Novel Azacrown Ethers Incorporating Sugars: Synthesis and Complex Formation

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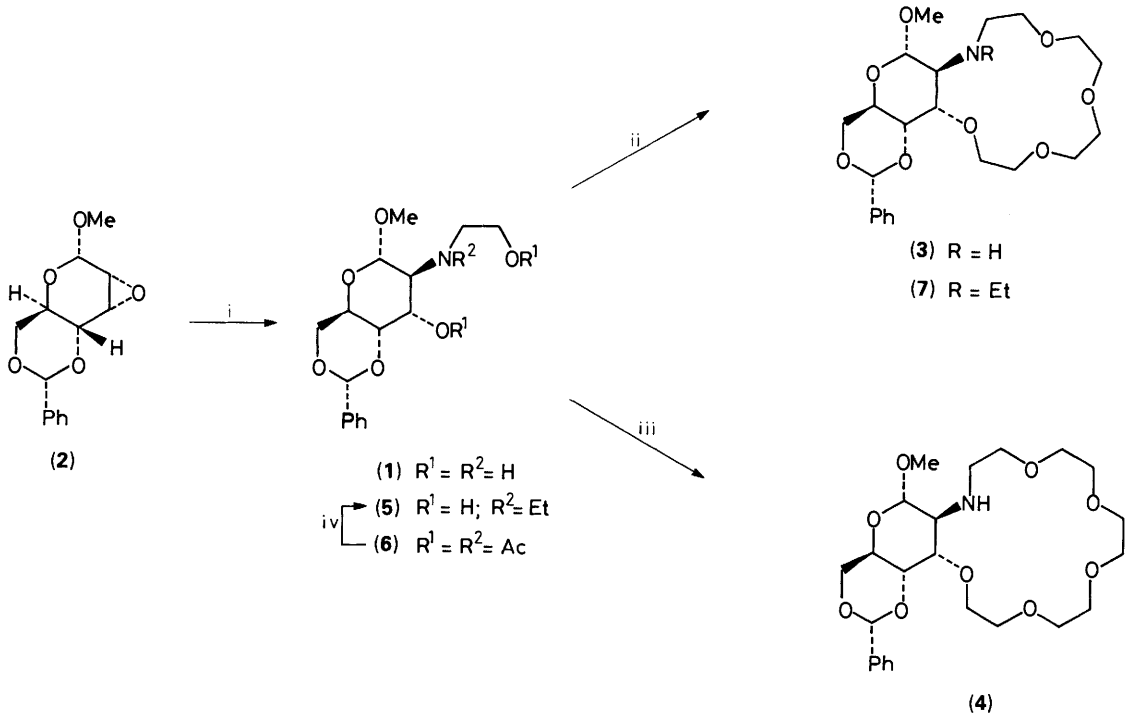
Azacrown ethers derived from amino-deoxy sugars in which the sugar moiety forms part of the macrocycle, or is pendant from it, have been synthesised and their complexing ability towards cations compared.

Several syntheses of chiral diazacrown ethers in which a sugar unit forms part of the macrocyclic ring have been previously reported.[1-3] We have recently published details of the synthesis of chiral monoazacrown ethers with pendant sugars bonded to the nitrogen atom of a previously constructed macrocycle.[4] We now report a synthesis of monoazacrown ethers by elaboration of sugar amines to give products in which the sugar forms part of the macrocyclic ring, and a comparative study of their complexing abilities with those of their pendant sugar counterparts.

The key intermediate, methyl 4,6-*O*-benzylidene-2-deoxy-2-(*N*-2-hydroxyethyl)amino-α-D-altropyranoside (**1**), was obtained by ring-opening of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**2**) with ethanolamine.[4] The Scheme shows the sequence of reactions employed to synthesise the macrocycles in which the sugars are incorporated. The products from cyclisation with the appropriate polyethylene bistosylates[5] were isolated and purified by preparative thin layer chromatography on Kieselgel 60 PF254 using toluene–methanol (5:1) as eluant. The 15-monoazatetraoxacrown-5 (**3**) was obtained as a crystaline material in 24% yield, while the 18-monoazapentaoxacrown-6 (**4**) resisted crystallisation. Since the yield of the 15-crown-5 (**3**) was affected by the undesired reaction of the bistosylate at the secondary amine, we carried out the synthesis on the *N*-ethyl derivative (**5**), the preparation of which was accomplished by acetylation of (**3**) to yield the triacetyl derivative (**6**), followed by reduction with lithium aluminium hydride. Condensation of (**5**) with triethylene glycol bistosylate resulted in a yield of 31% of the 15-(*N*-ethyl)-monoazatetraoxacrown-5 (**7**).

It was desired to compare the complex-forming abilities of the azoxacrowns (**5**)—(**7**) with those of the crowns in which the sugar moieties are pendant; to this end the benzylidene group of the previously described[4] *N*-altropyranosyl 15-monoazatetraoxacrown-5 (**8**) was removed with hot ethanoic acid[6] to yield the diol (**9**), from which the derivatives (**10**) and (**11**) were prepared by acetylation and tosylation respectively.

The Table shows the association constants for sodium, potassium, and ammonium ions with the new crowns, together with those of the previously described (**12**)[4] and (**13**),[5] as measured in chloroform by the u.v. technique developed by Cram.[7] As expected, the unsubstituted 15-crown-5 gave the



Scheme. *Reagents:* i, $H_2NCH_2CH_2OH$; ii, $TsO(CH_2CH_2O)_3Ts$, Bu^{t}ONa, Bu^{t}OH, dioxan, 20 h; iii, $TsO(CH_2CH_2O)_4Ts$, Bu^{t}OK, Bu^{t}OH, dioxan, 20 h; iv, $LiAlH_4$, THF

Table. Association constants (Log K_a) in $CDCl_3$ at 22 °C

	log K_a (± 0.05)		
Compound	Na^+	K^+	NH_4^+
(3)	4.73	4.54	4.45
(4)	5.18	4.84	4.90
(7)	4.96	4.64	4.56
(8)	5.84	5.45	5.53
(10)	5.41	4.98	4.78
(11)	6.02	5.42	5.27
(12)	6.11	5.61	4.98
(13)	6.03	5.52	5.72

strongest complexes. When the sugar is incorporated into the macrocyclic ring [compounds (**3**), (**4**), and (**7**)] there is a reduction in the log K_a values, but this is not so marked in the case of the pendant sugar crowns (**8**) and (**10**)—(**12**). The likely reason for these observations is an entropy effect due to the relative rigidity conferred on the ring by the fused sugar moiety in (**3**), (**4**), and (**7**) and concomitant steric hindrance to the binding of the ion, effects which are absent in the pendant sugar types. *N*-Alkylation as in (**7**) predictably increases the log K_a values for potassium and sodium ions by increasing the donor ability of the nitrogen ligand. A comparison of log K_a values for the substituted pendant sugar crowns (**10**) and (**11**) shows that the presence of acetyl groups produces poorer complexation than the benzylidene derivative (**8**) while tosyl groups cause a relative increase. Two possibilities are that there is additional bonding by the tosyl groups to the ion held in the cavity of the crown ether or that complexation is primarily to the tosyl group itself *i.e.* the complex is not of the classic crown ether type. The present work does not distinguish these two possibilities although the similarity of log K_a values would suggest that the former is the most likely explanation.

Experimental

Monoazacrown Ethers (**3**), (**4**), *and* (**7**).—*General procedure.* The hydroxyethylamino derivatives (**1**) or (**5**) (4.5 mmol) and sodium or potassium were dissolved in t-butanol (38 ml) under an atmosphere of argon and a solution of triethyleneglycol ditosylate or tetraethyleneglycol ditosylate (4.5 mmol) in dioxane was added during 3—4 h at 40 °C. The solution was cooled, the precipitated sodium or potassium tosylate removed by filtration, and the filtrate evaporated *in vacuo*. The residue was suspended in water (30 ml), washed with hexane (15 ml), and extracted with dichloromethane (3 × 20 ml). Evaporation of the extracts gave a residue (1.8—2.3 g) which was subjected to preparative thin layer chromatography using toluene–methanol (10:2) as eluant.

15-*Monoazatetraoxacrown*-5 (**3**) was obtained as crystals from ethanol (0.476 g, 24%), m.p. 54—56 C, $[\alpha]_D^{20}$ 31.5° (*c* 1, $CHCl_3$) (Found: C, 59.9; H, 7.5; N, 3.2%; M^+, 439. $C_{22}H_{33}NO_8$ requires C, 60.14; H, 7.52; N, 3.19%; M^+, 439); δ($CDCl_3$) 2.22 (1 H, br, s NH), 2.73—3.0 (2 H, q, NCH_2), 3.15 (1 H, d, 2-H), 3.41 (3 H, s, OCH_3), 3.50—4.40 (19 H, m, 8 × CH_2, 3 × CH), 4.60 (1 H, d, 1-H), 5.59 (1 H, s, PhC*H*), and 7.20—7.52 (5 H, m, Ph).

18-*Monoazapentaoxacrown*-6 (**4**), *oil*, (0.543 g, 25%), $[\alpha]_D^{20}$ 26.6° (*c* 0.96, $CDCl_3$) (Found: C, 58.9; H, 7.6; N, 2.95%; M^+, 483. $C_{24}H_{37}NO_9$ requires C, 59.63; H, 7.66; N, 2.90%; M^+, 483); δ($CDCl_3$) 2.28 (1 H, s, NH), 2.73—3.11 (3 H, m, NCH_2, 2-H), 3.43 (3 H, s, OCH_3), 3.50—4.40 (23 H, m, 10 × CH_2, 3 × CH), 4.56 (1 H, d, 1-H), 5.56 (1 H, s, PhC*H*), and 7.35—7.61 (5 H, m, Ph).

(N-*Ethyl*)-15-*monoazatetraoxacrown*-5 (**7**), *oil*, (0.658 g, 31%), $[\alpha]_D^{20}$ 56.0° (*c* 0.97, $CHCl_3$) (Found: C, 61.6; H, 7.95; N, 2.95%; M^+, 467. $C_{24}H_{37}NO_8$ requires C, 61.67; H, 7.92; N, 3.00%; M^+,

467); δ($CDCl_3$) 1.05 (3 H, t, CH_3), 2.40—2.92 (4 H, m, 2 × NCH_2), 3.08 (1 H, d, 2-H), 3.36 (3 H, s, OCH_3), 3.50—4.40 (19 H, m, 8 × CH_2, 3 × CH), 4.65 (1 H, d, 1-H), 5.54 (1 H, s, PhC*H*), and 7.25—7.62 (5 H, m, Ph).

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References

1 M. Pietraszkiewicz and J. Jurczak, *J. Chem. Soc., Chem. Commun.*, 1983, 132; M. Pietraszkiewicz, P. Salanski, and J. Jurczak, *ibid.*, 1983, 1184.
2 M. Pietraszkiewicz and J. Jurczak, *Tetrahedron*, 1984, **40**, 2967; M. Pietraszkiewicz, P. Salanski, and J. Jurczak, *ibid.*, 1984, **40**, 2971.
3 P. Bako, L. Fenichel, and L. Toke, *Acta Chim. Acad. Sci. Hung.*, 1984, **115**, 323.
4 G. Toth, W. Dietrich, P. Bako, L. Fenichel, and L. Toke, *Carbohydr. Res.*, 1987, **168**, 141.
5 H. Maeda and Y. Nakatsuji, *J. Chem. Soc., Chem. Commun.*, 1981, 471.
6 R. L. Whistler and M. L. Wolfram, 'Methods in Carbohydrate Chemistry,' vol. I (Academic Press, N.Y., 1963) p. 214.
7 S. S. Moore, T. L. Townowski, M. Newcomb, and D. J. Cram, *J. Am. Chem. Soc.*, 1977, **99**, 9398.

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