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ORIGINAL ARTICLE

Syntheses and complexing ability of α-D-gluco- and α-D-xylofuranoside-based lariat ethers

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Abstract Chiral monoaza-15-crown-5 lariat ethers attached to a 1,2-*O*-isopropylidene-α-D-glucofuranoside unit (**10–13**), monoaza-16-crown-5 lariat ethers fused to 1,2-*O*-isopropylidene-α-D-glucofuranoside- (**18**) and to 1,2-*O*-isopropylidene-α-D-xylofuranoside units (**23** and **24**) have been synthesized. The alkali metal- and ammonium picrate extracting ability of these macrocycles was investigated in dichloromethane–water system. In general, the 15-membered macrocycles (**10–13**) showed, for almost all cations, a more considerable extracting ability, than the 16-membered lariat ethers (**18, 23** and **24**). Plasticized PVC membrane electrodes (ISEs) were prepared from the α-D-glucofuranoside-based triphenylmetyl (trityl) ether derivative (**18**), and its potentiometric selectivities and complex formation constants were determined with the segmented sandwich membrane method. Furthermore, the binding affinities of ionophores to different metal ions were also measured by competitive ESI–MS experiments. One of the 1,2-*O*-isopropylidene-α-D-glucofuranoside-based lariat ethers (**13**) exhibited a high selectivity for silver ion (Ag^+).

Keywords Complexing ability · Crown ethers · Extracting property · Ionselectivity

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Introduction

Lariat ethers are designed to achieve strong and selective binding of metal cations via the cooperative binding provided by the crown ether moiety and the side-arm incorporating a heteroatom [1–3]. An important advantage of azacrown ethers over oxacrown ethers is the presence of soft nitrogen donor atoms which may offer characteristic complexing and transporting abilities. A lot of thermodynamic studies have been performed on the complexation of lariat crown ethers in an effort to elucidate the factors that influence the cation-ligand complexation [4, 5]. Many research groups have investigated the influence of the side arms on the complex forming abilities. Recently, the effect of the side arm on the complexation of metal ions was studied by Bredikhin et al. using lariat ethers of 15-crown-5 type [6] and by Bartsch et al. with monoaza-15-crown-5 lariat ethers as the models [7].

Chiral macrocycles containing different carbohydrate units form a special group of the crown ethers. The incorporation of the carbohydrate scaffold is advantageous in the synthesis of macrocycles: a part of the starting carbohydrates is inexpensive and easily available commercial product. They are biocompatible, and available in enantiomerically pure form. The basic chemistry of these compounds is well-explored. Carbohydrates are well-endowed with functionalities which enable them to establish secondary binding sites, as well as catalytic sites. These compounds can be used in two main fields: one is the separation of racemic ammonium salts; the other is the application as chiral phase transfer catalyst in asymmetric syntheses. Both applications are related to the complex forming ability of the macrocycles. Many optically active crown ethers and cryptands have been synthesized from monosaccharides [8–12]. Earlier, the complexation of a

few sugar-based derivatives with alkali metal-, ammonium- and *t*-butylammonium picrates were investigated and discussed by Stoddart et al. [8, 12]. Formerly, the alkali metal binding selectivity of chiral macrocycles derived from D-mannitol and L-threitol were studied by Jurczak et al. [13]. Chiral lariat ethers fused to different monosaccharides, such as D-glucose, D-galactose, D-mannose etc. were introduced and investigated by us in the last decades [14, 15]. A part of the sugar-based lariat ethers was applied successfully as chiral phase transfer catalyst in asymmetric reactions [16–20].

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 systems [10, 21–23]. The extracting ability of the macrocycles depends mainly on the complex forming ability influenced by the size of the cavity, the type and number of heteroatoms, and also on the lipophilicity. These characteristics determine the distribution of a cation between the water and the organic phases. Earlier, we found that hydroxypropyl and methoxypropyl substituents on the nitrogen atom of the sugar-based macrocycles of type monoaza-15-crown-5 increased strongly the cation extracting ability [10]. For this reason, this structural element of the lariat ethers was retained in our new experiments.

In the present paper, complexing abilities of α-D-glucofuranoside- and xylofuranoside-based lariat ethers containing hydroxypropyl and methoxypropyl side arms on the nitrogen atom of the hetero ring were investigated. Two types of macrocycles were synthesized. In the first group, the glucofuranoside moiety is connected to the monoaza-15-crown-5 ring by a flexible bond (**A**), while in the other group, the furanoside unit is annulated to the macro ring (**B** and **C**) (Fig. 1).

We wished to synthesize lariat ethers of monoaza-15-crown-5 and monoaza-16-crown-5 type based on protected α-D-glucofuranoside and xylofuranoside. We wished to alkylate the free 3-hydroxyl group of the furanoside to increase the lipophylicity of the substrate. Our intention was to study the effect of the monosaccharides connected to the macrocycles and that of the *N*-substituents (side arms) on the complex forming ability and ion selectivity.

Extracting abilities were measured in liquid–liquid system towards alkali metal ions and ammonium ion. The cation selectivities and complex formation constants of one of the crown compounds (**18**) were determined using the segmented sandwich membrane method. In addition, we wanted to test the relative binding affinities of the sugar-based ionophores towards the metal ions by means of electrospray ionization mass spectrometry (ESI–MS). The motivation came from previous studies on various systems demonstrating that ESI–MS is relatively well suited for screening the complexation

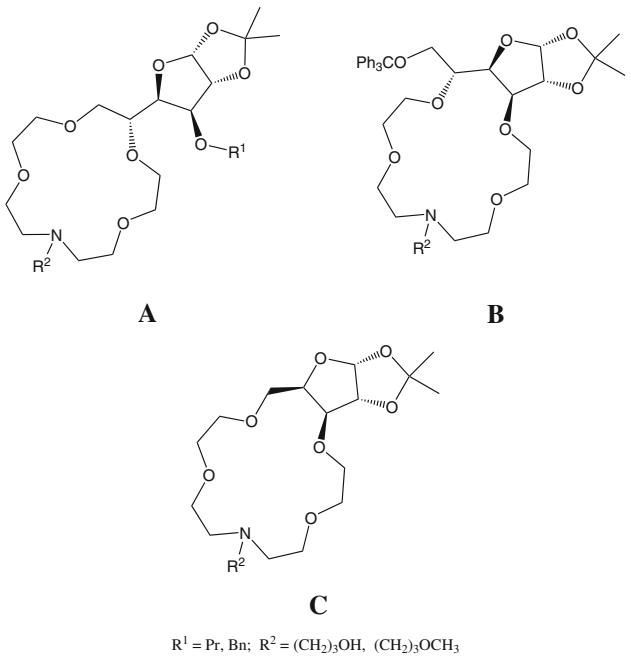


Fig. 1 Structures of gluco- and xylofuranoside-based lariat ethers

interactions and by competitive experiments, several target ions can be tested at the same time [24–35].

Experimental

General

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. NMR spectra were obtained on a Bruker DRX-500 or Bruker-300 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. Ionselectivity experiments by direct infusion from water–methanol 2:8 solution were performed on a Micromass Quattro Micro QQQ mass spectrometer with ESI ionization. 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 were purchased from Aldrich Chem. Co.

Preparation of compounds 4–13, 16–18, 21–24

1,2-O-Isopropylidene-3-O-benzyl-α-D-glucofuranoside ***(4)*** *[36]*

1,2:5,6-Di-*O*-isopropylidene-3-*O*-benzyl-α-D-glucofuranoside (**2**) (13.60 g, 38.8 mmol) was dissolved in 50 % aq. acetic acid (280 mL) and the solution was stirred overnight

at room temperature. After completion of the reaction, the acid was neutralized with Na_2CO_3, then extracted with $CHCl_3$ (3 × 50 mL). The organic phase was dried (Na_2SO_4), then evaporated to give product **4** (11.2 g, 93 %); $[\alpha]_D^{22} = -45.8$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.42–7.31 (m, 5H, ArH), 5.95 (d, $J = 3.6$ Hz, 1H, H-1), 4.74 (d, $J = 11.7$ Hz, 1H, CH_2Ph), 4.64 (d, $J = 3.6$ Hz, 1H, H-2), 4.55 (d, $J = 11.7$ Hz, 1H, CH_2Ph), 4.17–4.08 (m, 2H, H-5, H-4), 4.06–3.99 (m, 1H, H-3), 3.82 (dd, $J = 11.4$, 6 Hz, 1H, H-6a), 3.69 (dd, $J = 11.4$, 6 Hz, 1H, H-6b), 2.52 (br s, 2H, 2 × OH), 1.49 (s, 3H, CCH_3), 1.33 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 137.71, 128.41, 127.85, 127.69, 111.71, 105.20, 82.00, 81.83, 78.82, 72.15, 69.36, 64.41, 26.74, 26.21; HRMS calcd for $C_{16}H_{22}O_6$ 310.1416, found 310.1419.

1,2-O-Isopropylidene-3-O-propyl-α-D-glucofuranoside ***(5)***

1,2:5,6-Di-*O*-isopropylidene-3-*O*-propyl-α-D-glucofuranoside (**3**) (5.67 g, 18.8 mmol) was dissolved in 50 % aq. acetic acid (140 mL) and the solution was stirred overnight at rt. After completion of the reaction, the acid was neutralized with Na_2CO_3, then extracted with $CHCl_3$ (3 × 50 mL). The organic phase was dried (Na_2SO_4), then evaporated to afford product **5** (4.88 g, 99 %); $[\alpha]_D^{22} = -44.7$ ($c = 1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 5.92 (d, $J = 3.5$ Hz, 1H, H-1), 4.57 (d, $J = 3.5$ Hz, 1H, H-2), 4.13 (dd, $J = 7.5$, 3.5 Hz, 1H, H-4), 4.05–4.00 (m, 1H, H-5), 3.98 (d, $J = 3.5$ Hz, 1H, H-3), 3.82 (dd, $J = 11.5$, 3.5 Hz, 1H, H-6a), 3.82 (dd, $J = 11.5$, 6 Hz, 1H, H-6b), 3.62 (dt, $J = 9$ Hz, 6 Hz, 1H, OCH_2CH_2), 3.47 (dt, $J = 9$, 6 Hz, 1H, OCH_2CH_2), 3.05 (br s, 1H, OH), 2.62 (br s, 1H, OH), 1.61 (sex, $J = 6$ Hz, 2H, CH_2CH_3), 1.49 (s, 3H, CCH_3), 1.32 (s, 3H, CCH_3), 0.93 (t, $J = 6$ Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 111.82, 105.16, 81.93, 81.70, 78.94, 72.21, 69.47, 64.35, 26.82, 26.33, 23.03, 10.51. HRMS calcd for $C_{12}H_{22}O_6$ 262.1416. Found 262.1411.

General procedure for preparation of bis-chloro compounds (6, 7, 16 and 21)

To a mechanically stirred solution of carbohydrate derivative having two free OH groups (**4**, **5**, **15** and **20**) in bis(2-chloroethyl)ether, 50 % aq. NaOH solution and Bu_4NHSO_4 were added. The mixture was stirred for 14 h at rt then poured into a 1:1 mixture of CH_2Cl_2 and water (used in a threefold volume of volume of the reaction mixture). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The excess of the bis(2-chloroethyl)ether was removed by vacuum distillation. The crude product was purified by column chromatography (silica gel, $CHCl_3$–CH_3OH 100:0 → 100:5).

1,2-O-Isopropylidene-3-O-benzyl-5,6-bis-O-[(2-chloroethoxy)ethyl]-α-D-glucofuranoside ***(6)***

Compound **4** (11.2 g, 36.1 mmol) was treated with bis(2-chloroethyl)ether (127 mL, 1.08 mol) in the presence of 50 % aq. NaOH (127 mL) and Bu_4NHSO_4 (12.26 g, 36.1 mmol). Chromatography afforded product **6** (10.77 g, 57 %); $[\alpha]_D^{22} = -19.8$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.39–7.29 (m, 5H, ArH), 5.89 (d, $J = 3.6$ Hz, 1H, H-1), 4.68 (d, $J = 8.7$ Hz, 1H, CH_2Ph), 4.62 (d, $J = 8.7$ Hz, 1H, CH_2Ph), 4.59 (d, $J = 3.6$ Hz, 1H, H-2), 4.23–4.14 (m, 1H, H-4), 4.13–4.09 (m, 1H, H-6a), 3.96–3.81 (m, 3H, H-3, H-5, H-6b), 3.80–3.49 (m, 16H, 2 × OCH_2CH_2O, 2 × OCH_2CH_2Cl, 2 × CH_2Cl), 1.48 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 137.78, 128.44, 127.80, 127.67, 111.73, 105.19, 81.90, 81.78, 78.93, 75.89, 72.33, 72.01, 71.34, 71.21, 70.91, 70.81, 70.58, 70.15, 42.84, 42.82, 26.80, 26.32; Elem anal calcd for $C_{24}H_{36}Cl_2O_8$ C, 55.07; H, 6.93; Cl, 13.55. Found C, 55.10; H, 6.90; Cl, 13.53; HRMS calcd for $C_{24}H_{36}Cl_2O_8$ 522.1787, found 522.1792.

1,2-O-Isopropylidene-3-O-propyl-5,6-bis-O-[(2-chloroethoxy)ethyl]-α-D-glucofuranoside ***(7)***

Compound **5** (4.88 g, 18.6 mmol) was treated with bis(2-chloroethyl)ether (65.4 mL, 558 mmol) in the presence of 50 % aq. NaOH (65.4 mL) and Bu_4NHSO_4 (6.32 g, 18.6 mmol). Chromatography led to product **7** (6.92 g, 78 %); $[\alpha]_D^{22} = -24.2$ ($c = 1$, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 5.89 (d, $J = 3.6$ Hz, 1H, H-1), 4.53 (d, $J = 3.6$ Hz, 1H, H-2), 4.12 (dd, $J = 9$, 3 Hz, 1H, H-4), 4.00–3.40 (m, 22H, H-3, H-5, H-6a, H6b, 2 × OCH_2CH_2O, 2 × OCH_2CH_2Cl, 2 × CH_2Cl, $OCH_2CH_2CH_3$), 1.60 (sex, $J = 7.2$ Hz, 2H, CH_2CH_3), 1.47 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3), 0.93 (t, $J = 7.2$ Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 111.61, 105.22, 81.93, 81.74, 78.88, 75.81, 72.23, 71.92, 71.27, 71.16, 70.94, 70.80, 70.53, 70.06, 42.80, 42.77, 26.86, 26.39, 23.15, 10.57; Elem. anal calcd for $C_{20}H_{36}Cl_2O_8$ C, 50.53; H, 7.63; Cl, 14.91. Found C, 50.57; H, 7.59; Cl, 14.87; HRMS calcd for $C_{20}H_{36}Cl_2O_8$ 474.1787. Found 474.1783.

General procedure for preparation of bis-iodo compounds (8, 9, 17 and 22)

Bis-chloro compound (**6**, **7**, **16** and **21**) was dissolved in dry acetone and after addition of anhydrous NaI the solution

was refluxed for 30 h. The reaction mixture was filtered, then concentrated. The residue was dissolved in $CHCl_3$, filtered then washed with water three times. The organic phase was dried (Na_2SO_4), then evaporated to give the corresponding product.

*1,2-O-Isopropylidene-3-O-benzyl-5,6-bis-O-[(2-iodoethoxy)ethyl]-α-D-glucofuranoside (**8**)*

Bis-chloro compound **6** (3.60 g, 6.9 mmol) was treated with NaI (4.14 g, 27.6 mmol) in acetone (60 mL) to afford compound **8** (4.45 g, 91 %); $[\alpha]_D^{22} = -15.4$ ($c = 1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.37–7.33 (m, 4H, ArH), 7.32–7.28 (m, 1H, ArH), 5.89 (d, $J = 3.5$ Hz, 1H, H-1), 4.68 (d, $J = 11.5$ Hz, 1H, CH_2Ph), 4.62 (d, $J = 11.5$ Hz, 1H, CH_2Ph), 4.59 (d, $J = 3.5$ Hz, 1H, H-2), 4.17 (dd, $J = 9$, 3 Hz, 1H, H-4), 4.12 (d, $J = 3$ Hz, 1H, H-3), 3.95–3.84 (m, 3H, H-5, H-6a, H-6b), 3.78–3.50 (m, 12H, 2 × OCH_2CH_2O, 2 × OCH_2CH_2Cl), 3.24 (t, $J = 7$ Hz, 2H, ICH_2), 3.22 (t, $J = 7$ Hz, 2H, ICH_2), 1.48 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 137.83, 128.40, 127.75, 127.62, 111.79, 105.24, 81.96, 81.84, 78.99, 75.80, 72.27, 72.06, 71.39, 71.14, 70.90, 70.88, 70.62, 70.08, 26.76, 26.30, 3.24, 3.19; Elem anal calcd for $C_{24}H_{36}I_2O_8$ C, 40.81; H, 5.14; I, 35.93. Found C, 40.82; H, 5.20; I, 35.90. HRMS calcd for $C_{24}H_{36}I_2O_8$ 706.0500. Found 706.0504.

*1,2-O-Isopropylidene-3-O-propyl-5,6-bis-O-[(2-iodoethoxy)ethyl]-α-D-glucofuranoside (**9**)*

Bis-chloro compound **7** (6.92 g, 14.6 mmol) was reacted with NaI (8.75 g, 58.4 mmol) in acetone (130 mL) to afford compound **9** (7.90 g, 82 %); $[\alpha]_D^{22} = -23.5$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 5.89 (d, $J = 3.6$ Hz, 1H, H-1), 4.52 (d, $J = 3.6$ Hz, 1H, H-2), 4.11 (dd, $J = 9$, 3 Hz, 1H, H-4), 4.01–3.42 (m, 18H, H-3, H-5, H-6a, H-6b, 2 × OCH_2CH_2O, 2 × OCH_2CH_2Cl, $OCH_2CH_2CH_3$), 3.23 (t, $J = 7$ Hz, 4H, 2 × ICH_2), 1.61 (sex, $J = 7.2$ Hz, 2H, CH_2CH_3), 1.48 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3), 0.93 (t, $J = 7.2$ Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 111.73, 105.24, 81.90, 81.77, 78.93, 75.69, 72.31, 71.86, 71.22, 71.05, 70.91, 70.83, 70.59, 70.12, 26.81, 26.34, 23.11, 10.52, 3.23, 3.14; Elem anal calcd for $C_{20}H_{36}I_2O_8$ C, 36.49; H, 5.51; I, 38.55. Found C, 36.48; H, 5.56; I, 38.52, HRMS calcd for $C_{20}H_{36}I_2O_8$ 658.0500. Found 658.0494.

General procedure for the preparation of lariat ethers (10–13, 18, 23–24)

Bis-iodo compound was dissolved in dry CH_3CN, then anhydrous Na_2CO_3 and the appropriate amine were added, and the mixture was refluxed with stirring under Ar. After the reaction was complete (40–50 h), the mixture was filtered, volatile compounds were removed in vacuum, and the residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4) then concentrated in vacuum. The crude product was purified by column chromatography.

*1,2-O-Isopropylidene-3-O-benzyl-α-D-glucofuranoside-based monoaza-15-crown-5 lariat ether with hydroxypropyl side arm (**10**)*

Bis-iodo compound **8** (2.20 g, 3.1 mmol) was treated with 3-aminopropan-1-ol (0.24 mL, 3.1 mmol) in the presence of Na_2CO_3 (1.97 g, 18.6 mmol) in CH_3CN (40 mL). Chromatography on Al_2O_3 ($CHCl_3$–CH_3OH 100:0 → 100:3) resulted in lariat ether **10** (1.16 g, 71 %); $[\alpha]_D^{22} = -26$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.38–7.28 (m, 5H, ArH), 5.88 (d, $J = 3.6$ Hz, 1H, H-1), 4.67 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.59 (d, $J = 3.6$ Hz, 1H, H-2), 4.52 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.17 (d, $J = 9.3$ Hz, 1H, H-4), 4.12–4.04 (m, 1H, H-3), 3.98–3.40 (m, 17H, H-5, H-6a, H-6b, 2 × OCH_2CH_2O, 2 × OCH_2CH_2N, CH_2OH), 2.95–2.63 (m, 6H, 3 × NCH_2), 1.79–1.59 (m, 2H, CH_2CH_2OH), 1.47 (s, 3H, CCH_3), 1.30 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 137.40, 128.46, 127.86, 127.73, 111.73, 105.14, 81.80, 81.60, 79.09, 75.86, 75.33, 75.06, 71.90, 70.08, 70.01, 69.07, 68.55, 63.89, 57.05, 54.71, 54.52, 26.82, 26.79, 26.34. FAB-MS, *m/z* 526 [M^++1], 548 [M^++Na]; HRMS calcd for $C_{27}H_{43}NO_9$ 525.2938. Found 525.2943.

*1,2-O-Isopropylidene-3-O-propyl-α-D-glucofuranoside-based monoaza-15-crown-5 lariat ether with hydroxypropyl side arm (**11**)*

Bis-iodo compound **9** (3.95 g, 6.0 mmol) was reacted with 3-aminopropan-1-ol (0.46 mL, 6.0 mmol) in the presence of Na_2CO_3 (3.82 g, 36 mmol) in CH_3CN (80 mL). Chromatography on Al_2O_3 ($CHCl_3$–CH_3OH 100:0 → 100:3) resulted in the formation of lariat ether **11** (1.72 g, 60 %); $[\alpha]_D^{22} = -26$ ($c = 1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 5.85 (d, $J = 3.5$ Hz, 1H, H-1), 4.52 (d, $J = 3.5$ Hz, 1H, H-2), 4.12 (dd, $J = 9.5$, 3.5 Hz, 1H, H-4), 3.99 (ddd, $J = 11$, 8, 3.5 Hz, 1H, H-5), 3.88 (d, $J = 3.5$ Hz, 1H, H-3), 3.85–3.77 (m, 4H, H-6a, H-6b, CH_2OH), 3.73–3.53 (m, 13H, 2 × OCH_2CH_2O, 2 × OCH_2CH_2N, $CH_2CH_2CH_3$) 3.38 (dt, $J = 9$ Hz, 7 Hz, 1H, $CH_2CH_2CH_3$), 2.87–2.63 (m, 6H, 3 × NCH_2), 1.78 (br s, 1H, OH), 1.75–1.63 (m, 2H, CH_2CH_2OH), 1.58 (sex, $J = 7$ Hz, 2H, CH_2CH_3), 1.46 (s, 3H, CCH_3), 1.30 (s, 3H, CCH_3), 0.92 (t, $J = 7$ Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) 111.62, 105.15, 81.82, 79.11,

75.47, 72.22, 71.74, 71.03, 70.29, 70.10, 69.27, 68.74, 54.71, 54.49, 28.45, 26.78, 26.32, 23.12, 10.71. FAB-MS, *m/z* 478 [M^++1], 500 [M^++Na]. HRMS calcd for $C_{23}H_{43}NO_9$ 477.2938. Found 477.2942.

*1,2-O-Isopropylidene-3-O-benzyl-α-D-glucofuranoside-based monoaza-15-crown-5 lariat ether with methoxypropyl side arm (**12**)*

Bis-iodo compound **8** (2.10 g, 3.0 mmol) was reacted with 3-methyoxypropylamine (0.31 mL, 3 mmol) in the presence of Na_2CO_3 (1.91 g, 18 mmol) in CH_3CN (40 mL). Chromatography on silica gel ($CHCl_3$–CH_3OH 100:0 → 100:5) resulted in the formation of lariat ether **12** (0.74 g, 46 %); $[\alpha]_D^{22} = -32.5$ ($c = 1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.37–7.29 (m, 5H, ArH), 5.88 (d, $J = 3.5$ Hz, 1H, H-1), 4.67 (d, $J = 11.5$ Hz, 1H, CH_2Ph), 4.59 (d, $J = 3.5$ Hz, 1H, H-2), 4.52 (d, $J = 11.5$ Hz, 1H, CH_2Ph), 4.16 (dd, $J = 9$, 3 Hz, 1H, H-4), 4.08 (d, $J = 3.5$ Hz, 1H, H-3), 3.96 (ddd, $J = 10$, 8, 3.5 Hz, 1H, H-5), 3.90–3.85 (m, 1H, H-6a), 3.86–3.82 (m, 1H, H-6b), 3.67–3.44 (m, 12H, 2 × OCH_2CH_2O, 2 × OCH_2CH_2N), 3.40 (t, $J = 6$ Hz, 2H, $CH_2CH_2OCH_3$), 3.31 (s, 3H, OCH_3), 2.98–2.54 (m, 6H, 3 × NCH_2), 1.78–1.69 (m, 2H, $CH_2CH_2OCH_3$), 1.47 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 137.48, 128.48, 127.92, 127.72, 111.76, 105.16, 81.76, 81.61, 79.19, 75.46, 72.50, 71.88, 71.12, 70.96, 70.33, 70.23, 70.14, 70.10, 58.59, 54.79, 54.46, 53.83, 27.51, 26.80, 26.33. FAB-MS, *m/z* 540 [M^++1], 562 [M^++Na]; HRMS calcd for $C_{28}H_{45}NO_9$ 539.3094. Found 539.3099.

*1,2-O-Isopropylidene-3-O-propyl-α-D-glucofuranoside-based monoaza-15-crown-5 lariat ether with methoxypropyl side arm (**13**)*

Bis-iodo compound **9** (3.95 g, 6.0 mmol) was treated with 3-methyoxypropylamine (0.61 mL, 6 mmol) in the presence of Na_2CO_3 (3.82 g, 36 mmol) in CH_3CN (80 mL). Chromatography on silica gel ($CHCl_3$–CH_3OH 100:0 → 100:3) gave lariat ether **13** (1.24 g, 42 %); $[\alpha]_D^{22} = -22.2$ ($c = 1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 5.85 (d, $J = 3.5$ Hz, 1H, H-1), 4.53 (d, $J = 3.5$ Hz, 1H, H-2), 4.11 (dd, $J = 9.5$, 3.5 Hz, 1H, H-4), 3.99 (ddd, $J = 11$, 8, 3.5 Hz, 1H, H-5), 3.87 (d, $J = 3.5$ Hz, 1H, H-3), 3.86–3.78 (m, 2H, H-6a, H-6b), 3.72–3.53 (m, 13H, 2 × OCH_2CH_2O, 2 × OCH_2CH_2N, $CH_2CH_2CH_3$), 3.41 (t, $J = 6$ Hz, 2H, $CH_2CH_2OCH_3$), 3.37 (dt, $J = 9$, 7 Hz, 1H, $CH_2CH_2CH_3$), 3.31 (s, 3H, OCH_3), 2.88–2.62 (m, 6H, 3 × NCH_2), 1.74–1.62 (m, 2H, CH_2-CH_2OH), 1.57 (sex, $J = 7$ Hz, 2H, CH_2CH_3), 1.47 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3), 0.91 (t, $J = 7$ Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 111.65, 105.12, 81.87, 79.06, 75.54, 72.26, 71.71, 71.09, 70.33, 70.06, 69.29, 59.04, 54.70, 54.48, 28.45, 27.52, 26.30, 23.18, 10.75. FAB-MS, *m/z* 492 [M^++1], 514 [M^++Na]; HRMS calcd for $C_{24}H_{45}NO_9$ 491.3094. Found 491.3090.

*1,2-O-Isopropylidene-6-O-trityl-α-D-glucofuranoside (**15**) [37]*

1,2-*O*-Isopropylidene-α-D-glucofuranoside (**14**) (6.40 g, 29 mmol) was dissolved in pyridine (60 mL) and triphyenlmethylchloride (10.44 g, 37.5 mmol) was added. The resulting solution was allowed to stand at rt. with occasional stirring for 48 h. Then, water was added until permanent turbidity has been observed. After 2 h, the mixture was poured into ice-water (1000 mL). The white precipitate was filtered, washed with water three times, and dissolved in $CHCl_3$. The solution was washed with 3 % *aq.* acetic acid until the pH of the aqueous phase became acidic, after that the organic phase was washed with water until neutrality, and dried (Na_2SO_4). After evaporation of the solvent, the crude product was crystallized from diethyl ether to provide compound **15** (7.88 g, 61 %); m.p. 137–139 °C; $[\alpha]_D^{22} = -19.9$ ($c = 2$, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.46 (d, $J = 8.1$ Hz, 6H, ArH), 7.36–7.20 (m, 9H, ArH), 5.95 (d, $J = 3.3$ Hz, 1H, H-1), 4.51 (d, $J = 3.3$ Hz, 1H, H-2), 4.34–4.27 (m, 1H, H-3), 4.25–4.16 (m, 1H, H-5), 4.15–4.08 (m, 1H, H-4), 3.47–3.41 (m, 1H, H-6a), 3.38–3.29 (m, 2H, H-6b, OH), 2.73 (br s, 1H, OH), 1.47 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 144.02, 128.86, 127.91, 127.35, 111.86, 105.24, 86.46, 82.11, 81.74, 78.76, 69.45, 64.62, 26.83, 26.25; HRMS calcd for $C_{28}H_{30}O_6$ 462.2042, found 462.2048.

*1,2-O-Isopropylidene-3,5-bis-O-[(2-chloroethoxy)ethyl]-6-O-trityl-α-D-glucofuranoside (**16**)*

Compound **15** (7.88 g, 17.1 mmol) was reacted with bis(2-chloroethyl)ether (60.0 mL, 513 mmol) in the presence of 50 % aq. NaOH (60 mL) and Bu_4NHSO_4 (5.81 g, 17.1 mmol). Chromatography furnished product **16** (9.20 g, 80 %); $[\alpha]_D^{22} = -11.9$ ($c = 1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.47 (d, $J = 7.5$ Hz, 6H, ArH), 7.28 (t, $J = 7.5$ Hz, 6H, ArH), 7.21 (t, $J = 7.5$ Hz, 3H, ArH), 5.83 (d, $J = 3.5$ Hz, 1H, H-1), 4.58 (d, $J = 3.5$ Hz, 1H, H-2), 4.26 (dd, $J = 9.5$, 3 Hz, 1H, H-4), 3.97 (d, $J = 3$ Hz, 1H, H-3), 3.90 (ddd, $J = 9.5$, 5, 3 Hz, 1H, H-5), 3.80–3.55 (m, 16H, 2 × OCH_2CH_2O, 2 × OCH_2CH_2Cl, 2 × CH_2Cl), 3.49–3.43 (m, 1H, H-6a), 3.27 (dd, $J = 9.5$, 6 Hz, 1H, H-6b), 1.46 (s, 3H, CCH_3), 1.30 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm):

144.10, 128.90, 127.83, 127.39, 111.83, 105.19, 86.41, 82.13, 81.66, 78.84, 75.41, 71.27, 71.16, 70.83, 70.72, 70.51, 70.04, 64.90, 42.75, 42.73, 26.77, 26.19; Elem. anal calcd for $C_{36}H_{44}Cl_2O_8$ C, 64.00; H, 6.56; Cl, 10.49. Found C, 64.06; H, 6.60; Cl, 10.45; HRMS calcd for $C_{36}H_{44}Cl_2O_8$ 674.2413. Found 674.2419.

*1,2-O-Isopropylidene-3,5-bis-O-[(2-iodoethoxy)ethyl]-6-O-trityl-α-D-glucofuranoside (**17**)*

Bis-chloro compound **16** (9.10 g, 13.8 mmol) was treated with NaI (8.27 g, 55.4 mmol) in acetone (150 mL) to give compound **17** (10.12 g, 91 %); $[\alpha]_D^{22} = -16.8$ ($c = 1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.47 (d, $J = 7.5$ Hz, 6H, ArH), 7.28 (t, $J = 7.5$ Hz, 6H, ArH), 7.21 (t, $J = 7.5$ Hz, 3H, ArH), 5.84 (d, $J = 3.5$ Hz, 1H, H-1), 4.58 (d, $J = 3.5$ Hz, 1H, H-2), 4.26 (dd, $J = 9.5$, 3 Hz, 1H, H-4), 3.98 (d, $J = 3$ Hz, 1H, H-3), 3.94–3.88 (m, 1H, H-5), 3.87–3.54 (m, 12H, 2 × OCH_2CH_2O, 2 × OCH_2CH_2I), 3.46 (d, $J = 9.5$ Hz, 1H, H-6a), 3.27 (dd, $J = 9.5$, 6 Hz, 1H, H-6b), 3.26 (t, $J = 6.5$ Hz, 2H, CH_2I), 3.02 (t, $J = 6.5$ Hz, 2H, CH_2I), 1.46 (s, 3H, CCH_3), 1.30 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 144.03, 128.82, 127.76, 127.42, 111.77, 105.25, 86.50, 82.18, 81.74, 78.80, 75.36, 71.22, 71.18, 70.78, 70.73, 70.50, 70.11, 64.82, 26.79, 26.22, 3.24, 3.18; Elem anal calcd for $C_{36}H_{44}I_2O_8$ C, 50.36; H, 5.17; I, 29.56. Found C, 50.38; H, 5.19; I, 29.55; HRMS calcd for $C_{36}H_{44}I_2O_8$ 858.1126. Found 858.1130.

*1,2-O-Isopropylidene-6-O-trityl-α-D-glucofuranoside-based monoaza-15-crown-5 lariat ether with hydroxypropyl side arm (**18**)*

Bis-iodo compound **17** (4.90 g, 6.0 mmol) was treated with 3-aminopropan-1-ol (0.46 mL, 6.0 mmol) in the presence of Na_2CO_3 (3.82 g, 36 mmol) in CH_3CN (100 mL). Chromatography on Al_2O_3 ($CHCl_3$) afforded lariat ether **18** (1.84 g, 49 %); $[\alpha]_D^{22} = -9.8$ ($c = 1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.47 (d, $J = 7.5$ Hz, 6H, ArH), 7.27 (t, $J = 7.5$ Hz, 6H, ArH), 7.20 (t, $J = 7.5$ Hz, 3H, ArH), 5.82 (d, $J = 3.5$ Hz, 1H, H-1), 4.53 (d, $J = 3.5$ Hz, 1H, H-2), 4.33 (dd, $J = 9.5$, 3 Hz, 1H, H-4), 4.04 (d, $J = 3$ Hz, 1H, H-3), 3.73–3.53 (m, 15H, H-5, 2 × OCH_2CH_2O, 2 × OCH_2CH_2N, CH_2OH) 3.45 (dd, $J = 10.5$, 2 Hz, 1H, H-6a), 3.25 (dd, $J = 10.5$, 5 Hz, 1H, H-6b), 2.96–2.83 (m, 2H, NCH_2), 2.76–2.46 (m, 4H, 2 × NCH_2), 1.66–1.54 (m, 2H, CH_2CH_2OH), 1.48 (s, 3H, CCH_3), 1.30 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 144.20, 128.84, 127.65, 126.77, 111.50, 104.92, 86.37, 82.31, 75.86, 70.23, 70.04, 69.48, 69.22, 69.18, 68.88, 64.17, 63.23, 56.00, 54.45, 54.18, 30.91, 26.71, 26.35; FAB-MS, *m/z* 678 [M^++1], 700 [M^++Na]; HRMS calcd for $C_{39}H_{51}NO_9$ 677.3564. Found 677.3571.

*1,2-O-Isopropylidene-α-D-xylofuranoside (**20**) [38]*

D-Xylose **19** (10.0 g, 67 mmol) was dissolved in acetone (260 mL) containing H_2SO_4 (10 mL, 96 %) by stirring over 30 min. A solution of Na_2CO_3 (13.0 g, 123.0 mmol) in water (112 mL) was added dropwise applying external cooling to keep the internal temperature below 20 °C. The mixture was stirred for 2.5 h, then solid Na_2CO_3 (7.0 g, 66 mmol) was added. The mixture was filtered, the filter cake was washed with acetone and the combined filtrates were concentrated in vacuum. The crude product was purified by column chromatography (silica gel, $CHCl_3$–CH_3OH 100:0 → 100:3) to afford compound **20** (10.81 g, 85 %); $[\alpha]_D^{22} = -19.4$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 5.98 (d, $J = 3.3$ Hz, 1H, H-1), 4.52 (d, $J = 3.3$ Hz, 1H, H-2), 4.30–4.26 (m, 1H, H-4), 4.20–4.17 (m, 1H, H-3), 4.10 (m, 2H, H-5a, H-5b), 1.48 (s, 3H, CCH_3), 1.32 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 111.64, 105.26, 82.73, 82.30, 79.37, 70.36, 26.77, 26.29; HRMS calcd for $C_8H_{14}O_5$ 190.0841, found 190.0840.

*1,2-O-Isopropylidene-3,5-bis-O-[(2-chloroethoxy)ethyl]-α-D-xylofuranoside (**21**)*

Compound **20** (5.40 g, 28.4 mmol) was reacted with bis(2-chloroethyl)ether (100.0 mL, 853 mmol) in the presence of 50 % aq. NaOH (100 mL) and Bu_4NHSO_4 (9.64 g, 28.4 mmol). Chromatography led to product **21** (5.60 g, 49 %); $[\alpha]_D^{22} = -32.2$ ($c = 1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 5.91 (d, $J = 3.5$ Hz, 1H, H-1), 4.59 (d, $J = 3.5$ Hz, 1H, H-2), 4.37 (td, $J = 6$, 3.5 Hz, 1H, H-4), 3.91 (d, $J = 3.5$ Hz, 1H, H-3), 3.81–3.60 (m, 18H, H-5a, H-5b, 2 × OCH_2CH_2O, 2 × OCH_2CH_2Cl, 2 × CH_2Cl), 1.49 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 111.73, 105.17, 82.64, 82.23, 79.44, 75.56, 72.11, 71.39, 71.23, 70.83, 70.79, 70.54, 42.80, 42.77, 26.84, 26.33; Elem anal calcd for $C_{16}H_{28}Cl_2O_7$ C, 47.65; H, 7.00; Cl, 17.58. Found C, 47.68; H, 7.02; Cl, 17.55. HRMS calcd for $C_{16}H_{28}Cl_2O_7$ 402.1212. Found 402.1219.

*1,2-O-Isopropylidene-3,5-bis-O-[(2-iodoethoxy)ethyl]-α-D-xylofuranoside (**22**)*

Bis-chloro compound **21** (5.60 g, 13.9 mmol) was treated with NaI (8.33 g, 55.6 mmol) in acetone (150 mL) to provide compound **22** (7.31 g, 90 %); $[\alpha]_D^{22} = -21.2$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm):

5.91 (d, $J = 3.3$ Hz, 1H, H-1), 4.59 (d, $J = 3.3$ Hz, 1H, H-2), 4.36 (td, $J = 6$, 3.3 Hz, 1H, H-4), 3.92 (d, $J = 3.3$ Hz, 1H, H-3), 3.81–3.60 (m, 14H, H-5a, H-5b, 2 × OCH_2CH_2O, 2 × OCH_2CH_2I), 3.26 (t, $J = 6.9$ Hz, 2H, CH_2I), 3.25 (t, $J = 6.9$ Hz, 2H, CH_2I), 1.49 (s, 3H, CCH_3), 1.32 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 111.81, 105.26, 82.60, 82.27, 79.40, 75.49, 72.02, 71.47, 71.11, 70.86, 70.85, 70.50, 26.77, 26.31, 3.29, 3.16; Elem anal calcd for $C_{16}H_{28}I_2O_7$ C, 32.78; H, 4.81; I, 43.30. Found C, 32.80; H, 4.84; I, 43.28; HRMS calcd for $C_{16}H_{28}I_2O_7$ 585.9924. Found 585.9928.

*1,2-O-Isopropylidene-α-D-xylofuranoside-based monoaza-16-crown-5 lariat ether with hydroxypropyl side arm (**23**)*

Bis-iodo compound **22** (3.60 g, 6.1 mmol) was treated with 3-aminopropan-1-ol (0.47 mL, 6.1 mmol) in the presence of Na_2CO_3 (3.90 g, 36.8 mmol) in CH_3CN (100 mL). The chromatography on Al_2O_3 ($CHCl_3$) gave lariat ether **23** (1.46 g, 59 %); $[\alpha]_D^{22} = -20.2$ ($c = 1$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$), δ (ppm): 5.91 (d, $J = 3.5$ Hz, 1H, H-1), 4.53 (d, $J = 3.5$ Hz, 1H, H-2), 4.34 (td, $J = 6$ Hz, 3 Hz, 1H, H-4), 3.98 (d, $J = 3$ Hz, 1H, H-3), 3.91 (dd, $J = 10$, 6 Hz, 1H, H-5a), 3.82–3.52 (m, 15H, H-5b, 2 × OCH_2CH_2O, 2 × OCH_2CH_2N, CH_2OH), 2.78–2.63 (m, 6H, 3 × NCH_2), 1.72–1.63 (m, 2H, CH_2CH_2OH), 1.48 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 111.62, 105.06, 82.81, 82.34, 79.37, 72.02, 70.83, 70.33, 69.81, 69.50, 69.14, 69.07, 64.09, 55.89, 54.40, 54.10, 28.39, 26.83, 26.37; FAB-MS, *m/z* 406 [M^++1], 429 [M^++Na]; HRMS calcd for $C_{19}H_{35}NO_8$ 405.2363. Found 405.2368.

*1,2-O-Isopropylidene-α-D-xylofuranoside-based monoaza-16-crown-5 lariat ether with methoxypropyl side arm (**24**)*

Bis-iodo compound **22** (3.4 g, 5.9 mmol) was treated with 3-methyoxypropylamine (0.6 mL, 5.9 mmol) in the presence of Na_2CO_3 (3.7 g, 35.1 mmol) in CH_3CN (100 mL). The chromatography on silica gel ($CHCl_3$–CH_3OH 100:0 → 100:3) furnished compound **24** (1.0 g, 41 %); $[\alpha]_D^{22} = -27.6$ ($c = 1$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$), δ (ppm) 5.90 (d, $J = 3.6$ Hz, 1H, H-1), 4.53 (d, $J = 3.6$ Hz, 1H, H-2), 4.34 (td, $J = 6$, 3.3 Hz, 1H, H-4), 4.05-3.95 (m, 2H, H-3, H-5a), 3.80–3.50 (m, 13H, H-5b, 2 × OCH_2CH_2O, 2 × OCH_2CH_2N), 3.41 (t, $J = 6.3$ Hz, 2H, CH_2OCH_3), 3.32 (s, 3H, OCH_3), 2.83–2.70 (m, 4H, 2 × NCH_2), 2.58 (t, $J = 6.3$ Hz, 2H, $NCH_2CH_2CH_2$), 1.72 (qui, $J = 6.3$ Hz, 2H, $CH_2CH_2OCH_3$), 1.49 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 111.63, 105.03, 82.71, 82.38, 79.28, 71.88, 70.86, 70.78, 70.58, 69.85, 69.58, 68.90, 58.60, 54.25, 54.15, 52.73, 27.55, 26.84, 26.35; FAB-MS, *m/z* 420 [M^+ +1], 442 [M^+ +Na]; HRMS calcd for $C_{20}H_{37}NO_8$ 419.2519. Found 419.2523.

Extraction ability [39]

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 allow complete phase separation. The picrate concentration in the aqueous phase was determined from its absorption at 354 nm ($\varepsilon = 14600$ 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 lipophilicity [40, 41]

Membrane and electrode preparation, and potentiometric measurements [42]

Membranes with and without the crown compound (**18**) as ionophore were prepared. Both types of membranes contained 0.41 mg (5 mM) lipophilic salt additive (potassium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, 60 mg dioctyl sebacate (DOS) plasticizer and 30 mg high molecular weight poly(vinyl chloride). The membrane with ionophore contained 0.44 mg (6.7 mM) of the lariat ether (**18**). The membrane components were dissolved in ca. 1 mL of tetrahydrofuran. This solution was cast into a 24 mm diameter glass ring. After evaporation of the solvent, a 7 mm disk (thickness ca. 200 μm) cut from the membrane was mounted into a Philips IS-561 electrode body (Eindhoven, The Netherlands). The inner solution was either 1 mM KCl for selectivity experiments or 0.01 M NaCl solution, which was buffered to pH 9.5 with 1 mM glycine buffer to keep (**18**) in its neutral form for the segmented sandwich membrane experiments. Membranes were conditioned overnight in the respective solution. The prepared ion-selective electrodes (ISE) were used with a Ag/AgCl double-junction reference electrode. The electromotive force (EMF) was measured at ambient temperature in magnetically stirred solutions using a 16-channel electrode voltmeter (Lawson Lab Inc., Malvern, Pa. 19355, USA). Unbiased potentiometric selectivity coefficients [40] were determined from the EMF data measured in metal chloride salts by performing a two-point calibration. Complex formation constant of the crown compound (**18**)

was determined with the segmented sandwich membrane method in 0.01 M NaCl, 1 mM glycine buffer (pH 9.5).

ESI–MS measurements [43]

The ESI–MS experiments were performed on a commercial Micromass Quattro Micro triple quadrupole instrument equipped with an electrospray ionization source. The ions were generated by direct infusion of the target molecules in MeOH–H_2O 8:2 solutions and a series of metal ions as nitrate, chloride or bromide salts. The spray capillary voltage was set to 3 kV, the cone voltage to 20 V and the extractor to 5.5 V. The ESI source was operated at 130 °C. The desolvation temperature was set to 220 °C with 800 L h^{-1} gas flow. Spectra were acquired in the 125–800 *m/z* mass range. The binding preference order of the ionophores to various metal ions was calculated from the area ratio of the corresponding adduct species. The concentration of the ionophores was set such that the protonated peak intensity was in the middle of the dynamic range of the MS.

Results and discussion

Synthesis

One part of the molecules comprised lariat ethers connecting to a protected glucofuranoside unit by a covalent bond and containing a 3-hydroxypropyl or 3-methoxypropyl side arm (**10**–**13**) (Scheme 1).

The starting 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside **1** was prepared from D-glucose using literature procedure [44]. The alkylation of protected **1** with benzyl bromide in the presence of NaH in THF gave benzyl ether **2** in a yield of 75 % [45]. The propyl derivative (**3**) was prepared in a similar way in a yield of 39 % [46]. The 5,6-*O*-isopropylidene-acetal moiety of intermediates **2** and **3** was removed by selective hydrolysis using 50 % acetic acid to afford compounds **4** and **5** in the yield of 93 and 99 %, respectively [36]. The 5,6-vicinal hydroxyl groups of the glucofuranoside derivatives so obtained (**4**, **5**) were utilized to establish the crown ring according to an earlier described protocol [10].

The vicinal hydroxyl groups of compounds **4** and **5** were alkylated with bis(2-chloroethyl)ether in the presence of 50 % *aq.* NaOH as the base and tetrabutylammonium hydrogensulfate as the catalyst in a liquid–liquid two-phase system to give intermediate **6** and **7** in 57 and 78 % yield, respectively, after purification by chromatography. The exchange of chlorine to iodine in intermediates **6** and **7** was accomplished by reaction with NaI in boiling acetone to afford bis-iodo derivatives **8** and **9** in a yield of 91 and 82 %, respectively. These compounds were then cyclized with two kinds of primary amines, 3-aminopropanol and 3-methoxypropylamine in the presence of dry Na_2CO_3 in boiling acetonitrile, to afford azacrown ethers **10-13** after purification by column chromatography. As the lariat ethers with the hydroxypropyl group (**10** and **11**) were obtained in somewhat higher yields than the methoxypropyl derivatives (**12** and **13**) (71 vs 60 % and 46 vs 42 %) a more efficient template affect can be assumed for the previous cases [47].

Scheme 2 shows the preparation of another type of 16-membered macrocycle (**18**), where the azacrown ring is fused to the α-D-glucofuranoside moiety. The macro-ring contains three stereogenic centers.

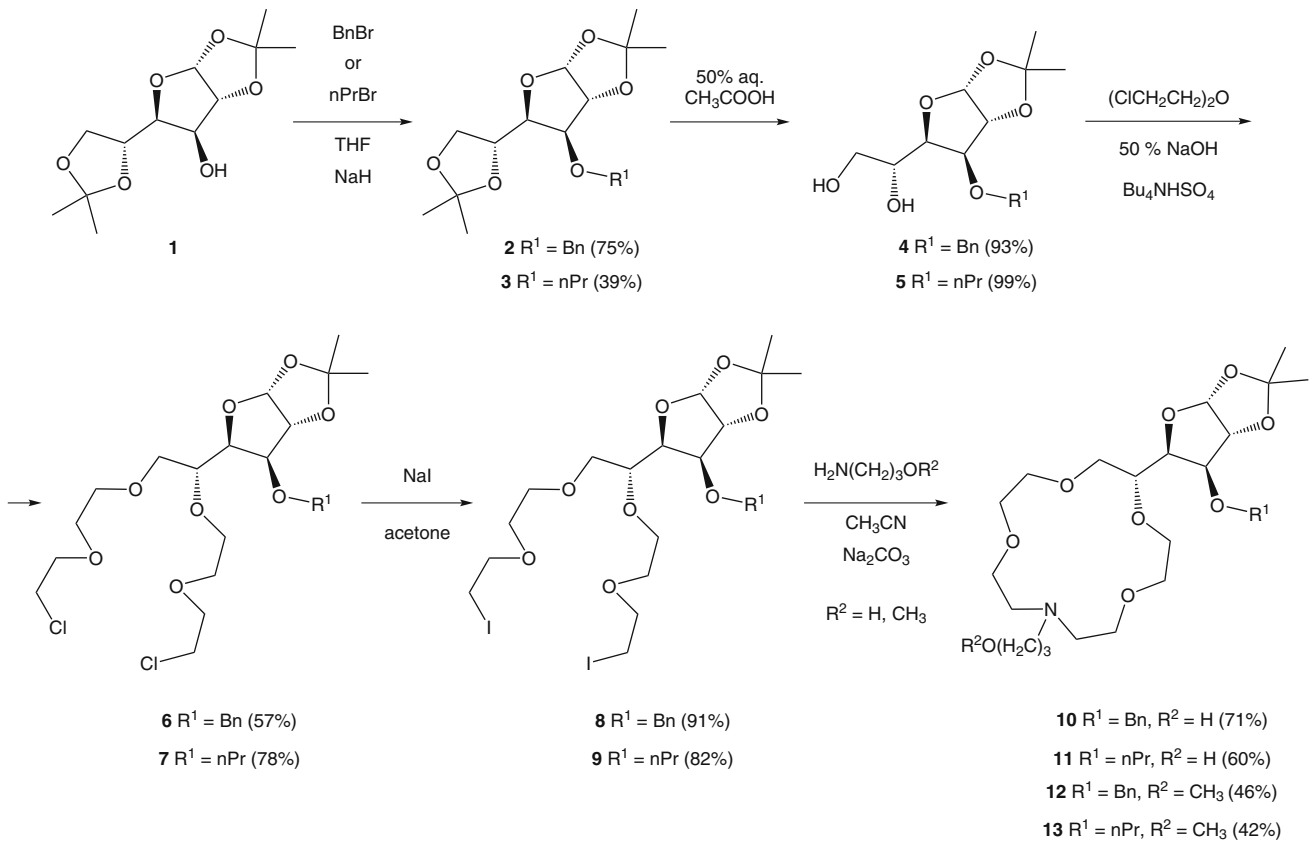
The starting 1,2-*O*-isopropylidene derivative (**14**) was obtained by the partial hydrolysis of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) [44]. The trihydroxy compound **14** was alkylated selectively on the primary hydroxyl group with triphenylchloromethane in pyridine as the solvent to furnish ether **15** in a yield of 61 % [37]. The free hydroxyl groups 3 and 5 served as the connecting points to establish the crown ring in the fashion described above. The double alkylation of intermediate **15** with bis(2-chloroethyl) ether gave bischloro-podand **16** in a yield of 80 %. The halogen exchange with NaI led to the bisiodo compound **17** in a yield of 91 %, finally, the ring closing reaction with 3-aminopropanol afforded target macrocycle **18** in a 49 % yield.

The xylofuranoside-based 16-membered macrocycles **23** and **24** were synthesized employing similar approach (Scheme 3).

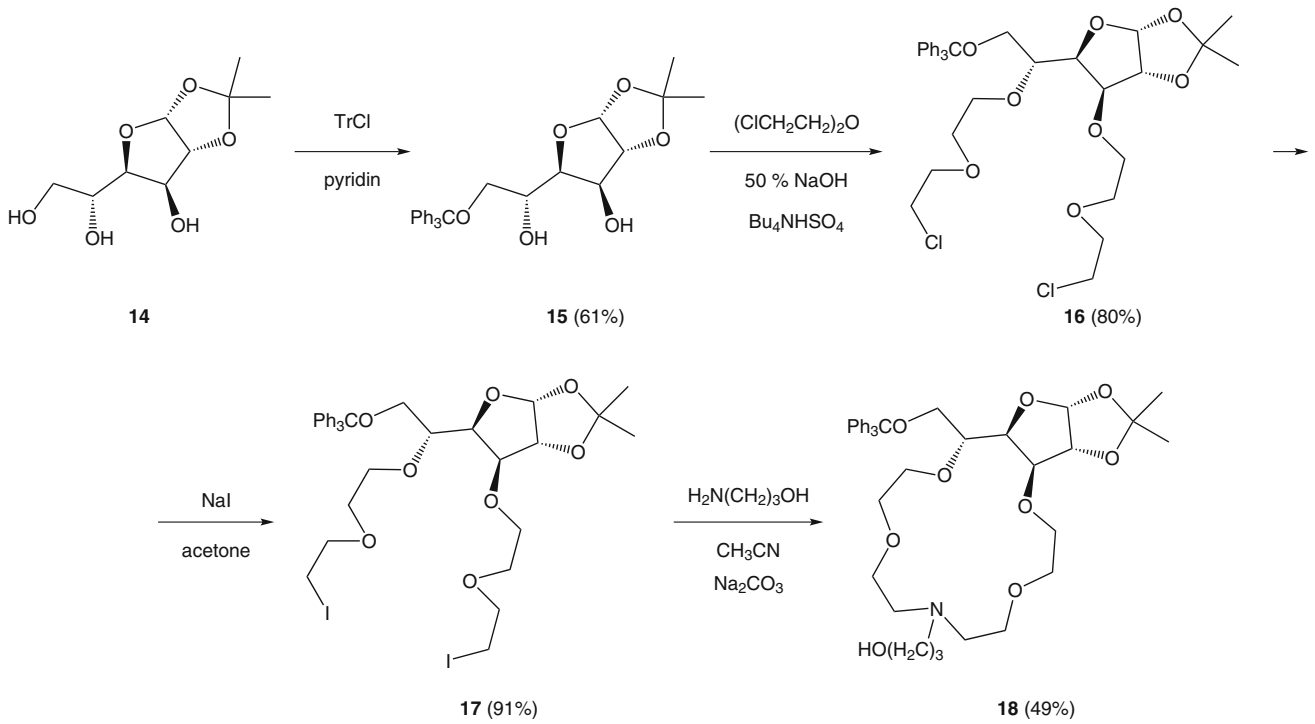
1,2-*O*-Isopropylidene-α-D-xylofuranoside (**20**) was prepared from D-xylose (**19**) by treatment with sulfuric acid in acetone [38]. The 3- and 5-hydroxyl groups were alkylated with bis(2-chloroethyl)ether to yield **21** in moderate yield (49 %). Next, chlorine atoms were exchanged by iodine yielding **22** (90 %). Finally, the azacrown ring was formed by reaction with 3-aminopropanol and 3-methoxypropylamine in good yields (59 %) for **23** and 41 % for **24**, respectively.

Extracting properties

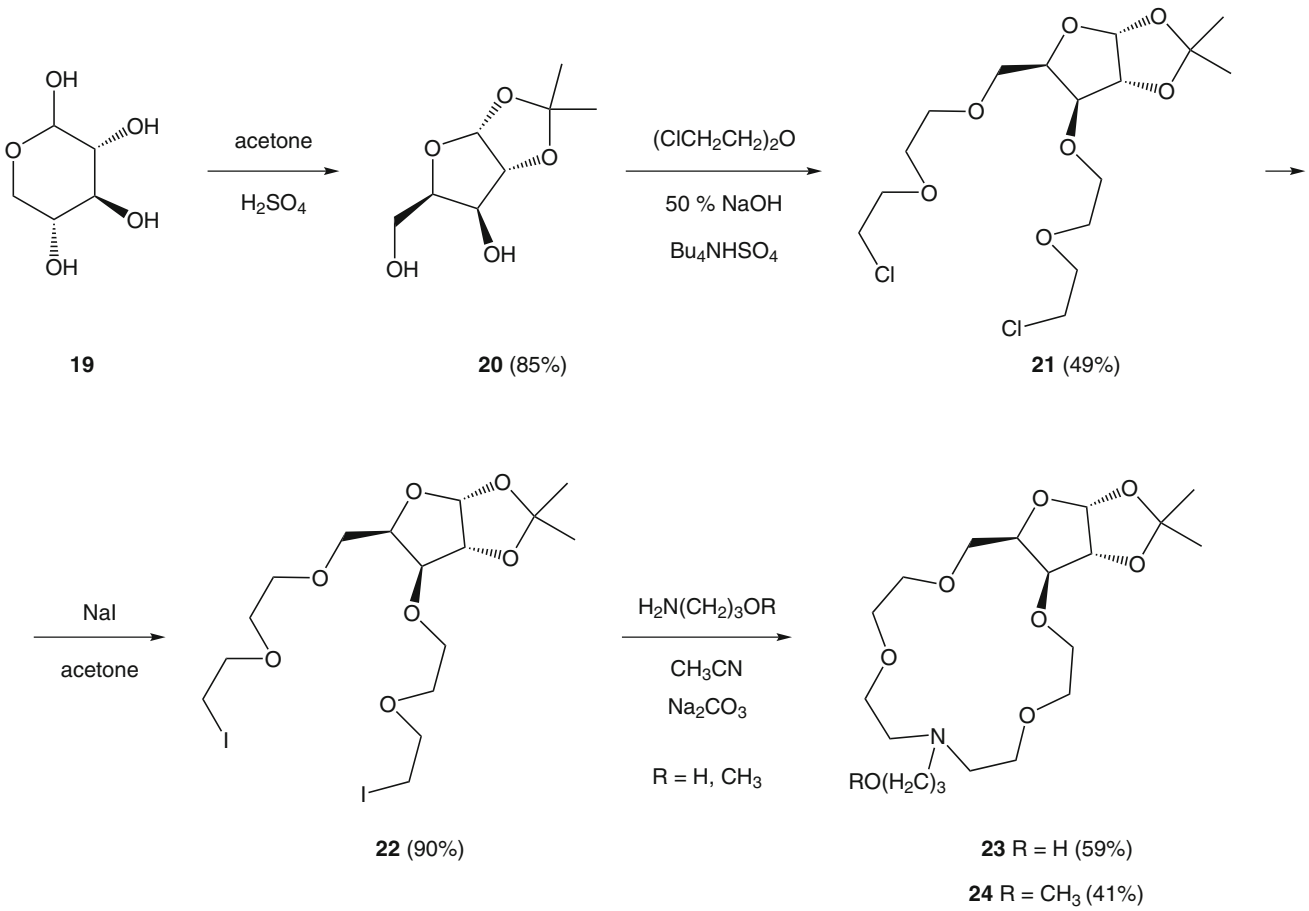
The liquid–liquid phase transfer catalytic properties of the chiral lariat ethers **10–13, 18, 23** and **24** were characterized by the extraction of lithium, sodium, potassium, rubidium, cesium, and ammonium picrate salts, from water into dichloromethane following the procedure described by Kimura et al. [39]. The concentration of the picrates in the aqueous phase was measured by UV spectroscopy. The data were collected in Table 1. The amount of the salts transferred to the organic phase is expressed as the percentage of the initial amount of salt (extractability %) in



Scheme 1 Synthesis of glucofuranoside-based lariat ethers



Scheme 2 Synthesis of glucofuranoside-based lariat ether containig a trityl group



Scheme 3 Synthesis of xylofuranoside-based lariat ethers

the water phase. The differences between the alkali metal picrate extraction abilities of the host molecules refer to the selectivity. The extracting ability of the macrocycles depends mainly on the complex forming ability, but also on the lipophilicity. Lipophilicity of the lariat ethers (**10–13, 18, 23–24**) was calculated using substructure-based partitioning coefficient estimation with the MarvinSketch (ChemAxon) software [40, 41]. For comparison purposes, properties of the unsubstituted monoaza-15-crown-5 (**25**) were also measured [14].

The complexing ability of the macrocycles synthesized (**10–13, 18, 23** and **24**) should be compared very carefully, as the ring size, the *N*-substituents and the connecting carbohydrate moieties are different. These all may have a significant effect on the complex forming ability and on the lipophilicity. Macrocycles **10–13** have the same monoaza-15-crown-5 hetero ring as reference crown **25**. It can be seen that lariat ethers **10–13** possess, with the exception for Cs^+ ion, a significantly more considerable extent of extracting ability as compared to reference crown **25**. On the basis of the ratio of the ring/cation diameter, the complexation should be the best for Na^+ ion. However, the complexation is also influenced by the side arms, and the lipophilicity will also be modified. Comparing the complexing ability of macrocycles **10–13**, **18**, **23** and **24**, it can be seen that, in general, the 15-membered macrocycles (**10–13**) show, for almost all cations, a higher extracting ability than the 16-membered lariat ethers (**18, 23, 24**).

Stoddart et al. proved that 18-crown-6 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 [8]. This must be true also for the derivatives of monoaza-15-crown-5 (**25**). Comparing the complexing ability of macrocycles **10** and **11** with *N*-hydroxypropyl side arm, one can see that the benzyl and propyl substituent on the sugar moiety has not much effect on the complexing ability (50–77 %). Both compounds (**10** and **11**) show a certain extent of selectivity (74 and 77 %) for the K^+ cation. Lariat ethers **12** and **13** with *N*-methoxypropyl side arm revealed, with one exception, a weaker complex forming ability, than species **10** and **11** with with *N*-hydroxypropyl substituents. It is noted that the increased lipophilicity of lariat ethers **12** and **13** does not justify the tendency mentioned.

Table 1 Alkali metal and ammonium picrate extraction data and lipophilicity of chiral lariat ethers

Host molecule	Percent of picrate extracted[a]						Lipophilicity log P
	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	
10	50	60	74	51	55	57	1.54
11	52	54	77	49	52	64	0.70
12	47	43	22	24	20	41	2.19
13	52	75	45	46	40	59	1.34
18	36	41	36	37	30	41	5.24
23	39	33	25	27	26	30	−0.20
24	38	29	20	20	20	33	0.45
25	25	26	15	21	49	13	−0.82

[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 %

Macrocycle **13** exhibits a rather high extent of selectivity (75 %) for Na^+ cation. The 16-membered lariat ethers (**18, 23** and **24**) show weak/medium extracting abilities, and they do not reveal striking selectivity toward any cations. It is worth mentioning that although macrocycle **18** with a trityl substituent exhibits the highest value for lipophilicity (5.24), there is practically no selectivity (30-41 %) for the different cations. In the case of the xylofuranoside-based macrocycles (**23** and **24**) the *N*-substituents did not have much effect on the extracting ability; the range of the latter for derivatives **23** and **24** was 25–39 and 20–38 %, respectively. Both lariat ethers (**23** and **24**) extracted best lithium picrate (39 and 38 %).

Potentiometric experiments with ion-selective electrodes incorporating ionophore 18

The most lipophilic lariat ether **18** was selected as ionophore in plasticized polymer membrane based ion-selective electrode. The selectivity coefficients of ion-selective membranes prepared with macrocycle **18** was determined for selected alkali and alkaline earth metals (Table 2).

In accordance with the extraction studies, the sodium ion was preferred. The selectivity coefficient depends on the composition of the membrane (ionophore, lipophilic anion concentration), stoichiometry and stability constants of the formed complexes. To investigate further the complex of crown **18** and sodium, potentiometric segmented sandwich membrane experiments were performed. The membrane containing the ionophore (**18**) was mechanically pressed together with the membrane that did not contain ionophore. The complex formation constants for single charged ions with 1:1 stoichiometry of ion-ionophore complex can be calculated from the resulting membrane potential (E_{ISM}) with the following equation:

$$\beta_{IL} = (L_T - R_T) \exp\left(\frac{E_{ISM}F}{RT}\right)$$

where L_T and R_T are the concentrations of ionophore and lipophilic anion, respectively. R, T and F are gas constant, absolute temperature, and Faraday constant, respectively. The complex formation constant for the crown compound (**18**)—sodium complex is log $\beta_{IL} = 5.14 \pm 0.05$, which is a few order of magnitudes lower, than the log β_{IL} of commercially available ionophores. This explains the relatively poor selectivity of the ISE toward interfering ions.

Binding affinities of ligands (10–13, 18, 23–24) to metal ions measured by ESI–MS

During the ESI MS measurements, aqueous solutions of LiCl, KBr, CsCl, $CaCl_2$, $ZnCl_2$, $Mg(NO_3)_2$, $Pb(NO_3)_2$, $Hg(NO_3)_2$, $Cu(NO_3)_2$ were used. All experiments were carried out in positive ion mode, with ionophore concentration of 10^{-3} M in MeOH/H_2O 8/2 solvent and the metal ions at 10^{-4} M. The halides were measured in a separate injection. Compared to proton affinity, the studied ionophores' affinity towards most metal ions is low. In most cases, no metal adduct peak was observed, as the ring *N* is easily protonated, even in pure water. The relative areas of the ionophores + metal peaks were summarized in Tables 3 and 4.

Table 2 Unbiased potentiometric selectivity coefficients for selected alkali and alkaline earth metals

Host molecule	log $K^{Pot}_{Na^+,M^+}$			
	Li^+	K^+	Mg^{2+}	Ca^{2+}
18	−0.3	−0.7	−0.7	−1.1

Table 3 Relative peak areas of various metal ion adducts with reference to the protonated molecular ion

	10 (%)	**11** (%)	**12** (%)	**13** (%)	**18** (%)	**23** (%)	**24** (%)	**25** (%)
Li^+	0.8	1.0	0.8	0.7	0.0	0.0	0.0	0.7
K^+	0.0	0.0	0.0	0.1	0.0	0.0	0.0	1.8
Cs^+	0.0	0.0	0.1	0.4	0.0	0.0	0.0	0.0
Zn^{++}	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.8
Ag^+	64.9	61.1	73.5	80.0	14.1	4.0	8.7	2.3

Table 4 Relative peak areas of Na^+ and Ag^+ cation adducts with reference to the protonated molecular ion and to each other

	10	**11**	**12**	**13**
Na^+/H^+	0,10679	0,13898	0,06279	0,03804
Ag^+/H^+	1,21827	0,70872	1,03509	1,17246
Ag^+/Na^+	**11,41**	**5,10**	**16,49**	**30,82**

The Ag^+ affinity was studied in a separate experiment. The affinity of compound **25**, the underivatized azacrown was comparable towards Ag^+ and to K^+ affinity. Surprisingly, derivatives **10–13**, **18**, **23** and **24** all show increased Ag^+ affinity. Comparative Na^+/Ag^+ measurements were also carried out for compounds **10–13**; the Ag^+ concentration was kept constant 10^{-3} M, and the Na^+ concentration was varied in the range of 10^{-6}–10^{-2} M.

The best result was observed for compound **13**. Using the same salt concentration for Na^+ and Ag^+, the ratio of the area for Na^+/Ag^+ was 0.03 (0.09 for **10**, 0.20 for **11** and 0.06 for **12**). The selectivity towards Ag^+ is more pronounced, when the ring size is smaller and when the *N*-substituent is methylated. The substituent on the tetrahydrofuran (furanoside) ring has a little effect on the Na^+/H^+ and Ag^+/H^+ selectivities. The outstanding selectivity of macrocycle **13** for Ag^+ cation is to be examined further. Our experience is rather surprising, as the selective ionophores described earlier were macrocycles/lariat ethers typically with one or two sulphur atoms. However, there are also similar other cases, Williams et al. found, for example, that the presence of nitrogen atoms in the macrocyclic ring is essential for silver selectivity over other transition metals and alkali metal ions [48]. Overall, we can say that Ag^+ binds to the azacrown ring, and the binding strength is greatly modulated by the *N*-substitution.

Conclusions

It was shown that the binding of 1,2-*O*-isopropylidene-α-D-glucofuranoside and 1,2-*O*-isopropylidene-α-D-xylofuranoside units to the monoaza-15-crown-5 macrocycle with hydroxypropyl and methoxypropyl side arms increase significantly the complex forming ability and the lipophilicity. The lariat ethers **10–13** possess, with the exception for Cs^+ ion, a significantly higher extent of extracting ability as compared to reference crown **25.** Comparing the complexing ability of macrocycles **10–13**, **18**, **23** and **24**, it can be seen that, in general, the 15-membered macrocycles (**10–13**) reveal, for almost all cations, a more considerable extracting ability, than the 16-membered lariat ethers (**18, 23, 24**).

Potentiometry was used to determine the ion-selectivity coefficients of crown compound **18**, and to assess the **18** crown–sodium complex formation constant. The resulting low selectivity values could be explained by the relatively low complex formation constant of the **18** crown– sodium complex.

As with the potentiometric measurements, the ESI–MS experiments indicate that 15-membered rings show higher metal affinity. The ion selectivity of the 1,2-*O*-isopropylidene-α-D-glucofuranoside-based lariat ether (**13**) for Ag^+ was 30 times higher than that for the Na^+ cation. The surprising Ag^+ binding effect is greatly enhanced by the *N*-substitution which stabilizes the Ag^+ coordination.

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References

1. Weber, E.: Crown ethers—complexes and selectivity. In: Patai, S., Rappoport, Z. (eds.) Crown Ethers and Analogs, Chapter 4, pp. 305–319. Wiley, New York (1989). **(and references cited therein)**
2. Izatt, R.M., Pawlak, K., Bradshaw, J.S., Bruening, R.L.: Thermodynamic and kinetic data for macrocycle interaction with cations, anions, and neutral molecules. Chem. Rev. **95**, 2529–2586 (1995)
3. Gokel, G.W., Schall, O.F.: Lariat ethers. In: Gogel, G.W. (ed.) Comprehensive Supramolecular Chemistry, pp. 97–152. Pergamon, New York (1996)
4. Davison, R.B., Izatt, R.M., Christensen, J.J., Schultz, R.A., Dishong, D.M., Gokel, G.W.: Stability-constants, enthalpies, and entropies for metal ion lariat ether interactions in methanol solution. J. Org. Chem. **49**, 5080–5084 (1984)

5. Adamic, R.J., Lloyd, B.A., Eyring, E.M., Petrucci, S., Bartsch, R.A., Pugia, M.J., Knudsen, B.E., Liu, Y., Desai, D.H.: Sodium-ion complexation by ionizable crown ethers in methanol water solvents—a thermodynamic and kinetic evaluation of side-arm interaction. J. Phys. Chem. **90**, 6571–6576 (1986)
6. Bredikhin, A.A., Gubaidullin, A., Bredikhina, Z.A., Fayzullin, R.: Crystallographic evidence of side-arm lariat effect in the series of chiral ortho- and para-methoxyphenoxymethyl-15-crown-5 complexes with sodium perchlorate. J. Mol. Struct. **1032**, 176–184 (2013)
7. Bratton, L.D., Strzelbicka, B., Bartsch, R.A.: Synthesis of N-pivot lariat ethers and their metal ion complexation behavior. ARKIVOC **12**, 80–88 (2003)
8. Stoddart, J.F.: Chiral crown ethers. In: Eliel, E.L., Wielen, S.H. (eds.) Topics in Stereochemistry, vol. 17, pp. 207–288. Wiley, New York (1988)
9. Miethchen, R., Fehring, V.: Carbohydrate-based crown ethers containing 1,4-linked D-glucopyranose moieties. Synthesis 94–98 (1998)
10. Bakó, P., Czinege, E., Bakó, T., Czugler, M., Tőke, L.: Asymmetric C–C bond forming reactions with chiral crown catalysts derived from D-glucose and D-galactose. Tetrahedron **10**, 4539–4551 (1999). **(and references cited therein)**
11. Itoh, T., Shirakami, S.: Synthesis of chiral azacrown ethers derived from alpha-D-glucose and their catalytic properties on the asymmetric Michael addition. Heterocycles **55**, 37–43 (2001)
12. Stoddart, J.F.: Synthetic chiral receptor molecules from natural products. In: Izatt, R.M., Christensen, J.J. (eds.) Progress in Macrocyclic Chemistry, vol. 2, pp. 173–250. Wiley-Interscience, New York (1981)
13. Gruza, M.M., Pokrop, A., Jurczak, J.: Synthesis and determination of alkali metal binding selectivities of chiral macrocyclic bissulfonamides derived from D-mannitol and L-threitol. Pol. J. Chem. **79**, 223–230 (2005)
14. Bakó, P., Makó, A., Keglevich, G., Menyhárt, D.K., Sefcsik, T., Fekete, J.: Alkali metal- and ammonium picrate extraction and complex forming capabilities of D-glucose and D-mannose-based lariat ethers. J. Incl. Phenom. **55**, 295–302 (2006)
15. Jarosz, S., Listkowski, A.: Sugar derived crown ethers and their analogs: synthesis and properties. Curr. Org. Chem. **10**, 643–662 (2006)
16. Bakó, P., Keglevich, G., Rapi, Z.: Asymmetric phase transfer reactions catalyzed by chiral crown ethers derived from monosaccharides. Lett. Org. Chem. **7**, 645–656 (2010)
17. Bakó, P., Rapi, Z., Keglevich, G., Szabó, T., Sóti, P.L., Vígh, T., Grűn, A., Holczbauer, T.: Asymmetric C–C bond formation via Darzens condensation and Michael addition using monosaccharide-based chiral crown ethers. Tetrahedron Lett. **52**, 1473–1476 (2011)
18. Rapi, Z., Bakó, P., Keglevich, G., Szöllősy, Á., Drahos, L., Hegedűs, L.: Synthesis of ribo-hexopyranoside- and altrose-based azacrown ethers and their application in an asymmetric Michael addition. Carbohydr. Res. **365**, 61–68 (2013)
19. Rapi, Z., Démuth, B., Keglevich, G., Grün, A., Drahos, L., Sóti, P.L., Bakó, P.: Enantioselective Michael addition of malonates to aromatic nitroalkenes catalyzed by monosaccharide-based chiral crown ethers. Tetrahedron Asymmetry **25**, 141–147 (2014)
20. Bakó, T., Bakó, P., Szöllősy, Á., Czugler, M., Keglevich, G., Tőke, L.: Enantioselective Michael reaction of 2-nitropropane with substituted chalcones catalysed by chiral azacrown ethers derived from alpha-D-glucose. Tetrahedron Asymmetry **13**, 203–209 (2002)
21. Bakó, P., Bakó, T., Mészáros, A., Keglevich, G., Szöllősy, Á., Bodor, S., Makó, A., Tőke, L.: Phase transfer catalyzed asymmetric epoxidation of chalcones using chiral crown ethers derived from D-glucose and D-mannose. Synlett 643–646 (2004)
22. Marchand, A.P., McKim, A.S., Kumar, K.A.: Synthesis and alkali metal picrate extraction capabilities of novel, cage-functionalized diazacrown ethers. Effects of host preorganization on avidity and selectivity toward alkali metal picrates in solution. Tetrahedron **54**, 13421–13426 (1998)
23. Kumar, S., Kaur, N., Singh, H.: Synthetic ionophores. 14. Effect of pyridine and thioether ligating units on Ag^+ selectivity in 18-membered diamide-diester macrocycles. Tetrahedron **52**, 13483–13492 (1996)
24. Di Marco, V.B., Bombi, G.G.: Electrospray mass spectrometry (ESI-MS) in the study of metal-ligand solution equilibria. Mass Spectrom. Rev. **25**, 347–349 (2006)
25. Daniel, J.M., Friess, S.D., Rajagopalan, S., Wendt, S., Zenobi, R.: Quantitative determination of noncovalent binding interactions using soft ionization mass spectrometry. Int. J. Mass Spectrom. **216**, 1–27 (2002)
26. Veenstra, T.D.: Electrospray ionization mass spectrometry in the study of biomolecular non-covalent interactions. Biophys. Chem. **79**, 63–79 (1999)
27. Brodbelt, J.S.: Probing molecular recognition by mass spectrometry. Int. J. Mass Spectrom. **200**, 57–69 (2000)
28. Loo, J.A.: Studying noncovalent protein complexes by electrospray ionization mass spectrometry. Mass Spectrom. Rev. **16**, 1–23 (1997)
29. Wang, K., Gokel, G.W.: The use of mass spectrometry to assess complexation phenomena in receptor compounds. Pure Appl. Chem. **68**, 1267–1272 (1996)
30. Leize, E., Jaffrezic, A., Van Dorsselaer, A.: Correlation between solvation energies and electrospray mass spectrometric response factors. Study by electrospray mass spectrometry of supramolecular complexes in thermodynamic equilibrium in solution. J. Mass Spectrom. **31**, 537–544 (1996)
31. Blair, S.M., Kempen, E.C., Brodbelt, J.S.: Determination of binding selectivities in host-guest complexation by electrospray/quadrupole ion trap mass spectrometry. J. Am. Soc. Mass Spectrom. **9**, 1049–1059 (1998)
32. Rosu, F., De Pauw, E., Gabelica, V.: Electrospray mass spectrometry to study drug-nucleic acids interactions. Biochimie **90**, 1074–1087 (2008)
33. Rosu, F., Gabelica, V., Houssier, C., De Pauw, E.: Determination of affinity, stoichiometry and sequence selectivity of minor groove binder complexes with double-stranded oligodeoxynucleotides by electrospray ionization mass spectrometry. Nucleic Acids Res. **30**, e82 (2002)
34. Wang, W.J., Kitova, E.N., Klassen, J.S.: Influence of solution and gas phase processes on protein-carbohydrate binding affinities determined by nanoelectrospray Fourier transform ion cyclotron resonance mass spectrometry. Anal. Chem. **75**, 4945–4955 (2003)
35. Révész, Á., Schröder, D., Svec, J., Wimmerova, M., Sindelar, V.: Anion binding by bambus[6]uril probed in the gas phase and in solution. J. Phys. Chem. A **115**, 11378–11386 (2011)
36. Kapeller, D.C., Hammerschmidt, F.: Novel formal synthesis of stereospecifically C-6 deuterated D-glucose employing configurationally stable alkoxymethyllithiums. Tetrahedron **66**, 591–598 (2010)
37. Bishop, C.T.: Synthesis of 3,5-di-*O*-methyl-D-glucose. Can. J. Chem. **35**, 61–64 (1957)
38. Moravcová, J., Čapková, J., Staněk, J.: One-pot synthesis of 1,2-*O*-isopropylidene-α-D-xylofuranose. Carbohydr. Res. **263**, 61–66 (1994)
39. Kimura, K., Maeda, T., Shono, T.: Extraction of alkali-metal picrates with poly(crown ether) and bis(crown ether). Talanta **26**, 945–949 (1979)
40. Viswanadhan, V.N., Ghose, A.K., Revankar, G.R., Robins, R.K.: Atomic physicochemical parameters for three dimensional

structure directed quantitative structure-activity relationships. 4. Additional parameters for hydrophobic and dispersive interactions and their application for an automated superposition of certain naturally occurring nucleoside antibiotics. J. Chem. Inf. Comput. Sci. **29**, 163–172 (1989)
41. Csizmadia, F., Tsantili-Kakoulidou, A., Panderi, I., Darvas, F.: Prediction of distribution coefficient from structure. 1. Estimation method. J. Pharm. Sci. **86**, 865–871 (1997)
42. Mi, Y., Bakker, E.: Determination of complex formation constants of lipophilic neutral ionophores in solvent polymeric membranes with segmented sandwich membranes. Anal. Chem. **71**, 5279–5287 (1999)
43. Czirok, J.B., Jagerszki, G., Toth, K., Revesz, A., Drahos, L., Bitter, I.: Click synthesis of triazole-linked calix[4]arene ionophores. Potentiometric and ESI-MS screening of ion-selectivity. J. Incl. Phenom. **78**(1–4), 207–215 (2014)
44. Schmidt, O.T.: Isopropylidene derivatives. In: Whistler, R.L., Wolfrom, M.L. (eds.) Methods in Carbohydrate Chemistry, vol. 2, pp. 318–325. Academic Press Inc, New York and London (1963)
45. Xue, X.C., Yin, Z.J., Meng, X.B., Li, Z.J.: A carbohydrate-based approach for the total synthesis of (−)-dinemasone B, (+)-4a-epi-dinemasone B, (−)-7-epi-dinemasone B, and (+)-4a,7-di-epi-dinemasone B. J. Org. Chem. **78**, 9354–9365 (2013)
46. Szeja, W.: Alkylation of carbohydrates in a catalytic 2-phase system. Pol. J. Chem. **55**, 1503–1509 (1981)
47. Laidler, D.A., Stoddart, J.F.: Synthesis of crown ethers and analogues. In: Patai, S. (ed.) The Chemistry of Ethers, Crown Ethers, Hydroxyl groups and Their Sulfur Analogues, Part 1, pp. 3–9. Wiley, New York (1980)
48. Williams, S.M., Brodbelt, J.S., Huang, Z., Lai, H., Marchand, A.P.: Complexation of silver and co-recovered metals with novel aza-crown ether macrocycles by electrospray ionization mass spectrometry. Analyst **128**, 1352–1359 (2003)