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CHIRAL ASYMMETRIC CROWNS INCORPORATING THE 4,6-*O*-BENZYLIDENE DERIVATIVES OF METHYL α-D-MANNOPYRANOSIDE AND METHYL α-D-ALTROPYRANOSIDE. THE INFLUENCE OF STEREOCHEMISTRY UPON COMPLEXATION OF ORGANIC CATIONS

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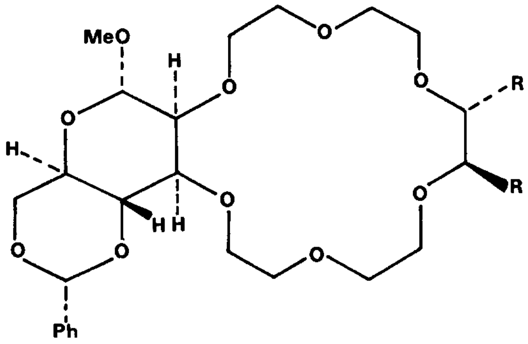
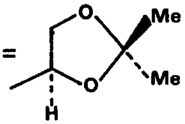
Methyl 4,6-*O*-benzylidene-α- and β-D-gluco-[2] and α- and β-D-galacto-[2]pyranosides are suitable precursors for the synthesis of anancomerically *trans*-fused 18-crown-6 derivatives in which the *gauche* crown oxygens at the ring junctions are diequatorial with respect to the pyranosidic rings. In this communication, we report on the complexing behaviour of *(i)* the anancomerically *cis*-fused 18-crown-6 derivatives α-D-(1) and α-DD-(2) incorporating methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[3] α-D-(4) and *(ii)* the anancomerically *trans*-fused 18-crown-6 derivative α-D-(3) incorporating methyl 4,6-*O*-benzylidene-α-D-altropyranoside[4] α-D-(7). Whereas, at the ring junctions, the α-D-*manno* derivatives α-D-(1) and α-DD-(2) have *gauche* crown oxygens with an axial-equatorial arrangement, the α-D-*altro* derivative α-D-(3) has *anti* crown oxygens with, of course, a diaxial arrangement.

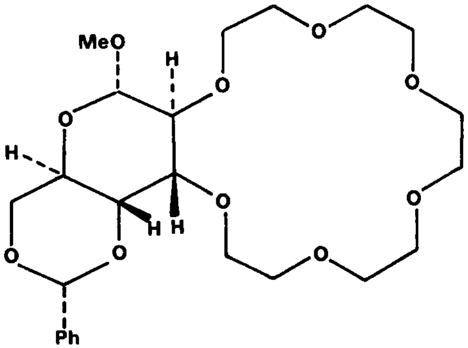
The "half crown" diols α-D-(6) and α-D-(9) obtained from the reaction sequences α-D-4 → α-D-5 → α-D-6[5] and α-D-7 → α-D-8 → α-D-9[6] were condensed (NaH/DMSO) with $Ts(OCH_2CH_2)_3OTs$ (1.1 molar equivs.) to afford, respectively, the α-*manno* α-D-(1), $[\alpha]_D$ + 30.6° (*c* 0.5,$CHCl_3$)[7] and α-D-*altro* α-D-(3), $[\alpha]_D$ + 60.1° (*c* 0.5, $CHCl_3$)[8] 18-crown-6 derivatives.[9] The "half crown" ditosylate[10] D-(11) derived from



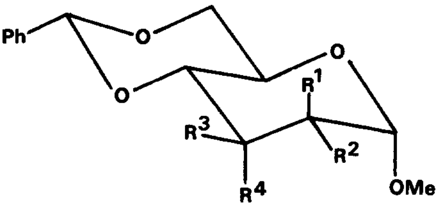
α-D-1 R = H

α-DD-2 R =





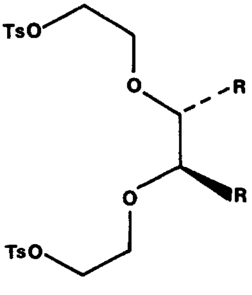
α-D-3



	R^1	R^2	R^3	R^4
α-D-4	OH	H	OH	H
α-D-5	$OCH_2CH{=}CH_2$	H	$OCH_2CH{=}CH_2$	H
α-D-6	OCH_2CH_2OH	H	OCH_2CH_2OH	H
α-D-7	OH	H	H	OH
α-D-8	$OCH_2CH{=}CH_2$	H	H	$OCH_2CH{=}CH_2$
α-D-9	OCH_2CH_2OH	H	H	OCH_2CH_2OH

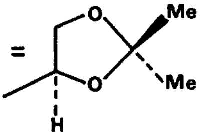
D-mannitol was condensed (NaH/DMSO) with α-D-5 to afford[11] the α-D-*manno-manno*-18-crown-6 derivative α-DD-(2), $[\alpha]_D$ + 24.6° (*c* 0.5, $CHCl_3$).[12]

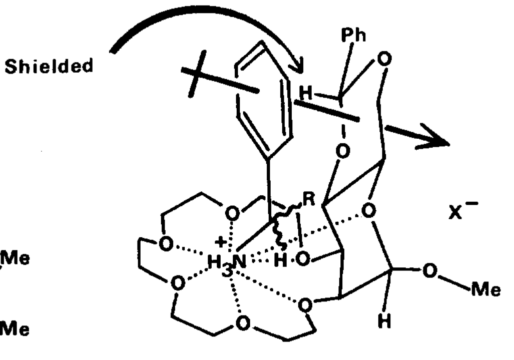
The association constants (K_a) for complexing of α-D-1, α-DD-2, and α-D-3 with $Me_3CNH_3^+SCN^-$ in $CDCl_3$ were estimated[13] to be 39000, 1300, and < 50 M^{-1}, respectively. In CD_2Cl_2, α-D-1 to α-D-3 form 1:1 complexes at +30°C with selected SCN^- and ClO_4^- salts derived from Me_3CNH_2 (12), $PhCH_2NH_2$ (13), and *(R)*- and *(S)*-$PhCHMeNH_2$ *(R)*- and *(S)*-(14) as indicated by the substantial changes in the ^1H n.m.r. spectra of the crowns. In the case of the α-D-*manno* derivatives, the signals for the anomeric H are shifted downfield by 0.23-0.28 p.p.m. on 1:1 complex formation. This dramatic change is accompanied by much smaller downfield shifts for the OCH_3 protons (0.03-0.07 p.p.m.) and significant *upfield* shifts[14] (up to 0.11 p.p.m.) for the benzylidene CH. These observations indicate that the pyranosidic ring oxygens in α-D-1 and α-DD-2 participate along with the six crown oxygens in complex formation. On cooling down to low temperatures (-55 to -95°C), the signals for the benzylidene CH separate (see Table) in all cases into a higher intensity high field signal and a lower intensity low field signal. The signals for the anomeric H in complexes of α-D-1 with 13.HX and *(R)*-14.HSCN separates into a higher intensity low field signal and a lower intensity high field signal.[15] These results suggest that the major complex is associated with the β-face of α-D-1. Support for this assignment comes from inspection of CPK space-filling molecular models which reveals that the phenyl ring in the generalised complex α-D-1-β-$PhCHRNH_3^+X^-$ (R=H or Me) can enter into a stabilising dipole-induced dipole interaction[16] with the 4,6-*O*-benzylidene ring (*cf.* ref 2b). In so doing, the benzylidene CH comes into the shielding zone of the phenyl ring and thus not only can we account for the *upfield* shift of this proton at +30° but we can also explain the emergence (see Table) of the higher intensity signal (for the major β-complex)[16] at high field in the low temperature spectra. The fact that this feature also characterises the low



10 R = H

D-11 R =





α-D-1-β-$PhCHRNH_3^+X^-$

Table. Temperature dependent ^{1}H n.m.r. spectral data and thermodynamic parameters for the 1:1 complexation of selected $RNH_3^+X^-$ salts 12.HSCN, 13.HSCN, 13.$HClO_4$, and *(R)*-14.HSCN and *(S)*-14.HSCN by the chiral asymmetric crowns α-D-1, α-DD-2, and α-D-3[a]

Crown	$RNH_3^+X^-$	R	δ Benzylidene CH at *T*°C Maj	Min	δ Anomeric H at *T*°C Maj	Min	Complex ratio (*T*/°C) Maj : Min	$\Delta G^{\ddagger}_{d}$[b] (Maj → Min) ± 0.3 kcal mol^{-1}
α-D-1	13.HSCN	CH_2Ph	5.54	5.69	5.11	5.05	74 : 26 (-75)	11.1
	13.$HClO_4$	CH_2Ph	5.48	5.68	5.04	4.97	74 : 26 (-60)	13.0
	(R)-14.HSCN	CHMePh	5.58	5.72	5.13	4.90	82 : 18 (-80)	11.2
	(S)-14.HSCN	CHMePh	5.67	5.78	5.10	5.14	82 : 18 (-90)	11.2
α-DD-2	12.HSCN	CMe_3	-	-	5.10	5.90	88 : 12 (-95)	10.3
	13.HSCN	CH_2Ph	5.52	5.85	-	-	93 : 7 (-55)	14.0
	13.$HClO_4$	CH_2Ph	5.46	5.77	-	-	84 : 16 (-45)	14.0
	(R)-14.HSCN	CHMePh	5.68	5.80	-	-	90 : 10 (-80)	11.5
	(S)-14.HSCN	CHMePh	5.59	5.90	-	-	84 : 16 (-80)	12.2
α-D-3	12.HSCN	CMe_3	-	-	(4.78)	(4.87)	50 : 50(-108)	8.3

[a] All spectra were recorded in CD_2Cl_2 at 220 MHz on a Perkin Elmer R34 spectrometer with Me_4Si as "lock" and internal standard.

[b] The free energies of activation ($\Delta G^{\ddagger}_{d}$) for dissociation of the 1:1 complexes formed by α-D-1 and α-DD-2 correspond to values calculated from the Eyring equation using rate constants determined by line shape analysis of the benzylidene CH signal at a temperature close to coalescence in each case. The $\Delta G^{\ddagger}_{d}$ value for the complex α-D-3-12.HSCN was obtained from the rate constant calculated at the coalescence temperature for the anomeric H signal using the standard approximate expression.

temperature ^{1}H n.m.r. spectra of the 1:1 complexes formed between α-DD-2 and $PhCHRNH_3^+X^-$ (R=H or Me) leads us to the conclusion that the major complex involves the β-face here as well.[17] The Table lists the relative populations of the two anisometric complexes and the free energies of activation ($\Delta G^{\ddagger}_{d}$) for dissociation of the major complexes. The $\Delta G^{\ddagger}_{d}$ values of 10.3 and 8.3 kcal mol^{-1} for α-DD-2-12.HSCN and α-D-3-12.HSCN can be compared with values of 4.2 and < 2.3 kcal mol^{-1} respectively for their free energies of complexation ($-\Delta G$).[18] This analysis suggests[19] a free energy of association for these complexes of ca. 6 kcal mol^{-1}. In α-DD-2-12.HSCN, steric factors involving *(i)* perturbation of the "all-*gauche*-O-C-C-O" conformation[20] of the 18-membered ring by the *cis*-fused mannopyranosidic ring and *(ii)* repulsive interactions between the carbohydrate portions of α-DD-2 and the t-butyl group of 12.HSCN mitigate against complexation. In α-D-3-12.HSCN, the conformation of the macrocyclic ring, which must include at least one *anti* O-C-C-O unit, clearly disfavours complex formation.

We draw the following conclusions: *(i)* Stereochemical factors can play a crucial role in determining the thermodynamic and kinetic stabilities of organic cationic complexes of 18-crown-6 derivatives (*cf.* ref 20). *(ii)* Stereochemical factors can lower the rate constants for association of organic cationic complexes considerably below the diffusion-controlled rate observed[21] for complexes of 18-crown-6.

References and Footnotes

1. Address all correspondence to this author at the Corporate Laboratory, Imperial Chemical Industries Ltd., P.O. Box No. 11, The Heath, Runcorn, Cheshire WA7 4QE.
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4. N.K. Richtmeyer, *Methods in Carbohydrate Chemistry*, Ed. R.L. Whistler and M.L. Wolfrom, Vol. I, Academic Press, New York, 1962, p. 107.
5. The diol α-D-(4), when treated with an excess of $CH_2=CHCH_2Br$ and KOH in toluene, gave the diallyl ether α-D-(5), $[\alpha]_D$ + 149° (*c* 0.5, CH_3OH). Ozonolysis of α-D-5 in methanol, followed by borohydride reduction, afforded α-D-6, $[\alpha]_D$ + 19.6° (*c* 0.5, $CHCl_3$).
6. The diol α-D-(7), when treated with an excess of $CH_2=CHCH_2Br$ and KOH in toluene, gave the diallyl ether α-D-(8), $[\alpha]_D$ + 50.8° (*c* 0.5, $CHCl_3$). Ozonolysis of α-D-8 in methanol, followed by borohydride reduction, afforded α-D-9, $[\alpha]_D$ + 67.2° (*c* 0.5, $CHCl_3$).
7. ^1H N.m.r. data (CD_2Cl_2) for α-D-1 : δ 7.52-7.33 (m, 5H, aromatic protons), 5.59 (s, 1H, benzylidene CH), 4.73 (br s, 1H, H-1), 4.26-3.40 (m, 26H, other CH and CH_2 protons), and 3.37 (s, 3H, OCH_3).
8. ^1H N.m.r. data (CD_2Cl_2) for α-D-3 : δ 7.50-7.30 (m, 5H, aromatic protons), 5.54 (s, 1H, benzylidene CH), 4.60 (br s, 1H, H-1), 4.31-3.44 (m, 26H, other CH and CH_2 protons), and 3.35 (s, 3H, OCH_3).
9. α-D-1 and α-D-3 were obtained after chromatography on alumina (ether) and silica (ether-methanol), respectively.
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11. α-DD-2 was obtained in 34% yield after chromatography on silica (ethyl acetate).
12. ^1H N.m.r. data (CD_2Cl_2) for α-DD-2 : δ 7.51-7.31 (m, 5H, aromatic protons), 5.63 (s, 1H, benzylidene CH), 4.73 (br s, 1H, H-1), 4.30-3.25 (m, 31H, other CH and CH_2 protons; s at 3.36, 3H, OCH_3), and 1.37, 1.36, 1.33, and 1.30 (4 x s, 12H, 4 x CH_3).
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14. The only exception to this statement was provided by α-DD-2-*(R)*-14.HSCN where the downfield shift of the benzylidene CH amounted to 0.02 p.p.m.
15. The exception to this statement is provided by the α-D-1-*(S)*-14.HSCN complex (see Table). However, examination of molecular models shows that the methyl group in the cation comes into steric interaction with the pyranosidic ring when the phenyl ring is involved in a secondary binding interaction with the 1,3-dioxan ring (see text).
16. (a) J.E. Anderson, *Tetrahedron Lett.*, 4713 (1965); (b) K.D. Carlson, C.R. Smith, and I.A. Wolff, *Carbohydr. Res.*, **13**, 403 (1970).
17. Although, in the case of the α-DD-2-12.HSCN complex, an unambiguous assignment of major and minor complexes to α- and β- complexes is not possible, we tend to favour associating the major complex with the α-face. The steric interaction of the bulky CMe_3 group with the pyranosidic ring could be responsible for the low field shift of the anomeric H (δ 5.90) in the β-complex.
18. Note that $-\Delta G = RT \ln K_a$.
19. Free energies of association must at best be crude estimates, since K_a and hence $-\Delta G$ values are estimated by a two phase technique in $CDCl_3$ and $\Delta G^{\ddagger}$ values are obtained by a single phase technique in CD_2Cl_2.
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