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Alkali Metal- and Ammonium Picrate Extraction and Complex Forming Capabilities of D-Glucose and D-Mannose-based Lariat Ethers

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Abstract

The alkali metal- and ammonium picrate extracting ability of D-glucose- and D-mannose-based 15-crown-5 ethers and related lariat ethers was investigated in dichloromethane – water system. A heteroatom was waried in the crown ether containing a 4,6-O-benzylidene-α-D-glucopyranoside unit **6**, (X = O), **2** (X = S) and **8a** (X = NH). Extracting ability of the latter species (**8a**) was excellent (97–99%) in regard of all cations (Li^+, Na^+, K^+, Rb^+, Cs^+ and NH_4^+) examined, it was not, however, selective. Introduction of a side arm on the nitrogen atom of **8a** decreased the extracting ability, but increased the selectivity. In this series of compounds (**8b–f, 4**), **4** with a pyridylethyl substituent allowed the extraction of sodium picrate in 72%. The glucose-based macrocycles **8a**, **8e** and **8f** formed a stronger complex with the cations examined than the mannose-based analogues **9a**, **9e** and **9f**, that can be explained by the all-gauche conformation of the former ones. It was pointed out that in the case of crowns with tertiary amine moieties, the basicity increases the quantity of the picrates extracted. According to complex forming measurements by FAB-MS, the best sodium ion selectivity was achieved by the γ-hydroxypropyl substituted lariat ether (**8e**). Possible structures of the complexes formed by the two types of monosacharides with sodium cation were evaluated by molecule modelling calculations.

Introduction

Lariat ethers are designed to achieve strong and selective three-dimensional binding of metal cations via the cooperative binding provided by the crown ether moiety and the side-arm containing a heteroatom [1–3]. An important advantage of aza-crown ethers over oxa-crown ethers is the presence of soft nitrogen donor atoms which can offer characteristic complexing and transporting abilities. A variety of thermodynamic studies on the complexation of lariat crown ethers have been performed in an effort to elucidate the factors that influence cation-ligand complexation [4, 5]. A special group of the crown ethers is the chiral macrocycles containing different carbohydrate-units. Many optically active crown ethers and cryptands have been synthesized from monosaccharides [6–10]. The complexation of these compounds with alkali metal-, ammonium- and t-butylammonium picrates were investigated and discussed by Stoddart *et al.* [6, 10]. Chiral lariat ethers derived from different monosaccharides, such as D-glucose, D-galactose, D-mannose e.g. were introduced by us in the last decade [11, 12], a part of which was applied successfully as chiral phase transfer catalyst in asymmetric reactions [12–16].

The phase transfer catalysts can be characterized well by the extracting ability (EA%) of picrate salts from water into the organic phase. The EA values describe well the cation binding ability of crown ethers and lariat ethers in liquid–liquid two phase system [17–20]. Extracting ability of the macrocycles depends mainly on the complex forming ability influenced by the size of the cavity and the type and number of heteroatoms, as well as on the lipophilicity. These characteristics determine the distribution of a cation between the water- and the organic phases.

Earlier it was pointed out by us that the N-substituents in the macrocycles of type **8** containing a 4,6-O-benzylidene-α-D-glucopyranoside unit have a great impact on the extracting ability of the cations. We

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experienced that benzyl- or aromatic substituents on the nitrogen atom decreased strongly the cation extracting ability [11]. In the present paper complexing abilities of lariat ethers containing a heteroatom at the end of the side arm are investigated. These kind of side arms are flexible enough to be able to promote or prevent complexation of the cations by the heteroatom (oxygen, nitrogen etc) at the end of the N-substituent. The side arm with a hydroxy-, methoxy- or 2-pyridyl group has an inpact also on the liphofility of the molecule that was calculated to be able to characterize the lariat ethers and to be able to compare the different extracting abilities. The strength of the complexes of the macrocycles with alkali picrates together with the selectivity towards the different cations was studied by FAB-MS in m-NBA matrix [21–23].

Experimental

General procedures

Melting points were determined using a Büchi 510 apparatus and are uncorrected. The specific rotation was measured on a Perkin-Elmer 241 polarimeter at 22 °C, while the IR spectra were recorded on a Perkin-Elmer 237 spectrophotometer. NMR spectra were obtained on a Brucker DRX-500 instrument in $CDC1_3$ with Me_4Si as an internal standard. Mass spectra were obtained from *m*-nitrobenzyl alcohol matrix on a Varian MAT312 instrument. Analytical and preparative thin layer chromatography was performed on silica gel plates (60 GF-254, Merck), while column chromatography was carried out using 70–230 mesh silica gel (Merck). Chemicals and the shift reagent $Eu(hfc)_3$ were from Aldrich Chem. Co.

Crown ether **6** was obtained in the reaction of methyl 4,6-O-benzylidene-α-D-glucopyranoside and tetraethyleneglycol ditosylate according to the literature [24]. The monoaza-15-crown-5 **8a** was synthesized by the reaction of dichloro copound **3** with *p*-toluene-sulfonamide removing the tosyl group by reduction [25]. Synthesis and characterization of the chiral lariat ethers **8b–f** was described previously [8, 11] for compounds **9a**, **9e**, **9f** [12].

*Synthesis of monothia-15-crown-5 (**2**, Scheme 1)*

A mixture of bischloro-compound **1** (2.17 g, 4.38 mmol) and Na_2S*9H_2O (2.39 g, 9.95 mmol) in ethanol (60 mL) was refluxed under stirring for 16 h. After cooling to room temperature the precipitate was filtered and washed with ethanol. The combined ethanol solutions were concentrated; the residual oil was dissolved in dichloromethane (60 mL), washed with water, dried (Na_2SO_4) and concentrated. The crude product was crystallized from ethanol to yield macrocycle **2** (1.7 g, 85%) in a pure form; m. p. 116–117 °C $[\alpha]_D^{22} = 52.4$ (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ [ppm] 3.43 (s, 3H, OCH_3), 3.44–4.03 (m, 21H, CH, CH_2 groups), 4.28 (dd, 1H, H-6), 4.84 (d, 1H, α-anomer-H), 5.52 (s, 1H, PhCH), 7.33–7.49 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ [ppm] 31.7 ($2 \times SCH_2$), 55.2 (OCH_3), 62.3 (5-CH), 69.1 (6-CH), 70.6 ($2 \times OCH_2$), 71.8 ($2 \times OCH_2$), 72.3 ($2 \times OCH_2$), 78.1 (3-CH), 79.8 (2-CH), 82.1 (4-CH), 98.4 (1-CH), 101.3 (*CH*Ph), 126.0 (ortho-Ph), 128.2 (meta-Ph), 129.1 (para-Ph), 137.4 (ipso-Ph); FAB-MS, *m/z* 457 $[M+1]^+$ (21%); 479 $[M+Na]^+$ (100%); HRMS calcd for $C_{22}H_{32}O_8S$ 456.1818, found 456.1815.

*Synthesis of D-glucose-based lariat ether with 2-(2-pyridyl-)ethyl side arm (**4**, Scheme 2)*

Anhydrous Na_2CO_3 (5.6 g, 52.8 mmol) was suspended in a solution of 2-(2-aminoethyl)pyridine (1.3 g, 10.6 mmol) and bisiodo compound **3** (5.3 g, 7.8 mmol) in dry acetonitrile (160 mL) under argon. The mixture was stirred at the boiling point for 32 h. After cooling to room temperature, the precipitate was filtered and washed with acetonitrile. The combined acetonitrile solutions were concentrated; the residual oil was dissolved in chloroform, washed with water, dried (Na_2SO_4) and concentrated. The crude product so obtained was purufied by column chromatography on silica gel with chloroform–methanol (100:1 → 100:10) to afford title compound **4** (2.5 g, 62%); m.p. 57–59 °C; $[\alpha]_D^{22} = 20.8$ ($c = 1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ [ppm] 2.71–3.1 (m, 8H, $4 \times CH_2$), 3.43 (s, 3H, OCH_3), 3.61–3.94 (m, 17H, CH_2 and CH groups), 4.28 (d, 1H, H-6), 4.83 (s, 1H, anomer-H), 5.52 (s, 1H, PhCH), 6.95–7.83 (m, 8H, Ph), 8.53 (m, 1H, NHPh). ^{13}C NMR ($CDCl_3$) δ [ppm] 35.6 (CH_2C-Py), 54.5 ($2 \times CH_2N$), 55.2 (OCH_3), 56.7 (NCH_2), 62.2 (5-CH), 69.1 (6-CH), 70.0 ($2 \times OCH_2$), 70.5 ($2 \times OCH_2$), 72.5 ($2 \times OCH_2$), 78.1 (3-CH), 79.9 (2-CH), 82.3 (4-CH), 98.4 (1-CH), 101.3 (*CH*Ph), 121.2 (CH–Py), 123.5 (CH–Py), 126.0 ($2 \times$ CH, ortho-Ph), 128.2 ($2 \times$ CH, meta-Ph), 128.9 (para-Ph), 136.4 (CH-Py), 137.4 (ipso-Ph), 149.2 (CH–Py), 160.5 (CH_2C–Py); FAB-MS, *m/z* 545 $[M^+ + 1]$, 567 (35%), $[M+Na]^+$ (100%). HRMS calcd for $C_{29}H_{40}N_2O_8$ 544.2785, found 544.2782.

Extraction ability [26]

Equal volumes (5 mL) of a dichloromethane solution of the crown ether ($c = 0.01$ mol L^{-1}) and of the aqueous alkali metal picrate ($c = 0.005$ mol L^{-1}) were introduced into an Erlenmeyer flask, which was then stoppered and shaken for 40 min at 22 °C. The mixture was then allowed to stand for at least 2 h in order to complete the phase separation. The phases were separated and the picrate concentration in the aqueous phase determined from its absorption at 354 nm ($\epsilon = 14600$ mol^{-1} cm^{-1}). The extraction ability is given as % of the picrate extracted into the organic phase. In the control experiments carried out in the absence of azacrown ethers, no detectable amounts of picrates were extracted into the organic phase.

Calculation of liphofility [27]

The calculation of liphofilicity was based on well-known *n*-octanol-water distribution (log *P*). The Pallas 3.1 intelligent software package was used for this purpose [27].

To get the log *P* values, the chemical structure of given compound must be drawn and Pallas 3.1 calculates it. Based on the chemical structure of the compounds, the intelligent program applied three different methods (CDI-Rekker-, atomic6- and annlog *P*); the final result are given by three values. The log *P* values of the compound-pairs glucose/mannose (**8**/**9**) are identical, as the program Pallas 3.1 is not able to discriminate the chiral isomers.

FAB-MS Binding experiments [22]

Complexation of the crown ethers (0.005 mol L^{-1}) with an alkali cation 'coctail' containing Li-, Na-, K-, Rb-, Cs-picrates (0.01 mol L^{-1}, each) in *m*-nitrobenzyl alcohol was studied by measuring the peak heights of $[\text{lariat ether} + \text{cation}]^+$ ions relative to the uncomplexed $[\text{lariat ether} + H]^+$ ion. FAB MS spectra were recorded with a JEOL DX 300 instrument (applying a beam energy of Xe, 6keV) and the peak heights were averaged over at least 12 scans).

Molecular modeling

MCMM (Monte Carlo Multiple Minimum) search [28] as implemented in MacroModel [29] involved the random variation (within the range of 0–180°) of a randomly selected subset of all torsional angles (a minimum of 2 and a maximum between 24 and 28 torsions – depending on the specific molecule), combined with the variable molecules selection (MOLS) method for translations and rotations of the complexing ions with respect to crown. The combined MCMM/MOLS procedure allowed random translation (0–3 Å) and rotation (0–180°) during a Monte Carlo step, calculations consisted of 30,000 steps. The perturbed structures were minimized using the TNCG algorithm. The resulting minimum energy complex structures were sorted by energy, and the unique structures within a 50 kJ mol^{-1} energy window above the global minimum were stored. Cation binding energies were calculated as the difference of the energy of the complex and the sum of the energies of its unligated components.

Calculations were carried out using the MMFF force field [30, 31] however, charges of the macrocycle were derived from AMBER*[32], since our own set of charges calculated for comparison purposes by the ESP method [33] (using a B3LYP/6-31G** wave function) showed better correlation with the latter (data not shown). The picrate anion carried ESP charges calculated with the described protocol, using Jaguar (Jaguar, Version 4.1, Schrödinger, Inc., Portland, OR.). Solvent-effects were modeled by the GB/SA algorithm (using water and chloroform as solvents) [34].

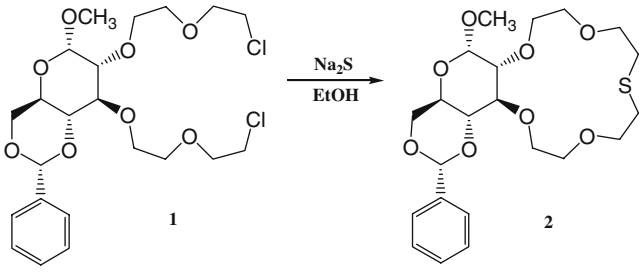
Results and discussion

Synthesis

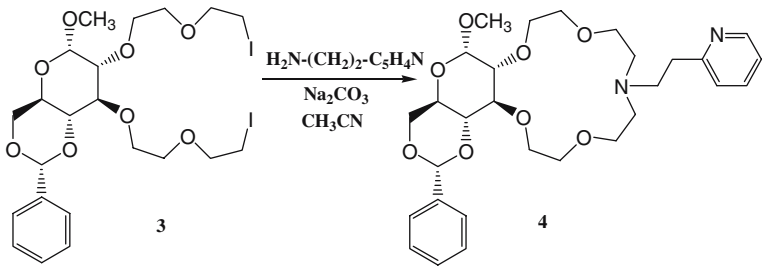
Glucopyranoside-based bichloro podand **1** [11] was the key-intermediate in the preparation of chiral monothiacrown **2**. The ring closure of **2** was achieved by sodium sulfide (Na_2S*9H_2O) in boiling ethanol, after a 16 h's reaction time to afford product **2** in 85% yield (Scheme 1). Among the lariat ethers, only the N-2-(2-pyridil-)ethyl derivative (**4**) was new that was synthesized by the reaction of bisiodo intermediate **3** [11] and 2-(2-aminoethyl)pyridine in the presence of sodium carbonate, in diluted acetonitrile at reflux for 38 h. Lariat ether **4** was obtained in 62% yield after chromatography (Scheme 2). The other D-glucose- and D-mannose-based chiral lariat ethers (**4**, **8** and **9**, respectively) (Figure 1. and 2.) were synthesized as described earlier [8, 12, 25].

Extracting properties

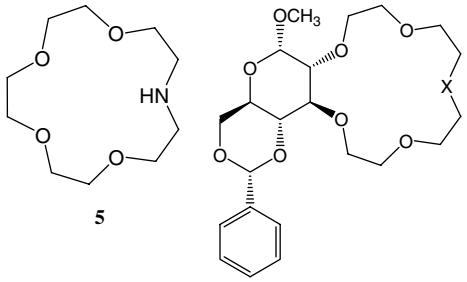
The phase transfer catalytic properties of the chiral crown ether (**6**), thiacrown ether (**2**), azacrown ether (**8a**) and lariat ethers (**8** and **9**), (in a liquid–liquid two-phase system) were characterized by the extraction of picrate salts (lithium-, sodium-, potassium-, rubidium-, cesium- and ammonium picrates) from water into dichloromethane following the procedure described by Kimura *et al*. [26]. The concentration of the picrates in water was measured by UV spectroscopy. The data were collected in Table 1. showing the amount of the salts transfered as the percentage of the initial amount of salt (extractability %). The differences between the alkali metal picrate extraction abilities of the host molecules refer to the selectivity. Liphofility of the macrocycles (**2**, **4**, **5**, **6**, **8a**–**f**, **9a**, **9e**, **9f**) was calculated by the Pallas 3.1 software [27]. The log *P* values listed in Table 1 characterize well the relative liphofility of the crown compounds. For comparison purposes, properties of the unsubstituted monoaza-15-crown-5 (**5**) were also measured. It can be seen from Table 1 that glucose-based crown ether **6** containing only oxygen atoms in the hetero ring has only a low extracting ability against all cations examined. The extracting ability of **6** is maximum for the Na^+ cation that is 15.8% and that is 13-fold of the similar value obtained for Cs^+ cation. Sugar-based



Scheme 1.



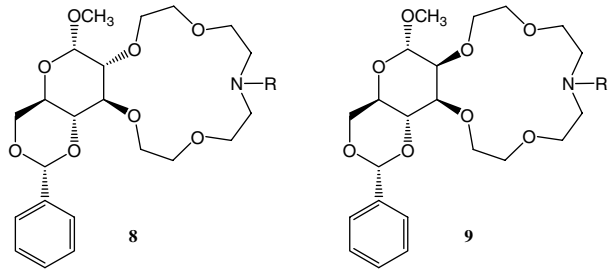
Scheme 2.



6	X= O [24]
2	X = S
8a	X = NH [25]

Figure 1. Monoaza-15-crown-5 (**5**) and glucose-based 15-crown-5 type macrocycles consisting of different heteroatoms (**6**, **2**, **8a**).

crown **2** containing a sulfur insted of an oxygen atom (X = S) has even a lower cation extracting ability and the order of selectivity is also changed revealing a maximum (4.4%) for the Li^+ cation. Lipophylity data show that both **6** and **2** are practically insoluble in water. Replacement of X for NH, as it is in **8a** (Figure 1), results in a dramatic increase in the extracting ability: a 97–99% quantity of the cations studied was transfered into the organic phase. No selectivity could, however, be observed. Regarding the better solubility of **8a** in water (log $P = 0.23$), the high extracting ability values are more than interesting. (In this case about three part is in the apolar phase and one part is in the aquous phase).



8b	R = $(CH_2)_3CH_3$ [11]	**9a**	R = H [12]
8c	R = $(CH_2)_2$-OH [8]	**9e**	R = $(CH_2)_3$-OH [12]
8d	R = $(CH_2)_2$-OCH_3 [8]	**9f**	R = $(CH_2)_3$-OCH_3 [12]
8e	R = $(CH_2)_3$-OH [8]		
8f	R = $(CH_2)_3$-OCH_3 [8]		
4	R = $(CH_2)_2$-C_5H_4N		

Figure 2. Glucose- and mannose-based chiral lariat ethers.

The cation extracting ability of monoaza-15-crown (**5**) lacking a sugar moiety is rather modest. The extracting ability for the metal cations is 13.4–26.2%, while for the NH_4^+ cation is 48.8%. The mostly low extracting abilities may be the consequence of the increased solubility of **5** in water (log $P = -0.82$). After discussing the role of heteroatom in the crown ring, let us consider the impact of the side arms in lariat ethers **8** and **9** (Figure 2). It can be seen from Table 1, that all lariat ethers studied (**8b–f, 4** and **9a, 9e, 9f**) extracted sodium picrate to the highest extent that is the consequence of the 15-ring cavity of **8** and **9**. For comparison purposes, the properties of N-butyl macrocycle (**8b**) [11] that is not a lariat ether, are also shown in Table 1. The extraction ability of **8b** is in the range of 21.0–58.2% that is accompained by a high lipophylity (log $P = 1.31$). It is noteworthy that the lariat ethers (**8c–f**) within the same series posses a lower lipophylity (log $P = -0.17$ to 0.44), but, at least for alkali cations, the extracting ability is even higher (24.6–66.4%). This refers to a stronger coordinating ability due to the side arm with methoxy or hydroxy group at the end. Lariat ether **8c** with a hydroxyethyl substituent [11] is well-soluble in water (log $P = -0.17$) still transports 24.6–55.1% of the alkali cations and 34.1% of the NH_4^+ cation into the dichloromethane phase. There is a slight selectivity for the Na^+ cation. An increase in the lipophylity by the etherification of the hydroxy group (as it is in **8d**; log $P = 0.13$) results in an increase in the extracting ability. Macrocycle **8d** transports a 36.8–61.0% portion of the metal cations and 53.1% of the NH_4^+ cation. The tendency observed for **8c**/**8d** is repeated for **8e**/**8f.** The 32.3–64.6% extracting ability of the N-(hydroxypropyl) lariat ether (**8e**) is changed to 44.8–66.4% by methylation of the hydroxy group (as it is in **8f**). In the above direction, log P changes from 0.12 to 0.44. If the extracting abilities obtained within pairs **8c**/**8e** and **8d**/**8f** are compared, one can see that a one carbon atom longer chain (as it is in **8e** and **8f**) results in increased values for all cations. This may be the consequence of an increase in the lipophylity, but a longer chain may also be beneficial, as it is more flexible. In the case of glucose-based crown ethers **8b–f**, the sequence for the metal cation binding ability was generally $Na^+ > Li^+ > K^+ > Rb^+ > Cs^+$.

In the series **8b–f, 4** lariat ether **4** with a 2-(2-pyridyl-) ethyl side arm (log $P = 0.54$) was found to be the most

Table 1. Alkali metal and ammonium picrate extraction data and lipophylicity of chiral crown ethers

Host Molecule	Percent of picrate extracted[a]						Lipophilicity log *P*
	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	
5	24.8	26.2	15.4	13.4	20.8	48.8	−0.82
6	3.8	15.8	5.4	5.2	1.2	5.6	1.10
2	4.4	1.4	0.3	1.8	0.6	0.3	1.41
8a	97.8	99.9	99.1	97.2	98.8	98.9	0.23
8b	28.7	58.2	26.9	24.7	21.0	55.9	1.31
8c	34.2	55.1	32.4	24.6	25.3	34.1	−0.17
8d	50.2	61.0	46.4	40.1	36.8	53.1	0.13
8e	40.2	64.6	38.3	38.7	32.3	40.0	0.12
8f	52.1	66.4	50.8	47.2	44.8	56.6	0.44
4	34.3	71.8	38.2	34.4	36.3	54.5	0.54
9a	44.2	47.6	45.2	39.2	45.8	70.3	0.23
9e	22.2	34.4	24.3	22.0	27.2	44.5	0.12
9f	26.5	45.5	29.2	30.0	26.1	48.0	0.44

[a]Room temperature; aqueous phase (5 mL); [picrate] = 5×10^{-3} M; organic phase (CH_2Cl_2, 5 mL); [crown ether] = 1×10^{-2} M. Defined as % picrate extracted into the organic phase, determined by UV spectroscopy, error = ± 1%.

efficient in the extraction of Na-picrate (71.8 %), that is approximately twice as much as the values for other metal cations (34–38%). The glucose-based lariat ethers **8c–f, 4** are able to extract NH_4^+ picrate in 34.1–56.6%.

The data obtained for mannose-based crown compounds **9a, 9e, 9f** show a similar trend observed for the glucose-based series (**8a, 8e** and **8f**). At the same time, the macrocycles related an mannose (**9a, 9e, 9f**) display a considerably lower extracting ability than the analogous glucose derivatives (**8a, 8e** and **8f**). This is demonstrated well by comparing the extracting ability values of **8a** with those of **9a** (97.2–99.9% *versus* 39.2–70.3%). The same tendency can be observed within the pairs **8e/9e** and **8f/9f**. The better complex forming ability of the glucose-based lariat ethers can only be explained by the more suitable conformation of its crown ring. Stoddart *et al*. proved that 18-crown-6 (**10**) forms the strongest complex with a variety of cations in the 'all-gauche' conformation and that any changes distorting the ideal conformation result in a weaker coordinating ability [6]. This must be true also for the derivatives of monoaza-15-crown-5 (**5**, Figure 3).

Comparing the stereostructure of azacrown ethers **8a** and **9a**, the glucopyranoside moiety making possible a 2,3-trans anellation is ideal from the point of view 'all gauche' conformation; at the same time, the mannopiranoside unit allows only a 2,3-cis anellation that is against the ideal conformation. This explanation is in accord with the experimental complexing ability of **8a** and **9a**. Introduction of a side arm cannot change the basic trend outlined, but the complexing properties and the selectivities can, of course, be modified.

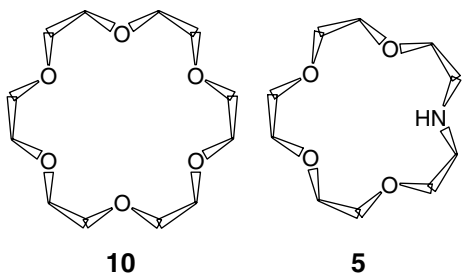


Figure 3. The all-gauche conformation of the 18-crown-6 and monoaza-15-crown-5 compounds.

We wished to investigate if the basicity of the host molecule plays a role in the extracting ability. In this respect a principal question is if the lariat ethers (that are tertiary amines) or azacrowns **8a** and **9a** (that are secondary amines) are of higher basicity. The pK_a values calculated for water solutions are not infirmative as in dichloromethane-water system the situation is more complicated. We thougth it to be possible that an amine with a strong basic character liberates a picrate anion form a metal picrate in water solution in an equilibrium process that can intrude in the organic phase. This idea could be justified experimentally; using diethylamine or dibutyl-amine instead of a crown compound in the extraction experiment, no picrate could be found in the organic phase within the experimental error. At the same time, application tributylamine in the extraction experiment resulted in a transfer of 14% of picrate into the organic phase. It seems to be probable that there is a similar situation for the lariat ethers; not only their coordinating ability, but their basicity is also responsible for the transfer of picrates from the water- to the organic phase. This phenomenon should also be considered in other instances where the picrate extraction of tertiary azacrowns was studied [17–20].

FAB-MS Binding experiments

The crown ether complexes can be detected by mass spectrometry in solution or in the gas phase. Crown ether complexes with alkali, earth alkali, and ammonium ions have the advantages to be easy to generated by different ionization methods; i.e. mainly FAB and ESI. The ranking of different cations binding to crowns

very much depends on the method used [35]. The extensive work of the groups of Brodbelt, Dearden and Armentrout gave correct results in the gas phase experiments [36–38].

We studied the binding selectivities of chiral lariat ethers in solution by applying FAB-MS [21–23]. 'Competitive FAB-MS spectra' were taken in *m*-nitrobenzyl alcohol (NBA) matrix in the presence of alkali picrate salts to achieve a fast and qualitative screening of the complexation abilities of ligands **6**, **2**, **8a, 8e**, **8f**, **4**, **9a, 9e** and **9f.** Table 2 summarizes the relative peak intensities (PI) of $[\text{ether} + \text{metal}]^+$ to uncomplexated $[\text{ether} + 1]^+$ peaks that were regarded to be 100%. Crown **6** lacking a molecular ion was an exception and, in this case, the $[\text{ether} + \text{K}]^+$ served as the basic peak. Assuming that all ligands form similar 1:1 complexes, the experimental values were expected to provide a rough estimation for the cation binding selectivities. The data suggested a relative order of $\text{K}^+ > \text{Rb}^+ > \text{Na}^+ > \text{Cs}^+$ for the cation complexing abilities of compound **6**. Regarding the sulfur- and the NH-analogues (**2** and **8a**, respectively), the selectivity was changed ($\text{Na}^+ > \text{K}^+ > \text{Rb}^+ > \text{Cs}^+$). It is noteworthy that the presence of a sulfur atom in the ring (as it is in **2**) results in a highly improved complex forming ability (PI = 58–494). In the series of the glucose-based azacrown ethers, the unsubstituted derivative (**8a**) reveals a relatively modest complexing ability with a lower selectivity (35–0) that is changed after the introduction of a side arm. The complex forming ability is increased towards the Na^+ cation, especially in the case of lariat ether **8e** with a γ-hydroxypropyl N-substituent (PI = 97). At the same time, complexation of the other cations (K^+, Rb^+ and Cs^+) is low (14–0). Consequently, the Na^+ selectivity of lariat ether **8e** is much better as compared to that of unsubstituted **8a**. Methylation of the hydroxy group (as it is in **8f**) results in the decrease of the complexing ability, but not the selectivity (55–0). Presence of the 2-(2-pyridyl-)ethyl substituent (as it is in **4**) decreases the selectivity (60–10). Comparison of the glucose- and mannose-based azacrown ethers shows a similar trend as was found in the picrate extracting experiments; the compounds built on glucopiranoside (**8a**, **8e** and **8f**) exhibit a higher complexing abilty as the mannose analogues (**9a**, **9e** and **9f**). Cation selectivity of the latter ones is also lower. Our explanation regarding the importance of the conformation of the crown ring is recalled.

Table 2. Cation binding selectivity of lariat ethers on the basis of by FAB-MS measurements in *m*-nitrobenzyl alcohol ($[\text{Crown} + 1]^+$ = 100%)

Host molecule	Relative peak intensity			
	Ether + Na^+	Ether + K^+	Ether + Rb^+	Ether + Cs^+
6[a]	22	100	34	9
2	494	335	106	58
8a	35	19	7	0
8e	97	14	6	0
8f	55	7	2	0
4	60	17	13	10
9a	19	13	5	2
9e	39	6	4	0
9f	30	5	2	0

[a] $[\text{Crown*K}]^+ = 100$.

Molecular modeling of different azacrown derivatives

Representative derivatives of glucose- and mannose-based macrocycles and their ion complexes were studied by the MCMM method. As the X-ray investigation of the complexes of the N-substituted monoaza-15-crown-5 type lariat ethers with sodium cation have proved the 1:1 structure [39–42], we calculated on this basis. As compared to the glucose-based crown ether **6** containing only oxygen atoms and **8a** containing NH group in the ring, we found that while the energetics of complex formation for **6** and **8a** are quite similar both in water and in the organic phase, a key difference exists between the derived conformations (Figure 4).

In case of **8a**, the structure of the azacrown-Na^+ picrate complex is nearly identical in water and the organic phase, since the NH group of the crown forms a strong H-bond with one of the nitro groups of picrate, while Na^+ coordinates the phenolic oxygen of the picrate limiting thus considerably the conformational variability of the complex. In case of **6**, the global minimum structure, obtained in water and in chloroform (modeling the organic phase), are however quite different (see Figure 4b). According to our results, the conformation that is most stable in water results in an excess energy of 11.6 kJ mol^{-1} in the organic phase prompting thus a conformational rearrangement. This might be part of the reason why phase transfer is so unfavorable for **6**. Global minimum conformations of lariat ethers **8f** and **9f** with γ-methoxypropyl side arms, as well as those of the corresponding Na^+ and picrate complexes in the organic phase (estimated using chloroform as a solvent) are shown in Figures 5 and 6.

The differences in the conformations of the ring systems, as well as the role of the bending side arms in the complexation can be seen well. Due to the *trans* disposition of the 2-C–O and 3-C–O units, the azacrown and the glucopyranoside rings are quasi-coplanar in **8f**.

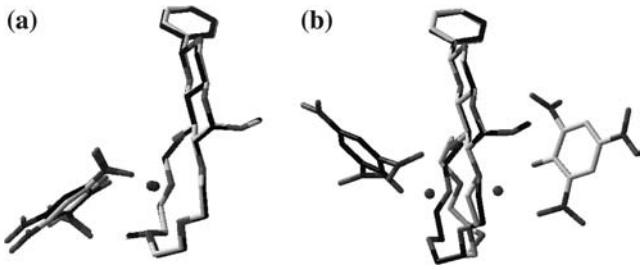


Figure 4. MCMM calculated global minimum conformation of the ternary complex (crown, Na^+- picrate) the azacrown **8a** (a) and crown **6** (b) obtained in water (white) and in the organic phase (C and H atoms shown in black) (only polar hydrogens shown).

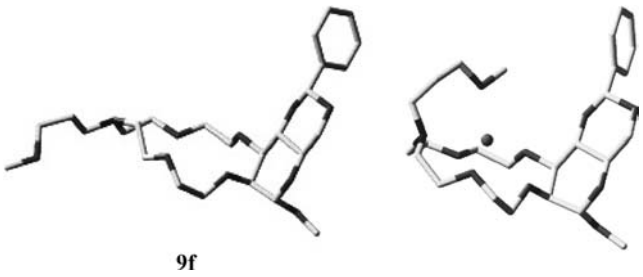


Figure 5. Calculated structure of mannose-based lariat ether **9f** and its Na^+ complex.

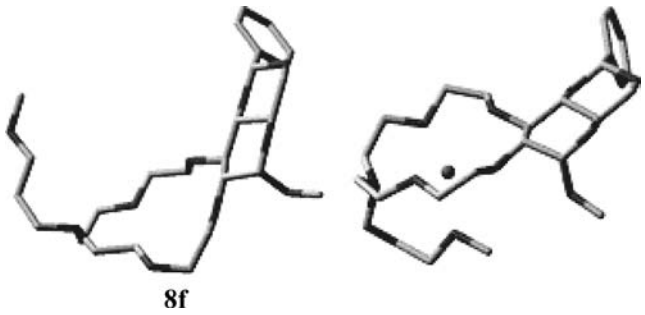


Figure 6. Calculated structure of glucose-based lariat ether **8f** and its Na^+ complex.

Cis orientation of the 2-C–O and 3-C–O moiety in mannose-based **9f** does not allow a similar stereostructure. Differences in the stereostructures have, of course, a major impact on the formation and stability of the complexes. In the complexes (**8f**/Na^+ and **9f**/Na^+), the heteroatoms of the ring and side arms are located in the proximity of the Na^+ cation.

The average distance between the azacrown heteroatoms and the Na^+ cation was found to be 2.45 Å in the glucose based-, while 2.47 Å in the mannose-based complex, with the methoxypropyl side-chain approaching the cation in the closes way in both cases (2.24 and 2.23 Å in the glucose- and in the mannose-based case, respectively), indicating clearly the complexation. It can be seen that the metal cation is not located in the cavity of the crown ring, rather above the plane of the hetero ring. An apparent difference between the structures of **8f**/Na^+ and **9f**/Na^+ is that the Na^+ cation was found to be on different sides; in the glucose-based lariat ether **8f**, it is on the side of the glycosidal methoxy group, while in mannose-based **9f**, the cation is on the opposite side. In the ternary complexes of **8f** and **9f** involving the picrate anion, the cation, anion and the methoxypropyl side-chain are however located on the opposite side of the glycosidal methoxy group. Even though the average Na^+-azacorwn heteroatom distance and even the Na^+-picrate oxygen distance is equal in the glucose and mannose based systems (2.66, 2.25 Å, respectively), the overall conformation of the complexes are still quite different. While the elongated glucose based macrocycle is quite open both on the cation's present side and on the opposite, in the mannose based molecule, only the side of the glycosidal methoxy group is open for an attack by a potential substrate. This might be the reason for the different enantioselective activity of these azacrown derivatives [16].

One of our aims in carrying out modeling studies was to develop a system that could be used for the energetic evaluation of crowns and their derivatives to screen out potent candidates. Since extracting ability values were shown to be related to the cation binding energies (17–20), we set out to approximate extracting ability by calculating the latter. We found that the different extracting ability of the glucose or mannose based crowns could be reliably predicted by calculating the respective cation binding energies of the species. The calculated difference of cation binding energies of an identically substituted glucose/mannose pair was found to be proportional to the ratio of their extracting ability. The 1.5 times greater extracting ability of the glucose derivative of the **8a**/**9a** pair corresponded to the cation binding energy being 3.82 kJ mol^{-1} more favorable for **8a**, in case of the **8f**/**9f** pair having a 1.9 ratio of the extracting abilities, we found that the cation binding energy of glucose-based system was 6.5 kJ mol^{-1} favourable, and in the case of the **8e**/**9e** pair with a ratio of 2.1, the calculated cation binding energy of **8e** was 7.21 kJ mol^{-1} favourable. The results suggest that calculating cation binding energies by a force field method might be used as a fast predictor of the extracting ability within pairs of equal or similar lipophilicity.

Conclusions

Extraction ability measurements of alkali metal picrates from water to dichloromethane suggested that among the glucose-based macrocycles the one containing an NH unit in the crown ring (as in **8a**) is the most efficient (97–99%). The derivative with a sulfur atom (as in **2**) is the less efficient (0.3–4.4%). In case of only oxygen atoms in the hetero ring (as in **6**) the extracting ability is of medium value (1.2–15.8%). Placing a two- or three carbon atom chain with hydroxy- or metoxy group at the end on the nitrogen atom the extracting ability is decreased, at the same time the selectivity is increased. Extracting ability and FAB-MS measurements proved that the complex forming ability of glucose-based macrocycles is higher than that of mannose-based derivatives. This was explained by the effect of the monosacharide on the configuration of the hetero ring. The results of MCMM calculations using the MMFF force field proved that the structure of complexes formed by the two types of monosacharides with the sodium cation is different.

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