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Synthesis and Complexing Properties of *N*,*N*'-Bis(2-hydroxyethyl) Diaza Crown Ethers

E. Yu. Kulygina, V. I. Vetrogon, S. S. Basok, and N. G. Luk'yanenko

Bogatskii Physicochemical Institute, National Academy of Sciences of Ukraine, Odessa, Ukraine

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Abstract — The stability constants of complexes of 12-, 15-, and 18-membered diaza crown ethers, *N*,*N*'-dimethyl diaza crown ethers, and *N*,*N*'-bis(2-hydroxyethyl) diaza crown ethers with alkali and alkaline-earth metal ions in 95% aqueous methanol at 25°C were determined. The stability of the complexes of unsubstituted diaza crown ethers with alkali metal cations is low, probably because of stabilization of the *exo*,*exo* conformation of the ligands due to interaction of the nitrogen lone electron pairs with the solvent. The complexes with the double-charged cations are appreciably more stable. *N*,*N*'-Dimethyl diaza crown ethers form stable complexes with all the ions studied. As compared to the dimethyl derivatives, N,N'-bis(2-hydroxyethyl) diaza crown ethers form more stable complexes with the Na^+, K^+, Ca^{2+}, Sr^{2+}, and Ba^{2+} ions, which is due to participation of the side hydroxyethyl groups in the coordination.

Macrocyclic polyethers with side groups containing donor atoms (lariat crown others) can form complexes with a three-dimensional coordination sphere, similar to that in cryptates, since the donor atoms of both the macroring and the side chains can be involved in the coordination. This gives rise to unusual complexing properties, which do not directly correlate with the extent of size matching between the cation and macroring cavity but strongly depend on the structure of side substituents [1–5]. In this respect, *N*-hydroxyethyl aza crown ethers are among the most interesting representatives of lariat ethers. In these compounds, the terminal hydroxy groups (or alkoxy groups in the case of *N*-alkoxyethyl derivatives) usually participate in the coordination with a cation [6–9]. However, despite the fact that a large set of such crown ethers have been studied, their complexing properties have been examined for only a limited number of alkali and alkaline-earth cations (mainly Na^+, K^+, and Ca^{2+}). The data were obtained in different solvents and by different methods, which prevents a comprehensive analysis of the influence exerted on the complexation by the ring structure and kind of the cation.

To find how the substituents at the N atoms affect the complexation and whether the side hydroxyethyl groups participate in the coordination with cations, we studied under identical conditions the interaction of unsubstituted diaza crown ethers **I**–**III**, *N*,*N*'-dimethyl diaza crown ethers **IV**–**VI**, and *N*,*N*'-bis(2-hydroxyethyl) diaza crown ethers with alkali and alkaline-earth metal ions. For diaza crown ethers **I**–**VI**, data are available on the stability constants of the complexes with only a few alkali and alkaline-earth metal ions [10].

N,*N*'-Dimethyl diaza crown ethers **IV**–**VI** were prepared by reductive methylation of **I**–**III** with formaldehyde in formic acid, following the protocol described in [11] (see scheme).

The most common route to *N*-hydroxyethyl aza crown ethers is the reaction of aza crown ethers with oxirane [12]. It is advisable to perform the reaction in water with a twofold excess of oxirane. The optimal reaction conditions should be strictly observed; in particular, as the optimal reaction time is exceeded, products of further addition of oxirane to the hydroxyethyl group start to accumulate in large amounts, which decreases the yield and complicates the purification of the target products. Even under the optimal conditions, the yields of the target products do not exceed 60%. The results are not improved when replacing water by aqueous or anhydrous methanol.

We have developed a more convenient procedure for preparing *N*,*N*'-hydroxyethyl-substituted diaza crown ethers **VII**–**IX**, based on the reaction of the corresponding aza crown ethers **I**–**III** with ethylene chlorohydrin in alkaline solution (see scheme). The highest yields of the target products are attained when 15–20% aqueous NaOH is added to a mixture of aza crown eher and ethylene chlorohydrin at room temperature over a period of 0.5 h, with the subsequent heating of the reaction mixture to 50–60°C over a period of 1.5–2 h. The reaction products were isolated by vacuum pyrolysis of the resulting complexes and puri-

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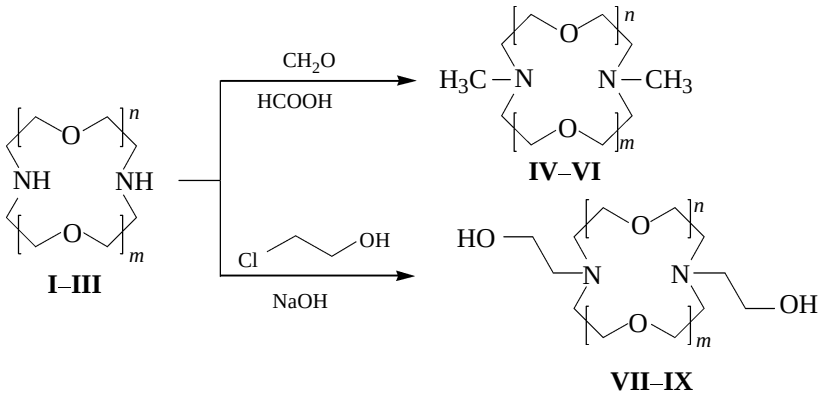
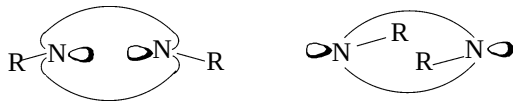


$n = m = 1$ (**I, IV, VII**); $n = 1$, $m = 2$ (**II, V, VIII**); $n = m = 2$ (**III, VI, IX**).

fied by repeated distillation. In the suggested procedure, the synthesis time is shorter and the target products are obtained in 15–30% higher yields compared to the best of the previously described procedures [12].

The stability constants of complexes of **I**–**IX** with Group IA and IIA metal cations were determined by potentiometric titration in 95 vol % aqueous methanol at 25°C. The values given in the table are averaged over three replicate runs.

Diaza crown ethers can exist in two limiting forms, *endo,endo* and *exo,exo*, differing in the orientation of the nitrogen lone electron pairs (inside or outside the ring):



endo,endo *exo,exo*

In diaza crown ethers unsubstituted at the N atom, the *exo,exo* conformation is preferable because of unfavorable electrostatic interactions of the lone electron pairs in the endo,endo form. Furthermore, in polar solvents, the exo,exo conformation is additionally stabilized by solvation effects [13]. Favorable for complexation is the endo,endo form in which the nitrogen lone electron pairs can interact with a cation. Apparently, the *exo,exo* and *endo,endo* transition requires certain energy, which should decrease the stability of the complexes. Indeed, the stability of the complexes of unsubstituted diaza crown ethers **I**–**III** with alkali metal ions is low (see table), which may be due to stabilization of the *exo,exo* form by interaction of the lone electron pairs with a proton-donor solvent. This factor was previously indicated in other papers [14, 15]. The interaction with double-charged cations having higher surface charge density is somewhat more efficient. This fact is well consistent with the existing concept that the stability of crown ether complexes is mainly determined by ion–dipole interactions [12].

In *N*,*N*'-dimethyl diaza crown ethers **IV**–**VI**, the

Stability constants ($\log K$ [$dm^3\ mol^{-1}$]) of diaza crown ethers **I**–**IX** with alkali and alkaline-earth metal ions in 95% methanol at 25°C

Comp. no.	Li^{2+}	Na^{2+}	K^{2+}	Rb^{2+}	Cs^{2+}	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
I	<2	<2	2.14 ± 0.06	2.62 ± 0.09	2.39 ± 0.09	2.84 ± 0.03	3.10 ± 0.06	3.58 ± 0.01	3.76 ± 0.03
II	<2	<2	<2	<2	<2	2.80 ± 0.02	2.90 ± 0.06	2.81 ± 0.09	2.65 ± 0.09
III	<2	<2	<2	<2	<2	<2	3.83 ± 0.05	5.28 ± 0.08	5.15 ± 0.06
IV	2.59 ± 0.09	2.56 ± 0.08	2.16 ± 0.03	2.66 ± 0.02	3.48 ± 0.06	3.43 ± 0.06	3.32 ± 0.05	3.59 ± 0.06	4.19 ± 0.01
V	2.86 ± 0.05	3.89 ± 0.04	3.27 ± 0.03	3.64 ± 0.03	4.10 ± 0.05	2.65 ± 0.05	4.59 ± 0.04	4.70 ± 0.04	4.85 ± 0.05
VI	<2	3.33 ± 0.03	4.55 ± 0.08	4.06 ± 0.05	3.85 ± 0.08	3.18 ± 0.07	4.81 ± 0.06	6.94 ± 0.09	6.67 ± 0.09
VII	2.57 ± 0.03	3.61 ± 0.01	2.66 ± 0.03	2.22 ± 0.05	2.18 ± 0.05	3.20 ± 0.02	6.59 ± 0.02	6.25 ± 0.01	6.12 ± 0.01
VIII	2.26 ± 0.06	4.53 ± 0.02	4.04 ± 0.02	3.21 ± 0.03	2.24 ± 0.07	3.66 ± 0.03	7.52 ± 0.01	7.53 ± 0.02	7.03 ± 0.02
IX	1.61 ± 0.02	4.60 ± 0.01	5.28 ± 0.01	4.37 ± 0.02	2.89 ± 0.04	<2	7.60 ± 0.02	8.44 ± 0.01	8.94 ± 0.01

exo,exo conformation is sterically unfavorable, and the *endo,endo* conformation becomes predominant. Apparently, this fact, in combination with somewhat increased basicity of the nitrogen atoms, provides formation of stable complexes of *N*-methylated aza crown ethers with both alkali and alkaline-earth metal ions. The stability of the complexes with alkali metal ions regularly varies depending on the extent of size matching between the cation and macroring cavity; with alkaline-earth metal cations, this trend is weakly pronounced (see table).

The hydroxyethyl substituents at the N atoms decrease their basicity: The protonation constants of diaza crown ethers **VII**–**IX** are by approximately an order of magnitude lower compared to **IV**–**VI**. This factor should cause the stability of the complexes to decrease. On the other hand, complexes of *N*,*N*'-bis-(hydroxyethyl) diaza crown ethers can be additionally stabiized by interaction of the cation with alcoholic oxygen atoms.

In contrast to classical crown ethers, aza crown ethers, and cryptands, the stability of the complexes of **VII**–**IX** with alkali metal cations does not vary regularly with increasing size of the macroring cavity. Irrespective of the cavity size, the most stable complexes are formed with Na^+ and K^+. Mutual comparison of the stability constants of the complexes formed by *N*,*N*'-dimethyl (**IV**–**VI**) and *N*,*N*'-bis(hydroxyethyl) (**VII**–**IX**) diaza crown ethers that have the same macroring size shows that, in the series of alkali metals, only with Na^+ and K^+ there are good grounds to postulate the participation of the side hydroxyethyl groups in the complexation. In all the other cases, crown ethers **VII**–**IX** form less stable complexes than their *N*-methyl analogs.

The effect of hydroxyethyl groups on the stability of complexes with alkaline-earth metal ions (Ca^{2+}, Sr^{2+}, Ba^{2+}) is very pronounced. The contribution of the hydroxyethyl groups to the complexation increases the stability constants in this case by 2–3 orders of magnitude. This is quite natural, since the oxygen atoms of the hydroxyethyl groups are relatively "hard" bases and should preferentially interact with cations having a high charge density.

Of particular interest is the high Ca/Na selectivity of **VII**–**IX**. Irrespective of the ring size, the Ca^{2+} complexes are ~1000 times more stable than the Na^+ complexes. With respect to this parameter, aza crown ethers **VII**–**IX** have no equal among synthetic macrocyclic ligands. The Ca/Na balance is of fundamental importance in many biological processes. Therefore, compounds **VII**–**IX** show promise for their simulation, as potentially bioactive substances, and as a basis for the development of sensors allowing determination of calcium in biological objects against the background of a large excess of sodium.

On the whole, with respect to the stability of complexes with alkaline-earth cations, hydroxyethyl-substituted diaza crown ethers occupy an intermediate position between the crown ethers and cryptands and can be a good alternative for them in the development of chemosensors.

EXPERIMENTAL

The melting points were determined in an open capillary and were not corrected. The ^{1}H NMR spectra were taken on Bruker AM-200 (200 MHz) and Bruker AM-250 (250 MHz) spectrometers in $CDCl_3$, internal reference tetramethylsilane. The mass spectra were taken on Varian MAT-112 and MKh-1321 spectrometers with direct sample inlet at the ionizing electron energy of 70 and 40 eV. The elemental analysis was performed at the analytical laboratory of the Physicochemical Institute, National Academy of Sciences of Ukraine. Thin-layer chromatography was performed on Silufol UV-254 plates (Kavalier). All commercial chemicals were used without additional purification, unless otherwise indicated. Diaza crown ethers **I**–**III** [16] and *N*,*N*'-dimethyl diaza crown ethers **IV**–**VI** [11] were prepared by published procedures. The purity of all the compounds **I**–**IX** was no less than 99% (GLC); their structures were confirmed by analytical and spectroscopic (mass spectrometry, ^{1}H NMR) methods. The spectra were consistent with published data [17].

***N*,*N*'-Bis(hydroxyethyl) diaza crown ethers VII**–**IX** *(general procedure).* A solution of 42 mmol of NaOH in 8.25 ml of water was added dropwise at room temperature over a period of 30 min to a stirred solution of 15 mmol of diaza crown ether **I**–**III** and 42 mmol of ethylene chlorohydrin. Then the mixture was gradually heated to 50–60°C over a period of 1–1.5 h, cooled, diluted with 7.5 ml of water, and extracted with chloroform (5 × 15 ml). After removing the solvent from the extract at a reduced pressure, the residue was heated in a vacuum with simultaneous distillation of diaza crown ethers **VII**–**IX**. If necessary, the products were additionally purified by repeated vacuum distillation.

Determination of the stability constants of complexes of aza crown ethers I–**IX.** Ligand solutions were prepared by dissolving weighed portions of the ligands in 95 vol % aqueous methanol. The ionic strength of the solutions was maintained constant (0.05 M) by adding tetraethylammonium perchlorate preliminarily recrystallized from methanol. The titra-

tion was performed with a tetraethylammonium hydroxide solution prepared by dilution of the commercial solution (25% in MeOH, Fluka) and standardized relative to potassium biphthalate.

The stability constants of the complexes were determined by potentiometric titration (competition with protons). The measurements were performed at 25°C with a combined glass electrode (Ingold) connected to an automatic titrator (DMS-716 Titrino). The standard internal solution of the external reference electrode (saturated aqueous KCl) of the combined glass electrode was replaced by a 0.05 M solution of Et_4NCl in MeOH, saturated with AgCl. The parameters (pH_0 and S) of the electrode function $pH_{meas} = pH_0 + S\log[H^+]$, the activity coefficients of the proton, and the ionic product $[H^+][OH^-]$ were determined by measuring the pH of a standard buffer solution with pH 7.10 (0.01 M succinic acid and 0.01 M lithium hydrogen succinate in 95% methanol [18]) and from the curve of titration of 0.01 M $HClO_4$ in 95% MeOH [prepared by dilution of concentrated (11.6 M) perchloric acid] with 0.01 M Et_4NOH in the presence of 0.05 M Et_4NClO_4. The resulting value, $\log([H^+] \times [OH^-]) = -15.2 \pm 0.1$, was used as a constant in the subsequent calculations.

The protonation constants of the ligands and the complexation constants β_{xyz} corresponding to the general complexation equilibrium $xM^{n+} + yL + zH^+ \rightleftarrows M_xL_yH_z^{(nx+z)+}$ were determined from the pH-metric data obtained in the course of neutralization of an acidic solution of the ligand with 0.01 M Et_4NOH in MeOH in an argon flow in the presence of metal salts or without them. The data were processed with the SIR-KO program [19] allowing simultaneous determination of the constants β_{xyz}, electrode parameters, and concentrations of the mixture components. For calculations, we used the total titration curve in the range pH 3–12. In the calculations, the electrode parameters determined in advance were assumed to be constant. In the determination of the stability constants of the complexes (β_{xyz}), the protonation constants of the ligands (β_{0yz}) were assumed to be equal to those determined by titration of the ligand in the absence of metals.

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