skeleton" can contribute to a change in both the selectivity of complexation and membrane activity. By introducing into

the composition of molecules of the same compound of substituents of a different nature, the ability of crown ethers to complexity and the ability to induce selective ion permeability of membranes can be varied.

Conductometric studies of sulfo derivatives-DB18C6 in ethanol show that for 4',4''(5'')-DB18C6-disulphonic acid the maximum value of the stability constant of the complex is obtained. From the obtained titration curves of the conductivity ($\Delta\chi$) dependence on the ratios of the salt concentration to the crown ether (C/L), it was found that the conductivity increases according to the increase in the salt concentrations without forming a plateau region. The quantitative characteristics of the interaction of the investigated crown ethers and salt ions are calculated (Table 6). The table presents the main thermodynamic parameters characterizing the process of interaction of alkali metals with sulfonated crown ethers: the interaction constants (K) and free Gibbs energies (ΔG) [21].

The interaction constant was calculated on the basis that there was no saturation region in the experiment and two points were chosen on the experimental curve for which the interaction constant was assumed to be equal; the data was substituted into the formula for calculating the constant in the absence of saturation.

3 Discussion

Analysis of the thermodynamic characteristics of the interaction of the change in the free Gibbs energy (ΔG) shows that the process of interaction of the studied crown ethers with ions of single and double valence metals proceeds spontaneously, i.e. $\Delta G < 0$. In this case, the interaction is possibly achieved due to the formation of ionic bonds between ions of dissociated salts and charged parts of crown ether molecules.

It is known that the stability constants in methanol and ethanol for crown ethers are several orders of magnitude higher than in water. Apparently, due to the fact that both methanol and ethanol are a much weaker solvating medium and therefore to a lesser extent compete with the crown ether for the cation [9, 22].

For solvents that are less polar than ethanol, the competitive solvation of the cation with these solvents should become less. It should be expected that the stability constants will be higher, especially for small cations. In this case, the effect of the anion will become more noticeable, since more or less intense formation of ion pairs will affect the results obtained [1].

It is established that the interaction constant depends on the nature of the solvent and higher when dissolved in ethanol. Nevertheless, the given value for all the investigated sulfonic derivatives-DB18C6, which are K^+ channel-formers, turned out to be an order of magnitude lower than for the known Ca^{2+} -complexons and Ca^{2+} -ionophores (Table 5) [5, 16, 24].

Table 6

The quantitative characteristics of the interaction of sulfoderivatives-DB18C6 with single and divalent ions in distilled water and ethanol at a temperature of 25°C

Crown ethers	Cation	lgK		$\Delta G(kJ)$	
		Distilled water	Ethanol	Distilled water	Ethanol
4'-third-butyl-4''(5'')-DB18C6-nsulfonic acid	K^+	4.21	5.53	-23.64±1.95	-30.99±1.30
	Na^+	4.38	5.38	-24.65±1.99	-35.83±1.50
	Ca^{2+}	4.99	3.85	-28.03±1.93	-21.86±1.71
4'-acetyl-4''(5'')-DB18C6-sulfonic acid	K^+	3.99	5.96	-22.37±1.83	-33.41±1.65
	Na^+	5.05	6.00	-28.35±1.80	-33.65±1.72
	Ca^{2+}	4.15	6.24	-23.29±1.93	-35.02±1.74
4'-acetyl-DB18C6-mono sulfonic acid	K^+	2.95	5.74	-16.82±0.9	-34.31±1.69
	Na^+	3.00	5.12	-22.70±1.07	-24.25±1.33
	Ca^{2+}	3.48	5.63	-19.15±1.10	-31.59±1.20
4', 4''(5'')-DB18C6-disulfonic acid	K^+	4.09	5.91	-22.92±1.19	-33.13±1.22
	Na^+	3.96	6.33	-22.24±1.58	-35.51±1.18
	Ca^{2+}	3.92	4.87	-21.98±1.56	-27.33±1.25

As already noted above, the sulfo derivatives-DB18C6 have the ability to induce in the bilayers the formation of single ionic conduction channels for monovalent cations, both with unilateral and bilateral introduction of them into membrane washing solutions. It turned out that the channel-shaped properties of the compounds studied correlated with their lipophilicity. The properties of single ion conduction channels induced by sulfoproizene-DB18C6 are similar. The ion conductivity channels studied have practically perfect cation selectivity, which is maintained in the pH range (4-7.5) demonstrating a low cation selectivity.

4 Conclusion

Summarizing the experimental results obtained, it can be concluded that, depending on the mechanism of membrane action of crown ethers, the features of their complexation and interaction with multilamellar layers vary markedly.

The formation of a quinoid structure in the 4'-acetyl-4''(5'')-DB18C6-sulfonic acid molecule causes its high Ca^{2+} selectivity of complexation, explains the increase in the contribution of the entropy term to the complexation reaction. For Ca^{2+} -complexons, the total enthalpy of the phase transition of the phospholipid melting process increases, whereas for Ca^{2+} -ionophores, Ca^{2+} -channel-formers and K^+ -channel-formers, these values decrease.

Crown ethers show a strictly defined specificity of biological action, and this feature depends on the mechanism of membrane action. The experimental material presented above reveals only some of the basic obligatory steps in the action of crown ethers on membranes, without affecting their biological action. It is actual to conduct

a detailed study of membrane active properties of crown ethers, which allow understanding the mechanisms of transmembrane ion transport and create the necessary theoretical basis for directed synthesis of new highly effective and environmentally friendly molecules that exhibit antimicrobial, cardiotropic, antineoplastic and other biological activities.

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