

## A New Type of Functionalized Cryptand-like Ionophore. Synthesis, Structure and Complexation

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New functionalized cryptand-like ionophores are prepared from appropriate diaza-crown ethers and epichlorohydrin, using FAB MS, potentiometry, <sup>13</sup>C-NMR spectroscopy, and T<sup>1</sup> relaxation times measurements, the conformation and complexation patterns are found to change dramatically with the change in size of the macrocycle.

The reaction of diaza-18-crown-6 with epichlorohydrin in methanol is known to furnish water-soluble polymeric ionophores.<sup>1</sup> Surprisingly, we have isolated almost exclusively monomeric **4** by carrying out the reaction in dioxane or dioxane containing a small amount of methanol. Similarly, compounds **5** and **6** were obtained under the same conditions<sup>†</sup> (*cf.* Scheme 1).<sup>‡</sup> The reaction proceeds *via* the intermediate **7a**, the conformation of which **7b** is thought to be responsible

for the intramolecular mode of cyclisation. The hydroxy group is strongly hydrogen bonded to donor sites of the macrocyclic ring—especially to nitrogen atom where five-membered ring thus formed should substantially enhance the stability of this conformation. This effect is strongly manifested in aprotic solvents such as dioxane.<sup>2</sup> In the conformation **7b**, the side chain is suitably oriented to facilitate the nucleophilic intramolecular attack on secondary nitrogen. In protic solvents such as methanol, however, the hydrogen bonding is assumed to be more dissipated and the side chain is not held in the proximity of the macrocyclic cavity thus promoting an intermolecular mode of reaction that leads to polymerisation. Complexation profiles for several alkaline cations of the newly prepared ionophores **4–6** were assessed on a semiquantitative level using FAB MS competition technique.<sup>3,4</sup> A comparison was made with corresponding potentiometric values. All the data are summarized in Table 1.

The selectivity of **4** for sodium is clearly visible in FAB MS data and accordingly there is more than one order of magnitude difference between stability constants of **4**·Na<sup>+</sup>

<sup>†</sup> Satisfactory data of elemental analyses were obtained for all the new compounds. In a typical experiment, 10 mm of free diaza-crown was treated with 20 mm of freshly distilled epichlorohydrin in 20 ml of dioxane at 100 °C for 8 h. Product was isolated by chromatography on neutral alumina (chloroform to chloroform–2% methanol).

<sup>‡</sup> The IUPAC nomenclature of the ligands studied: **1**: 20-hydroxy-4,7,13,16-tetraoxa-1,13-diazabicyclo[8.8.3]heneicosane; **2**: 23-hydroxy-4,7,10,16,19-pentaoxa-1,13-diazabicyclo[11.8.3] tetracosane; **3**: 26-hydroxy-4,7,10,16,19,22-hexaoxa-1,13-diazabicyclo[11.11.3] heptacosane.

**Table 1** Complexes of **4-6** with Na<sup>+</sup>, K<sup>+</sup>, Rb<sup>+</sup> and Cs<sup>+</sup> assessed by FAB-MS,<sup>a</sup> and potentiometry<sup>b</sup>

Compound	Method	Na <sup>+</sup>	K <sup>+</sup>	Rb <sup>+</sup>	Cs <sup>+</sup>
4	FAB <sup>a</sup>	100%	6%	4%	N
	Potentiometry <sup>b</sup>	4.36	3.32	2.90	2.72
5	FAB <sup>a</sup>	100%	18%	6%	N
	Potentiometry <sup>b</sup>	3.07	3.16	2.99	2.77
6	FAB <sup>c</sup>	100%	80%	32%	20%
	Potentiometry <sup>d</sup>	5.95	6.24	6.13	6.16

<sup>a</sup> Relative abundancies of ions corresponding to 1:1 complexes [M.L]<sup>+</sup> were measured. Competition experiments were measured as follows. The solution of an appropriate ligand in 90% methanol (5 mm) and equimolar mixture of the salts (5–50 mM solution of corresponding metal chlorides) were mixed with tenfold volume of glycerol containing an excess (calculated on amount of ligand) of tetrabutylammonium hydroxide. The ratio of two equivalents of each metal salt to ligand was used for all experiments. The stainless-steel tip of FAB probe was coated with a layer of the above prepared solution, the sample was placed in the ion source and the pressure was allowed to settle for 2 min. Spectra were recorded within the following 3 min, the peak heights were averaged over at least ten scans. Positive ion FAB-MS was performed using the primary atom beam of Xe on a Finnigan MAT 90 mass spectrometer. <sup>b</sup> Determination of stability constants for a 1:1 complexes (expressed in mol l<sup>-1</sup>) was carried out in 99% MeOH with NMe<sub>4</sub>OH (c 0.01 M) at 20 °C by means of automatic titrator Radiometer TTT85. Complexation constants with Na<sup>+</sup> and K<sup>+</sup> were determined by means of Na<sup>+</sup>-ISE (Crytur sodium ion selective electrode, Monokrystal Turnov, Czechoslovakia) and K<sup>+</sup>-ISE (Tacussal PKV, France). Titrants were 0.01 M solutions of NaCl and KCl in 99% MeOH. Complexation constants with Rb<sup>+</sup> and Cs<sup>+</sup> were determined competitively with Na<sup>+</sup> by means of Na<sup>+</sup>-ISE. Concentrations of RbCl and CsCl were 0.0005–0.001 M. Concentrations of crown ethers were ca. 0.001 M. The Ag/AgCl with LiCl as inner solution was used as reference electrode. The measuring system was calibrated before each titration. All measurements were repeated at least three times and showed good agreement. All calculations were performed with MINIQAD program. <sup>c</sup> In addition to the ionic species corresponding to 1:1 complexes indicated in Table 1, several other complexes were detected only for **6** in FAB-MS and their abundancies relative to that of sodium complex were: Ca<sup>2+</sup> (11%), Sr<sup>2+</sup> (17%), Ba<sup>2+</sup> (31%), Cu<sup>2+</sup> (136%) and Zn<sup>2+</sup> (24%). <sup>d</sup> The stability constants for L:M 2:1 complex formation (in mol l<sup>-1</sup>) obtained under the same conditions as indicated in footnote.<sup>b</sup>

and **4**·K<sup>+</sup> complexes found by potentiometric measurement. The corresponding data for **5** show little difference between sodium and potassium complexation. The complexing patterns of **6** are entirely different as only 2:1 L:M complexes were found potentiometrically in 99% methanol. In FAB MS, 1:1 complexes for all alkali metal cations are clearly visible, but contrary to **4** and **5**, abundant ion corresponding to 2:1 **6**·M complexes were invariably found. No such species was detected in spectra generated from smaller ligands **4** and **5**.

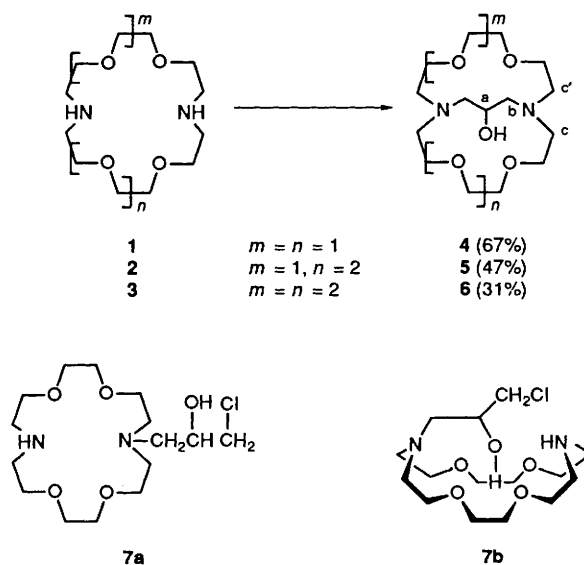
The following explanation of the difference in the complexation pattern found for **4-6** is based on CPK models inspection. Shallow tightly packed nest-like cavities of **4** and **5** are capable of spherical recognition contrary to butterfly-like **6**, where the macro-ring is divided into two smaller parts. Moreover, hydroxy group in the β-position to both nitrogens is strongly hydrogen bonded to them, thus forming the 12-crown-4-like arrangement that is known to form 2:1 complexes. This is schematically depicted in Scheme 2.

In order to obtain a deeper insight into the process of complexation we have performed the <sup>13</sup>C NMR relaxation times study for **4-6** and their sodium complexes. This technique<sup>5,6</sup> was used for assessment of molecular dynamics both in the presence and absence of cation. It gives inferential

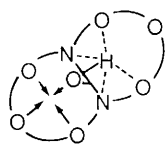
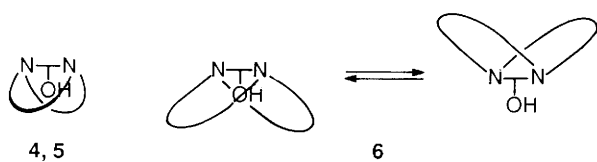
**Table 2** <sup>13</sup>C NMR<sup>a</sup> chemical shifts δ (in ppm relative to MeOH, MeOH = 49.9 ppm) and T<sub>1</sub> relaxation times (in s) for **4-6** and their Na<sup>+</sup> complexes

Compound	Carbon <sup>b</sup>	δ	Δδ <sup>c</sup>	T <sub>1</sub>	ΔT <sub>1</sub>
4	a	68.83	-1.78	1.022	0.346
	b	60.19	5.22	0.573	0.230
	c	56.61	-0.71	0.656	0.068
5	c'	57.42	-0.52	0.641	0.146
	a	69.87	-4.20	0.930	0.333
	b	59.33	7.07	0.527	N <sup>d</sup>
6	c	56.90	-3.54	0.573	0.073
	c'	57.20	-1.77	0.558	0.119
	a	67.24	0.44	0.932	0.085
6	b	58.97	-2.68	0.514	0.065
	c = c'	56.47	0.01	0.558	-0.041

<sup>a</sup> T<sub>1</sub> relaxation times were measured under proton-noise-decoupling conditions by the inversion recovery method using composite 180° pulse on Varian XL-200 spectrometer at 50.32 MHz. A waiting time of at least five times the longest relaxation time was used in each case. Eighteen different quadratically spaced pulse intervals (τ) were used for each individual measurement and always at least fourteen points were included for each T<sub>1</sub> calculation. Usually 128–768 scans were necessary for each τ value in order to obtain a reasonable signal to noise ratio. In every case the probe temperature was controlled at 35 °C (0.5 °C) by Varian XL-200VT unit. T<sub>1</sub> values were determined by a linear least-squares three parameter fit of the experimental data directly performed by a spectrometer computer. Mean T<sub>1</sub> values of six runs are given in the Table 2. Their standard deviations were less than 7%. The spectra were referenced to the signal of methanol. All experiments were performed in methanol-deuterium oxide (9:1) solution using 0.3 M concentration of ligands and one equivalent of sodium thiocyanate throughout the study. NMR samples consisted of 0.5–0.7 ml of solution in 0.5 mm OD tubes. No difference was found between T<sub>1</sub> values using samples degassed by three freeze-pump-thaw cycles and samples in which Argon was bubbled through for 15 min at -70 °C. <sup>b</sup> The numbering of carbons is shown in Scheme 1. <sup>c</sup> The symbol, Δ denotes the change of corresponding value induced by complexation with sodium thiocyanate. <sup>d</sup> N denotes that value could not be unambiguously determined due to signal overlapping.

**Scheme 1**

information on microstructural interactions in the individual molecular complexes. Only those carbon atoms that could be unambiguously assigned were taken into account. The data obtained are summarized in Table 2.



Scheme 2

The similarity of the data for **4** and **5** is immediately apparent, while **6** exhibits a completely different pattern of spectral changes on complexation. The differences in chemical shift of CH<sub>2</sub> carbons of the 2-hydroxy-1,3-propylene unit and in the mobility of CH carbon of the same unit led us to the conclusion that while the hydroxy group is pointing inside the cavities of **4** and **5**, the situation becomes completely different

in the sodium complexes. Upon complexation with the sodium cation, the smaller ligands **4** and **5** are forced to change their conformation and the hydroxy group is pushed out of cavity, thus changing dramatically the magnetic environment of both methylene carbons and the mobility of methine carbon on the hydroxypropylene unit.

Consequently, it could be concluded that three new cryptand-like ionophores **4–6** represent a new class of ligands that change their conformation and/or complexation pattern dramatically with the size of macrocyclic ring.

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