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COMPLEXATION SELECTIVITY BY CHIRAL ASYMMETRIC CROWNS INCORPORATING THE 4,6-*O*-BENZYLIDENE DERIVATIVES OF METHYL β-D-GLUCOPYRANOSIDE AND METHYL β-D-GALACTOPYRANOSIDE. A SECONDARY ANOMERIC EFFECT?

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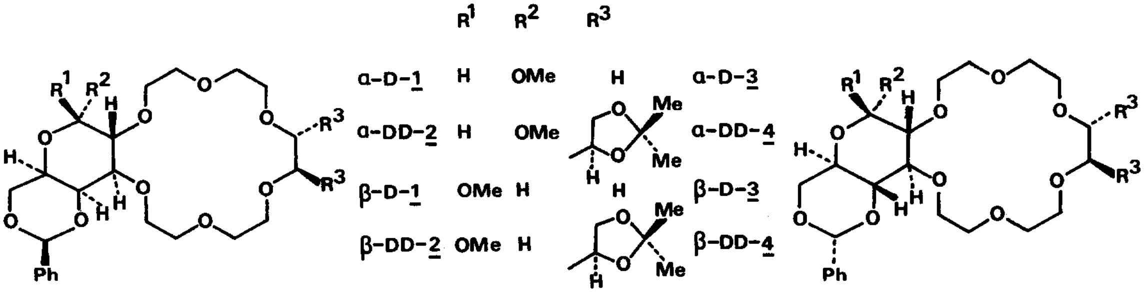
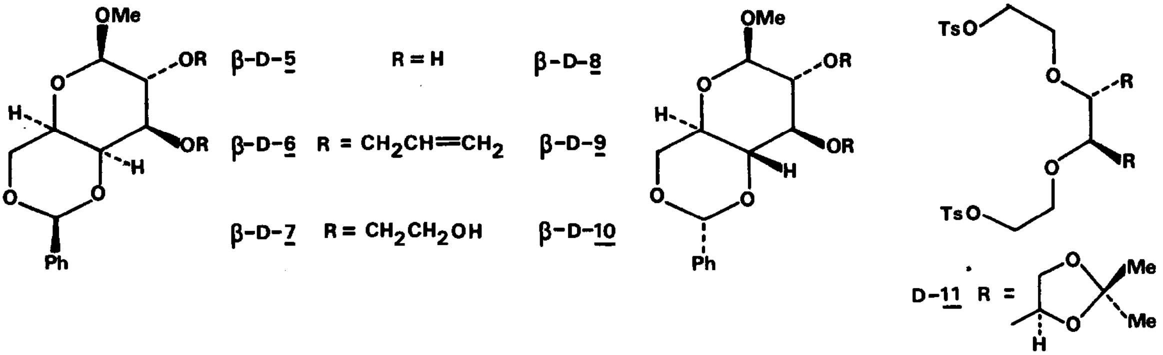
Chiral asymmetric crowns have been derived from the 4,6-*O*-benzylidene derivatives of methyl α-D-gluco-,[2a-c] α-D-galacto-,[2a-c] and α-D-manno-[2c,d] pyranosides. The temperature dependent ^{1}H n.m.r. spectra of the 1:1 complexes formed between the crowns α-D-(1) to α-DD-(4) and $RNH_3^+SCN^-$ salts in CD_2Cl_2 have been interpreted[2b] in terms of equilibria involving anisometric[6] α- and β-complexes of similar strengths in the case of the α-D-*galacto* crowns α-D-(1) and α-DD-(2) where both O-1 (α-complex) and O-4 (β-complex) on the pyranosidic ring participate[2b] along with the six crown oxygens in complex formation. With the α-D-*gluco* crowns α-D-(3) and α-DD-(4), where only O-1 (α-complex) can participate along with the six crown oxygens in complex formation, anisometric[3] α- and β-complexes of dissimilar strengths form with RNH_3^+ ions which contain a phenyl group with the appropriate constitutional disposition within R relative to the NH_3^+ ionic centre. The high selectivity in the complexation of $PhCH_2NH_3^+$ and $PhCHMeNH_3^+$ ions by the heterotopic faces of α-D-3 and α-DD-4 has been ascribed[2b] to a dipole-induced dipole interaction[4] between the 2-phenyl-1,3-dioxan ring in these crowns and the phenyl groups in the RNH_3^+ ions. As a result of this secondary interaction and the involvement of the axial O-1 in primary binding of the NH_3^+ ionic centre, it was of interest to explore the effect of inverting configuration at C-1 in α-D-1 to α-DD-4 on the selectivity of complexation of RNH_3^+ ions. Consequently, the anomers β-D-1 to β-DD-4 have been prepared and their 1:1 complexes in CD_2Cl_2 with selected $RNH_3^+SCN^-$ and $RNH_3^+ClO_4^-$ salts have now been studied by dynamic ^{1}H n.m.r. spectroscopy.

Treatment of methyl 4,6-*O*-benzylidene-β-D-galactopyranoside[5] β-D-(5) with NaH and 1·1 molar equivs. of $Ts(OCH_2CH_2)_5OTs$[6] in DMSO gave the β-D-*galacto*-18-crown-6 derivative β-D-(1), m.p. 141-143°, $[\alpha]_D$ + 30.2° (*c* 0.5, $CHCl_3$)[7] in 20% yield after chromatography on alumina (ether-methanol). By following a similar procedure, the β-D-*gluco*-18-crown-6 derivative β-D-(3), m.p. 78-80°, $[\alpha]_D$-47.0° (*c* 0.5, $CHCl_3$)[8] was obtained from methyl 4,6-*O*-benzylidene-β-D-glucopyranoside[9] β-D-(8) in 46% yield after chromatography on alumina (ether). As in the





β-D-5 R = H β-D-8

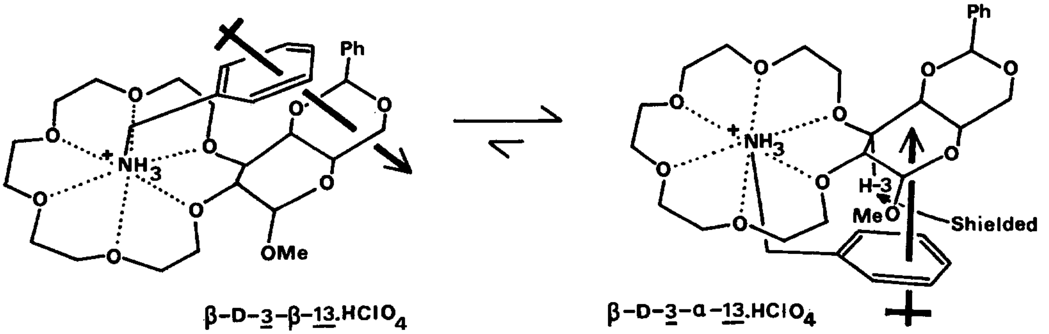
β-D-6 R = $CH_2CH{=}CH_2$ β-D-9

β-D-7 R = CH_2CH_2OH β-D-10

D-11 R =

α-series[2a,b] [*cf.* α-DD-2 and α-DD-4)], the "half crown" bistosylate[10] D-11 derived from D-mannitol was condensed with the "half crown" diols β-D-(7) and β-D-(10) obtained from the reaction sequences β-D-5 → β-D-6 → β-D-7[11] and β-D-8 → β-D-9 → β-D-10[12] to afford, respectively, the β-D-*galacto-manno*-[13] β-DD-(2), $[\alpha]_D$ + 26.5° (*c* 0.5, $CHCl_3$)[14] and the β-D-*gluco-manno*-[15] β-DD-(4), $[\alpha]_D$ - 98.4° (*c* 0.5, $CHCl_3$)[16] 18-crown-6 derivatives.

The association constants (K_a) for complexing of β-D-1, β-DD-2, β-D-3, and β-DD-4 with $Me_3CNH_3^+SCN^-$ in $CDCl_3$ were estimated[17] to be 5800, 4200, 1300, and 1000 M^{-1}, respectively.[18] In CD_2Cl_2, β-D-1 to β-DD-4 form 1:1 complexes 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). Complex formation is accompanied by substantial changes in the ^1H n.m.r. spectra of all these crowns. The spectral behaviour of the β-D-1-13.HSCN complex serves to illustrate the general situation which pertains for the β-*galacto* crowns. At +30°, the signals for the benzylidene CH (δ 5.62), H-1 (δ 4.39), and H-4 (δ 4.52) are shifted markedly downfield compared with their respective chemical shifts[7] in the spectrum of β-D-1. This observation indicates that O-4 participates along with the six crown oxygens in complex formation. On cooling down to -90°, the signals for the benzylidene CH and H-4 each separate into high (δ 5.63 and 4.56, respectively) and low (δ 5.76 and 4.75, respectively) intensity signals. The fact that the lower intensity signals in each case correspond to the lower field signals suggests that the minor complex is associated with the β-face of β-D-1. Thus, the major complex appears, rather unexpectedly, to involve binding to the α-face of β-D-1. The Table shows the generality of this conclusion for complexes of β-D-1 with 13.HX, *(R)*-14.HX, and *(S)*-14.HX and also lists the relative populations of the two complexes and the free energies of activation ($\Delta G_d^\ddagger$) for dissociation of the major complexes in both the *galacto* and *gluco* series. The spectra of the 1:1 complexes involving



β-D-3-β-13.HClO$_4$ β-D-3-α-13.HClO$_4$

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.$HClO_4$, *(R)*-14.HSCN, *(S)*-14.HSCN, and *(S)*-14.$HClO_4$ by the chiral asymmetric crowns β-D-1, β-DD-2, β-D-3, and β-DD-4[a]

Crown	$RNH_3^+X^-$	R	Downfield shift(p.p.m.) of benzylidene CH at +30°	δ Benzylidene CH at -90°		Complex ratio (T/°C) Maj : Min	$\Delta G^{\ddagger}_d$[b] (Maj → Min) ±0.3 kcal mol^{-1}
				Maj	Min		
β-D-1	12.HSCN	CMe_3	0.12	-	-	76 : 24(-100)	10.0
	13.HSCN	CH_2Ph	0.11	5.63	5.76	78 : 22(-90)	12.0
	13.$HClO_4$	CH_2Ph	0.08	5.58	5.70	78 : 22(-70)	10.8
	(R)-14.HSCN	CHMePh	0.10	5.59	5.72	70 : 30(-90)	10.5
	(S)-14.HSCN	CHMePh	0.11	5.65	5.75	87 : 13(-80)	11.7
	(S)-14.$HClO_4$	CHMePh	0.08	5.57	5.70	73 : 27(-90)	10.6
β-DD-2	12.HSCN	CMe_3	0.11	-	-	-	-
	13.HSCN	CH_2Ph	0.12	-	-	-	-
	(S)-14.HSCN	CHMePh	0.12	-	-	-	-
β-D-3	12.HSCN	CMe_3	0.05	-	-	-	-
	13.HSCN	CH_2Ph	0.03	5.54	5.69	78 : 22(-90)	10.2
	13.$HClO_4$	CH_2Ph	0.02	5.54	5.68	68 : 32(-90)	10.6
	(R)-14.HSCN	CHMePh	0.05	5.58	5.66	76 : 24(-100)	10.3
	(S)-14.HSCN	CHMePh	0.02	5.59	5.69	68 : 32(-80)	9.7
	(S)-14.$HClO_4$	CHMePh	0.02	5.57	5.65	76 : 24(-90)	10.2
β-DD-4	13.HSCN	CH_2Ph	0.03	5.62	5.74	86 : 14(-90)	10.8
	(S)-14.HSCN	CHMePh	0.03	5.60	5.69	72 : 28(-90)	10.6

[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 correspond to the average values calculated from the Eyring equation using rate constants determined by line shape analysis of the benzylidene CH signal at two different temperatures in each case.

β-DD-2 did not provide suitable temperature dependent behaviour in their potential ^{1}H n.m.r. probes and so did not afford thermodynamic data. The spectral behaviour of the β-D-3-13.$HClO_4$ complex serves to illustrate the general situation which pertains for the β-D-*gluco* crowns. Although the influence upon the chemical shift of the benzylidene CH on complex formation is much less marked than in the *galacto* series, this ^{1}H n.m.r. probe shows temperature dependence presumably as a result of the dipole-induced dipole interaction present in the β-D-3-β-13.$HClO_4$ complex which no doubt brings the benzylidene CH under the anisotropic influence of the phenyl ring. At -90°, a triplet (*J* = 10 Hz) with a peak area corresponding to *ca.* 0.8 of a proton emerged at high field (δ 2.62) and could be assigned to H-3 in the major complex on the basis of double irradiation studies. Since this shielding of H-3 is characteristic of nearly all the low temperature spectra of 1:1 complexes involving β-D-1 to β-DD-4 and phenyl-containing RNH_3^+ ions, we are led to propose the existence of a stabilising secondary anomeric effect in the α-complexes (*e.g.* β-D-3-α-13.$HClO_4$) which involves the dipole associated with the anomeric region of β-glycosides[19] and an induced dipole in the phenyl ring of appropriate RNH_3^+ ions. It is intriguing to reflect on the possibility that the anomeric effect which destabilises[20] β-glycosides intramolecularly may be a source of stability "intermolecularly" within a complex of a β-glycoside!

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.
2. (a) D.A. Laidler and J.F. Stoddart, *Carbohydr. Res.*, **55**, C1 (1977); (b) *J.C.S. Chem. Comm.*, 481 (1977); (c) W. Hain, R. Lehnert, H. Röttele, and G. Schröder, *Tetrahedron Lett.*, 625 (1978); (d) R.B. Pettman and J.F. Stoddart, *ibid.*, following communication.
3. The term anisometric (K. Mislow, *Bull. Soc. Chim. Belg.*, **86**, 595 (1977)) implies that the complexes are constitutionally isomeric as well as diastereoisomeric.
4. (a) J.E. Anderson, *Tetrahedron Lett.*, 4713 (1965); (b) K.D. Carlson, C.R. Smith, and I.A. Wolff, *Carbohydr. Res.*, **13**, 403 (1970).
5. B. Capon, W.G. Overend, and M. Sobell, *Tetrahedron*, **16**, 106 (1961).
6. D.A. Laidler and J.F. Stoddart, *Tetrahedron Lett.*, preceding communication.
7. ^{1}H N.m.r. data (CD_2Cl_2) for β-D-1 : δ 7.55-7.30 (m, 5H, aromatic protons), 5.52 (s, 1H, benzylidene CH), and 4.32-3.32 (m, 27H, other CH and CH_2 protons; s at 3.54, 3H, OCH_3).
8. ^{1}H N.m.r. data (CD_2Cl_2) for β-D-3 : δ 7.50-7.30 (m, 5H, aromatic protons), 5.52 (s, 1H, benzylidene CH), 4.37-4.26 (d, *J* = 8 Hz, 1H, H-1; q, *J* = 5,10 Hz, 1H, H-6e), 3.95-3.45 (m, 25H, H-3, H-4, H-6e, and CH_2 protons; s at 3.50, 3H, OCH_3), 3.45-3.25 (m, 1H, H-5), and 3.15 (t, *J* = 8 Hz, 1H, H-2). The above assignments were made as a result of homonuclear INDOR spectroscopy as well as by conventional double irradiation experiments.
9. D.S. Mathers and G.J. Robertson, *J. Chem. Soc.*, 696 (1933).
10. W.D. Curtis, D.A. Laidler, J.F. Stoddart, and G.H. Jones, *J.C.S. Perkin 1*, 1756 (1977).
11. The diol β-D-(5), when treated with an excess of CH_2=$CHCH_2Br$ and KOH in toluene, gave the diallyl ether β-D-(6), m.p. 131-132°, $[\alpha]_D$ + 32.7° (*c* 0.5,$CHCl_3$) in 73% yield. Ozonolysis of β-D-6 in methanol, followed by borohydride reduction, afforded (74%) β-D-7, m.p. 150-151°, $[\alpha]_D$ + 32.4° (*c* 0.5, $CHCl_3$).
12. The diol β-D-(8), when treated with an excess of CH_2=$CHCH_2Br$ and KOH in THF, gave the diallyl ether β-D-(9), m.p. 204-206°, $[\alpha]_D$ - 62.2° (*c* 0.5, $CHCl_3$) in 70% yield. Ozonolysis of β-D-9 in methanol, followed by borohydride reduction, afforded (80%) β-D-10, m.p. 112-114°, $[\alpha]_D$ - 64.3° (*c* 0.5, $CHCl_3$).
13. Condensation (NaH/DMSO) of equimolar proportions of β-D-7 and D-11 gave β-DD-12 in 15% yield after medium pressure liquid chromatography on silica (ether-light petroleum, b.p. 60-80°).
14. ^{1}H N.m.r. data (CD_2Cl_2) for β-DD-2 : δ 7.52-7.35 (m, 5H, aromatic protons), 5.51 (s, 1H benzylidene CH), 4.30-3.37 (m, 31H, other CH and CH_2 protons; s at 3.53, 3H, OCH_3), and 1.37, 1.36, 1.32, and 1.30 (4 x s, 12H, 4 x CH_3).
15. Condensation (NaH/DMSO) of equimolar proportions of β-D-10 and D-11 gave β-DD-4 in 43% after chromatography on alumina (ether) and vacuum distillation (b.p. 240° at 0.05 mm Hg).
16. ^{1}H N.m.r. data (CD_2Cl_2) for β-DD-4 : δ 7.50-7.30 (m, 5H, aromatic protons), 5.53 (s, 1H, benzylidene CH), 4.37-3.05 (m, 31H, other CH and CH_2 protons; *s* at 3.50, 3H, OCH_3), and 3.37 and 3.31 (2xs, 12H, 4xCH_3).
17. J.M. Timko, S.S. Moore, D.M. Walba, P.C. Hibberty, and D.J. Cram, *J. Am. Chem. Soc.*, **99**, 4207 (1977).
18. We have commented elsewhere (A.C. Coxon, D.A. Laidler, R.B. Pettman, and J.F. Stoddart, *J. Am. Chem. Soc.*, submitted) on the magnitude of these K_a values in relation to the stereochemistry of the complexes.
19. J.F. Stoddart, Stereochemistry of Carbohydrates, Wiley, New York, 1971, p. 58-87.
20. The acetal group associated with the anomeric centre in the β-D-3-α-13.$HClO_4$ complex is sterically more accessible to the phenyl ring of the $PhCH_2NH_3^+$ ion than is the acetal group of the 1,3-dioxan ring in the β-D-3-β-13.$HClO_4$ complex.

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