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Note

Synthesis and complexation properties towards the ammonium cation of aza-coronand analogues containing sucrose

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Abstract—1′,2,3,3′,4,4′-Hexa-*O*-benzyl-sucrose was converted in good yields into the macrocyclic receptors containing two and three nitrogen atoms in the ring. Their complexation properties towards the ammonium cation were significantly higher than for receptors without any nitrogen atoms in the ring.
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Sucrose, the most abundant disaccharide occurring in nature, is produced on the scale 150 million tons per year. Most of it is used in the food industry, but its application in other fields as a cheap organic raw material has also attracted considerable interest. Considerable effort has been applied to promote this saccharide as a scaffold for surfactants, pharmaceuticals or biodegradable polymers.[1] Although sucrose is, by far, the cheapest enantiomerically pure derivative and consequently, it might be regarded as a convenient chiron, its application in stereoselective organic synthesis is rather limited due to the fact that it has eight hydroxyl groups not much differing in reactivity, is not stable under acidic conditions and is almost insoluble in organic solvents.[1] However, examples of the synthesis of azasugars[2] or other heterocycles[3] have been described, but this was connected with the destruction of the disaccharide skeleton.

As a part of an on-going programme on the application of sucrose in the synthesis of useful analogues (with the preservation of the sugar skeleton) we have developed a convenient route to partially blocked derivatives: 2,3,3′,4,4′-penta- (**1**)[4] and 1′,2,3,3′,4,4′-hexa-*O*-benzyl-sucroses (**2**).[5] It was possible to differentiate all the primary hydroxyl groups in the penta-*O*-benzyl analogue **1**, which allowed the modification of each terminal position.[4,6] The sucrose amines, uronic acids and derivatives with an elongated side chain (2–7 carbon atoms) were conveniently obtained (e.g., **3** in Fig. 1).[4]

In free sucrose C-6 and C-6′ are close to each other, which results from the relatively strong hydrogen bonding between 1′-OH–2-OH and weaker hydrogen bonding between the 6′-OH and the oxygen atom from the glucopyranose ring.[7] We have found that C-6 and C-6′ are also close to each other in selectively protected sucroses: **1** and **2** (despite lacking the strong hydrogen bond between 1′-OH and 2-OH), since they could be connected either via a carbon or polyethylene glycol bridge.[4] The ring closing metathesis reaction performed for the diallyl derivative of **2** afforded the cyclic olefin **4**.[8] Alternatively, the reaction of **2** with polyethylene glycol ditosylates provided crown ether analogues (such as **5** and **6**).[4,9] The aza-crown derivative **7** was also prepared (Fig. 1).[9] The benzyl groups blocking the oxygen functions could be removed by simple hydrogenation providing the corresponding unprotected derivatives of sucrose.[4,9]

The complexation abilities of simple sucrose ‘crowns’ towards Group I metal cations and ammonium cation were moderate and low, respectively (see Table 1), as indicated by the association constants (what was

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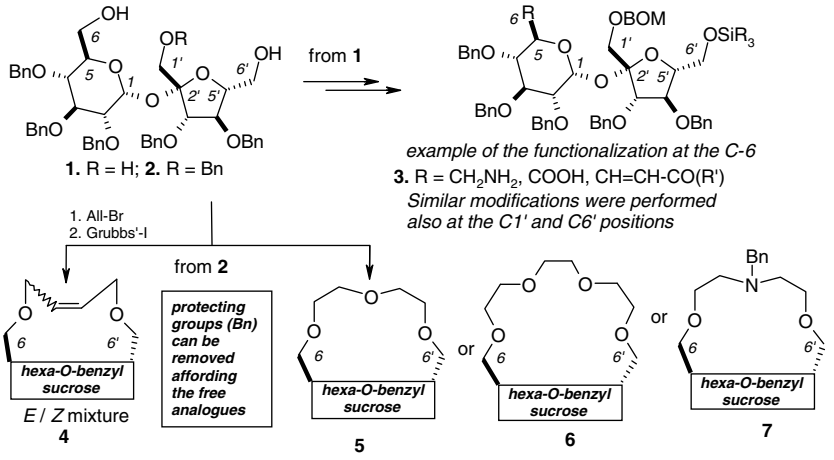


Figure 1. Synthesis of sucrose analogue from benzylated disaccharide.

Table 1. Complexation properties towards K^+ and the ammonium cation of aza-coronands analogues containing sucrose (in acetone-d_6)

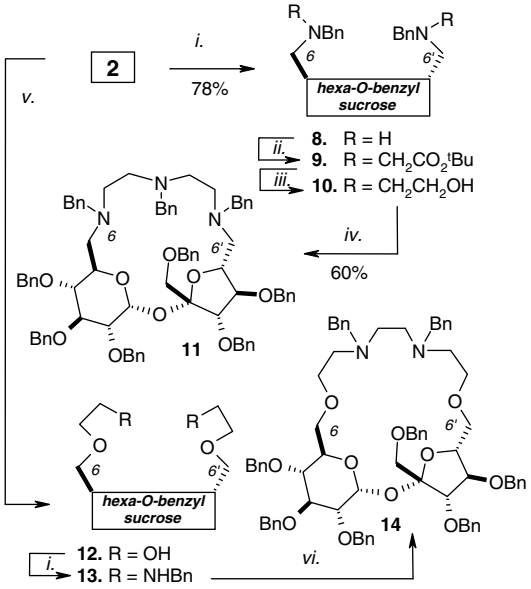
Compound	K_a (mol/dm^3) (acetone-d_6)	
	$NH_4^{(+)}$	$K^{(+)}$
5	17	258
6	25	66
7	125	234
11	560[a]	ND
14	230[a]	88[a]

The data for compounds **5**–**7** are taken from Ref. 9
ND = not determined.
[a] This work.

determined for the isothiocyanates (M-SCN)[9]). Change of the size of the cavity (from **5** to **6**) had almost no influence on the association constant for ammonium cation (in acetone-d_6), however replacing one oxygen atom with nitrogen significantly increased this constant ($K_{as} = 17$ mol/dm^3 for **5** and 125 mol/dm^3 for **7**).[9] We decided, therefore, to elaborate a general methodology for the preparation of aza-macrocycles with the sucrose scaffold; the results are shown in Scheme 1.

The synthesis of triaza-coronand **11** was initiated from hexa-*O*-benzyl sucrose (**2**). Both free hydroxyl groups in **2** were activated as mesyl esters, and this intermediate was further converted into diamine **8** by reaction with benzyl amine. Elongation by CH_2CH_2OH units was performed by the reaction of **8** with *tert*-butyl bromoacetate (to **9**), followed by the reduction of the ester functions with lithium aluminum hydride, which provided compound **10**. Activation of the hydroxyl groups (as mesyl esters) followed by reaction with benzylamine produced aza-coronand **11** in 60% yield.

Synthesis of compound **14** was performed from diol **12** with the elongated side chains at terminal positions (easily obtained from the parent **2** acc. to Ref. 9) in a similar sequence of reactions. Activation of the hydroxyl groups followed by reaction with $BnNH_2$ afforded



Scheme 1. Reagents and conditions: (i) (1) MsCl, Et_3N, CH_2Cl_2; (2) $BnNH_2$, CH_3CN, Na_2CO_3; (ii) $BrCH_2CO_2{}^tBu$; toluene, K_2CO_3, reflux, 48 h, 79%; (iii) LAH, THF; (iv) (1) MsCl, Et_3N, CH_2Cl_2; (2) substrate concentration ($c = 3.85 \times 10^{-3}$ mol/L), $BnNH_2$ (1.2 equiv), CH_3CN, Na_2CO_3, 60%; (v) Ref. 11; (vi) substrate concentration ($c = 3.45 \times 10^{-3}$ mol/L), $TsO(CH_2CH_2)OTs$ (1.2 equiv), CH_3CN, Na_2CO_3, 55%.

diamine **13**, which reacted with ethylene glycol ditosylate under standard conditions to afford receptor **14** in 55% yield (Scheme 1).

The association constants of the complexes with ammonium cation (determined from the NMR titration experiments[10] in acetone-d_6 with NH_4SCN) were significantly higher than for those already studied by us. For receptor **14** with two nitrogen atoms in the ring it was 230 mol/dm^3, while for that with smaller ring, but containing three nitrogen atoms (**11**) it was found to be 560 mol/dm^3. The association constants of the complex of **6** and **14** with potassium cation were similar, while

compound **11** showed almost no affinity towards potassium ion. These results are in agreement with the literature data showing that the aza-coronands have higher affinity than crown ethers towards ammonium cation and lower (or much lower) towards potassium ion.[11]

Further work on the preparation of aza-coronands with various cavity sizes and different number of N atoms as well as the study on their complexation properties is in progress.

In conclusion, we have developed an efficient synthetic strategy towards the aza-coronand analogues containing sucrose. Such receptors show enhanced ability for complexing ammonium cations which may allow their application for the recognition of chiral amines or aminoacids.

1. Experimental

NMR spectra were recorded with a Bruker AM 500 spectrometer for solutions in $CDCl_3$ (internal Me_4Si) unless otherwise stated. The resonances of the secondary carbon atoms were assigned by DEPT experiments. The ^1H- and ^{13}C-aromatic resonances occurring at the typical δ values (~7.2–7.3 and ~128 ppm in ^1H and ^{13}C NMR, respectively) were omitted for simplicity. In the ^1H NMR spectra only signals not overlapping with others were cited. Mass spectra were recorded with an ESI/MS Mariner (PerSeptive Biosystem) mass spectrometer. Column chromatography was performed on silica gel (Merck, 70–230 or 230–400 mesh). Organic solutions were dried over anhydrous magnesium sulfate.

1.1. Synthesis of macrocycle 11

1′,2,3,3′,4,4′-Hexa-*O*-benzylsucrose (**2**; 380 mg, 0.4 mmol) was dissolved in dichloromethane (12 mL) to which triethyl amine (3 mL) and DMAP (2 mg) were added. Mesyl chloride (0.15 mL, 1.75 mmol) was then added dropwise, the mixture was stirred at rt for 5 h and partitioned between water (15 mL) and dichloromethane (20 mL). The organic layer was separated, the aqueous one extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were washed with water, and dried. Evaporation of the solvent under reduced pressure left an oily residue, which was purified by column chromatography (hexane–EtOAc 3:1) to afford the corresponding dimesylate (420 mg, 95%) as colourless oil. MS *m*/*z*: 1039.3 [$M(C_{56}H_{62}O_{15}S_2)+H^+$].

The above obtained dimesylate (250 mg, 0.24 mmol) was dissolved in acetonitrile (10 mL) to which anh. Na_2CO_3 (100 mg) and benzylamine (0.15 mL, 1.37 mmol) were added and the solution was boiled under reflux for 48 h. Then it was cooled to rt and partitioned between water (10 mL) and ethyl acetate (20 mL). The organic layer was separated, the aqueous one extracted with ethyl acetate (2 × 15 mL), the combined solutions were dried and concentrated, and the product was purified by column chromatography (hexane–EtOAc, 1:1 to 1:2) to afford 6,6′-di(benzyloamino)-6,6′-dideoxy-1′,2,3,3′, 4,4′-hexa-*O*-benzylsucrose (**8**) as a yellowish oil (210 mg, 82%). ^1H NMR δ: 5.51 (d, 1H, $J_{1,2} = 3.5$ Hz, H-1). ^{13}C NMR δ: 138.9, 138.8, 138.6, 138.5, 138.45, 138.34 138.2, 137.9 (C_{quat}, OCH_2Ph, $HNCH_2Ph$), 90.3 (C-1), 84.0, 81.9, 80.9, 79.8, 79.1, 77.5 and 70.7 (C-2,3,3′,4,4′,5,5′), 75.4, 74.9, 73.4, 72.78, 72.6, 72.4, 70.3 (6 × O*C*H_2Ph, C-1′), 53.9, 53.5, 51.8, 49.3 (C-6,6′, 2 × N*C*H_2Ph). MS *m*/*z*: 1061.9 [$M(C_{68}H_{72}N_2O_9)+H^+$], 1083.0 [$M(C_{68}H_{72}N_2O_9)+Na^+$].

To a stirred solution of diamine **8** (200 mg, 0.19 mmol) in toluene (10 mL) anh. K_2CO_3 (100 mg, 0.7 mmol) was added followed by *tert*-butyl bromoacetate (0.2 mL). The mixture was stirred for 8 h and partitioned between water (10 mL) and toluene (30 mL). The organic layer was separated, the aqueous one extracted with EtOAc (2 × 10 mL), and the combined organic layers were washed with water and dried. Purification of the crude product by column chromatography (hexane–EtOAc, 5:1) afforded diester **9** (190 mg, 79%) as a yellowish oil. ^1H NMR δ: 5.56 (d, 1H, $J_{1,2} = 3.4$ Hz, H-1), 1.46 (s, 9H, $C(CH_3)_3$). ^{13}C NMR δ: 171.0, 170.7 (2 × *C*O_2tBu), 139.1, 139.0, 138.9, 138.6, 138.5, 138.4, 138.3 and 138.1 (C_{quat} OCH_2Ph, $HNCH_2Ph$), 104.9 (C-2′), 89.9 (C-1), 84.3, 83.8, 82.0, 80.3, 79.7, 79.0 and 71.9 (C-2,3,3′,4,4′,5,5′), 75.45, 74.47, 73.3, 72.8, 72.38, 72.36, 71.2 (6 × O*C*H_2Ph, C-1′), 59.0, 58.3, 57.6, 55.43, 55.37, 54.5 (C-6,6′, 2 × N*C*H_2Ph, 2 × *C*H_2CO_2tBu), 28.2 [2 × C(*C*H_3)$_3$], 25.6 [2 × *C*$(CH_3)_3$]. MS *m*/*z*: 1290.3 [$M(C_{80}H_{92}N_2O_{13})+H^+$], 1312.4 [$M(C_{80}H_{92}N_2O_{13})+Na^+$].

A solution of diester **9** (100 mg, 0.078 mmol) in dry THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (15 mg, 0.39 mmol) in dry THF (5 mL) and the mixture was stirred at room temperature for 6 h. Saturated aqueous sodium sulfate (5 mL) and ethyl acetate (10 mL) were added to decompose the excess of hydride and product **10** was isolated in usual way (72 mg, 80%). ^1H NMR δ: 5.64 (d, 1H, $J_{1,2} = 3.5$ Hz, H-1). ^{13}C NMR δ: 138.8, 138.6, 138.5, 138.3, 138.21, 138.17, 138.1 and 138.0 (C_{quat} OCH_2Ph, NCH_2Ph), 105.4 (C-2′), 90.4 (C-1), 84.2, 83.8, 81.5, 80.2, 79.8, 79.2 and 70.4 (C-2,3,3′,4,4′,5,5′), 75.3, 74.4, 73.4, 73.0, 72.5, 72.1, 70.7 (6 × O*C*H_2Ph, C-1′), 59.22, 59.16, 59.05, 58.98, 57.4, 56.2, 56.0, 54.1 (C-6,6′, 6 × O*C*H_2Ph, 2 × N*C*H_2Ph, 2 × *C*$H_2C$$H_2$OH). MS *m*/*z:* 1149.4 [$M(C_{72}H_{80}N_2O_{11})+H^+$]. The crude product **10** was used in the next step without further purification.

Compound **10** was converted in 97% yield into the dimesylate {MS *m*/*z*: 1327.5 [$M(C_{72}H_{84}N_2O_{15}S_2)+Na^+$]} according to the procedure described for the mesylation of **2**. A solution of this dimesylate (100 mg, 0.0767 mmol) in CH_3CN (20 mL) containing anh.

Na_2CO_3 (75 mg, 0.7 mmol) and benzylamine (0.014 mL, 0.099 mmol) was stirred at 70 °C for 48 h and partitioned between (10 mL) and ethyl acetate (25 mL). Organic layers were separated, the aqueous one extracted with EtOAc (2 × 20 mL), the combined organic layers were dried and concentrated, and the crude product was purified by column chromatography (hexane–EtOAc, 1:1 then 1:2) to afford the desired macrocycle **11** as yellowish oil (54 mg, 60%). ^{1}H NMR δ: 5.57 (d, 1H, $J_{1,2} = 3.3$ Hz, H-1). ^{13}C NMR δ: 138.8, 138.73, 138.68, 138.62, 138.57, 138.4, 138.3, 138.2 and 137.8 (C_{quat} OCH_2Ph, NCH_2Ph), 104.5 (C-2′), 90.0 (C-1), 84.8, 83.7, 82.0, 80.3, 80.0, 78.2 and 71.0 (C-2,3,3′,4,4′,5,5′), 75.5, 74.7, 73.3, 73.1, 72.43, 72.36, 70.1 (6 × OCH_2Ph, C-1′), 60.1, 59.0, 58.3, 57.5, 54.5, 52.5, 51.6, 50.7, 50.0 (C-6,6′, 6 × O CH_2Ph, 3 × NCH_2Ph, 2 × CH_2CH_2NBn). MS *m/z*: 1220.9 [M($C_{79}H_{85}N_3O_9$)+H^+]. Anal. Calcd for $C_{79}H_{85}N_3O_9$+H_2O: C, 76.64; H, 7.02; N, 3.40. Found: C, 76.58; H, 6.95; N, 3.40.

1.2. Synthesis of macrocycle 14

To a solution of the dimesylate (obtained by standard mesylation of known[9] **12**, 170 mg, 0.15 mmol) in acetonitrile (10 mL) anh. Na_2CO_3 (100 mg, 0.9 mmol) and benzylamine (0.1 mL, 0.917 mmol) were added and the solution was stirred under reflux for 72 h. Then it was cooled to rt and partitioned between water (10 mL) and ethyl acetate (15 mL). The layers were separated, the aqueous one extracted with ethyl acetate (2 × 10 mL) and the combined solutions were dried and concentrated. The product was purified by column chromatography (hexane–EtOAc, 1:1, then 1:4, then EtOAc/MeOH = 8:1) to afford **13** as yellow oil (125 mg, 72%). ^{1}H NMR δ: 5.63 (d, 1H, $J_{1,2} = 3.4$ Hz, H-1). ^{13}C NMR δ: 138.93, 138.9, 138.7, 138.31, 138.28, 138.22, 138.18 and 137.9 (C_{quat} OCH_2Ph, $HNCH_2Ph$), 104.5 (C-2′), 89.8 (C-1), 83.8, 82.1, 81.9, 79.9, 79.6, 77.5 and 70.6 (C-2,3,3′,4,4′,5,5′), 75.4, 74.8, 73.4, 72.8, 72.4, 72.3, 72.0, 71.4, 70.0, 69.5, 53.7, 53.5, 53.2, 48.5, 48.4 (C-1′,6,6′, 6 × OCH_2Ph, 2 × NCH_2Ph, 2 × OCH_2CH_2-NHBn). MS *m/z*: 575.6 [M($C_{72}H_{80}N_2O_{11}$)+2H^+] 1149.7 [M($C_{72}H_{80}N_2O_{11}$)+H^+]. Anal. Calcd for $C_{72}H_{80}N_2O_{11}$+2H_2O: C, 72.97; H, 6.76; N, 2.36. Found: C, 72.85; H, 6.71; N, 2.40.

A solution of diamine **13** (60 mg, 0.052 mmol) in acetonitrile (15 mL) containing anh. Na_2CO_3 (75 mg, 0.7 mmol) and ethylene glycol ditosylate (23 mg, 0.062 mmol) was stirred at 70 °C for 72 h and then partitioned between water (10 mL) and ethyl acetate (25 mL). The layers were separated, the aqueous one extracted with ethyl acetate (2 × 20 mL) and the combined organic solutions were dried and concentrated. The desired macrocycle **14** (33.5 mg, 55%) was obtained as a yellowish oil after purification by column chromatography (hexane–EtOAc, 1:2). ^{1}H NMR δ: 5.92 (d, 1H, $J_{1,2} = 3.4$ Hz, H-1). ^{13}C NMR δ: 139.7, 139.1, 138.83, 138.43, 138.39, 138.2, 138.06 and 138.03 (C_{quat} OCH_2Ph, $HNCH_2Ph$), 103.9 (C-2′), 88.3 (C-1), 83.3, 82.1, 80.6, 79.9, 79.1, 77.8 and 71.3 (C-2,3,3′,4,4′,5,5′), 75.5, 74.8, 73.3, 72.9, 72.5, 72.4, 72.2, 707, 70.4, 70.3, 70.0, 69.0, 59.8, 59.4, 53.4, 52.6, 52.0 (C-1′,6,6′, 6 × OCH_2Ph, 2 × NCH_2Ph, 2 × OCH_2CH_2NBn+ NCH_2CH_2N). MS *m/z*: 1175.9 [M($C_{74}H_{82}N_2O_{11}$)+H^+] 1197.9 [M($C_{74}H_{82}N_2O_{11}$)+Na^+]. Anal. Calcd for $C_{72}H_{80}N_2O_{11}$+2H_2O: C, 72.97; H, 6.76; N, 2.36. Found: C, 72.85; H, 6.71; N, 2.40.

1.3. Determination of the association constants of the complexes by NMR titration[10]

Determination of the association constant(s) was based on the change of the chemical shift of the H-1 signal of the receptor (**11** or **14**) after the addition of guest. Thus, the macrocyclic compound **11** or **14** (0.02 mmol) was dissolved in acetone-d_6 (1 mL) and its ^{1}H NMR spectrum was recorded. Then a solution of the isothiocyanate in acetone-d_6 ($c = 0.5$ mmol/L) was added in 5 μL portions. A ^{1}H NMR spectrum was recorded after the addition of each portion of guest solution. The shift of the signal of H-1 proton was determined in each case. The spectra were recorded until the shift of the signal was no longer observed (which corresponded to the saturation of the host–guest complex). The association constant was calculated with Origin MicroCal programme using the empirical equation determined by Fielding.[10]

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