#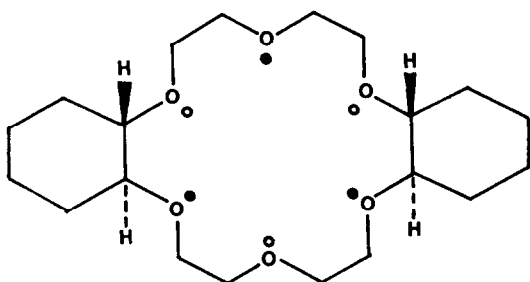 CHIRAL SYMMETRIC CROWNS INCORPORATING THE 4,6-O-BENZYLIDENE DERIVATIVES OF METHYL α-D-GLUCOPYRANOSIDE AND METHYL α-D-GALACTOPYRANOSIDE. A CONFIGURATIONAL IMPEDIMENT TO COMPLEXATION OF ORGANIC CATIONS BY 18-CROWN-6 DERIVATIVES

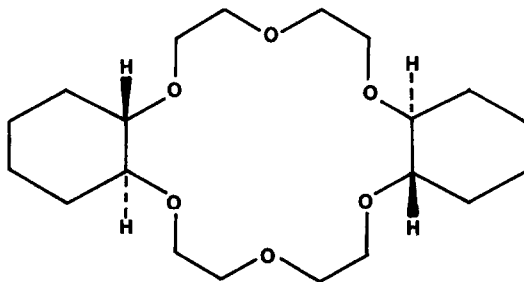Dale A. Laidler, J. Fraser Stoddart[1], and John B. Wolstenholme

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Recently, we have drawn attention[2] to the fact that stereochemical factors can play an important role in determining the relative stabilities of both organic and metal cationic complexes of 18-crown-6 derivatives which incorporate *(i)* two *cis*-fused cyclohexane rings, *(ii)* two *trans*-fused cyclohexane rings, and *(iii)* the methyl glycosides of the 4,6-O-benzylidene derivatives of D-glucose, D-galactose, and D-mannose. Nowhere is the effect illustrated more dramatically in structural terms than with the *trans-cisoid-trans* (1) and *trans-transoid-trans* (2) isomers of dicyclohexano-18-crown-6.[3] Although 1 is free to adopt[4] the desirable "all-*gauche*-OCH$_2$CH$_2$O" conformation, 2 is denied this right because of configurational constraints. The denial to 2 of binding sites which act cooperatively[5] provides[2] an obvious explanation as to why it forms[6] weaker complexes with metal cations than does 1. Unfortunately, we did not investigate the relative binding capacities of 1 and 2 towards RNH$_3^+$ ions in our earlier work.[6] However, the availability[7] of the bis-αα-glycoside-18-crown-6 derivatives[8] 2,3:2',3'-αα-DD-(3), 2,3:3',2'-αα-DD-(4), 2,3:2',3'-αα-DD-(5) and 2,3:3',2-αα-DD-(6) with the *trans-transoid-trans* configuration provides an excellent opportunity to assess the importance of gross stereochemical features upon complexation of *organic* cations.
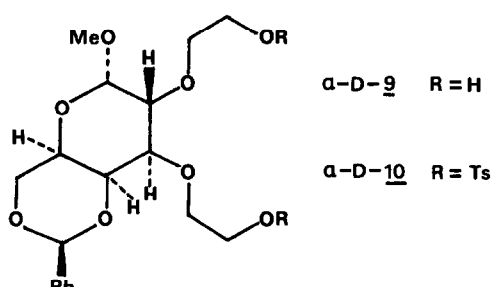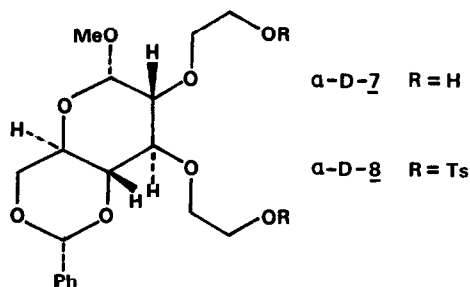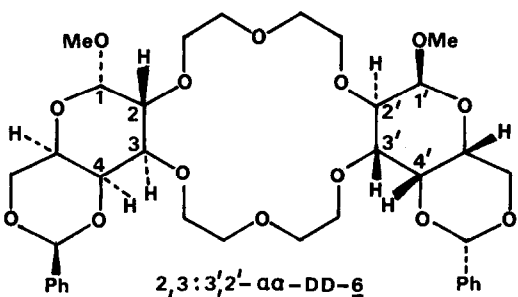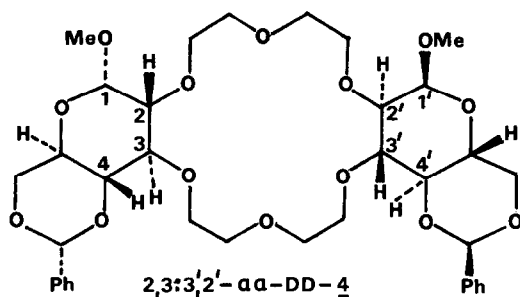
Condensations (NaH/DMSO) of the previously reported[9] diols α-D-(7) and α-D-(9) with their derived ditosylates[10] α-D-(8) and α-D-(10), respectively, gave the *constitutionally isomeric* bisglucosides[11] 2,3:2',3'-αα-DD-3, m.p. 229-230°, [α]$_D$ + 50.2°(c 1.0, CHCl$_3$) and 2,3:3',2'-αα-DD-4, m.p. 233-234°, [α]$_D$ + 36.6°(c 0.78, CHCl$_3$) and the *constitutionally isomeric* bisgalactosides[11] 2,3:2',3'-αα-DD-5, m.p. 238-240°, [α]$_D$ + 164° (c 0.23, CHCl$_3$) and 2,3:3',2'-αα-DD-6, m.p. 167-167.5°, [α]$_D$ + 180° (c 1.18, CHCl$_3$). *Constitutional* assignments to the isomeric compounds isolated from both condensations were made on the basis of dynamic ^{1}H n.m.r. spectroscopy in CD$_2$Cl$_2$ of 1:1 complexes formed with PhCH$_2$NH$_3^+$ClO$_4^-$ (11).HClO$_4$ and

1   2

MeO ... 2,3:2',3'-αα-DD-3

MeO ... 2,3:2',3'-αα-DD-5

2,3:3',2'-αα-DD-4

2,3:3',2'-αα-DD-6

α-D-7   R = H

α-D-8   R = Ts

α-D-9   R = H

α-D-10   R = Ts
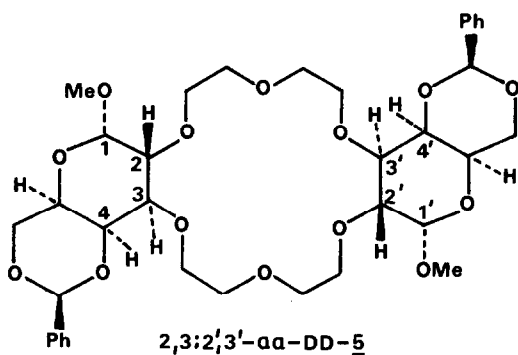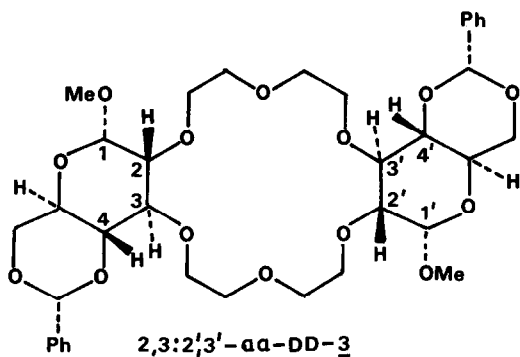
(R)- and (S)-PhCHMeNH₃⁺ClO₄⁻ (R)-, and (S)-(12).HClO₄.   Table 1 reveals that one of each of
the bisglucoside and bisgalactoside crowns forms anisometric[12] α- and β-complexes[13] (i.e. the
complex ratios are *not* 1:1) and so these two isomers can be assigned to 2,3:2',3'-αα-DD-3 and
2,3:2',3'-αα-DD-5, respectively. In each case, the other bisglucoside and bisgalactoside
crowns form (see Table 2) degenerate isometric[12] complexes (i.e. a 1:1 ratio is observed for
certain homotopic [1]H n.m.r. probes in the crown) and so 2,3:3',2'-αα-DD-4 and 2,3:3',2'-αα-
DD-6 can be identified as the constitutional isomers of 2,3:2',3'-αα-DD-3 and 2,3:2',3'-αα-
DD-5, respectively.

On the basis of chemical shift data (Table 1) for the 1:1 complexes (i) at +30° and (ii)
at low temperatures for the benzylidene methine and anomeric protons,[14] we believe that the
major complexes formed with 2,3:2',3'-αα-DD-3 and 2,3:2',3'-αα-DD-5 are associated with the
β-face. Our arguments are similar to those employed previously[13] with the related monoglyco-
side crowns. Moreover, the observations are predictable from an examination of molecular
models through (i) a comparison of the numbers of oxygen atoms at the primary binding sites
and (ii) the presence of secondary binding sites involving the 4,6-O-benzylidene rings in
the bisglucoside crown.

Table 1.   Temperature dependent [1]H n.m.r. spectral data[a] and thermodynamic parameters for 1:1 complexation of the $RNH_3^+ClO_4^-$ salts <u>11</u>.HClO$_4$, (R)-<u>12</u>.HClO$_4$, and (S)-<u>12</u>.HClO$_4$ by the crowns 2,3:2',3'-αα-<u>DD</u>-<u>3</u> and 2,3:2',3'-αα-<u>DD</u>-<u>5</u> with *heterotopic* faces.

Crown	R	δ 2 x Ph C*H*			δ H-1,1'			Complex ratio (T/°C)	$\Delta G_d^\ddagger$ [b]
		at 30°	at T°		at 30°	at T°			(Maj → Min)
			Maj	Min		Maj	Min	Maj:Min	±0.3 kcal mol^{-*}
2,3:2',3'-αα-<u>DD</u>-<u>3</u> [c]	PhCH$_2$	5.56	5.65	5.62	4.87	4.86	5.08	74:26(-100)	10.4
	(R)-PhCHMe	5.55	5.67	5.63	4.89	4.91	5.09	86:14(-105)	11.1
	(S)-PhCHMe	5.57	5.66	5.58	4.91	4.94	5.00	83:17(-105)	9.9
2,3:2',3'-αα-<u>DD</u>-<u>5</u> [d]	PhCH$_2$	5.59	5.74	5.60	5.02	5.06	5.19	62:38 (-70)	12.4
	(R)-PhCHMe	5.61	5.72	5.58	5.01	5.09	5.17	74:26 (-90)	9.9
	(S)-PhCHMe	5.59	5.72	5.60	5.03	5.13	5.17	68:32 (-80)	12.5

[a] All spectra were recorded in CD$_2$Cl$_2$ at 220 MHz on a Perkin Elmer R34 spectrometer with Me$_4$Si as "lock" and internal standard.
[b] The free energies of activation ($\Delta G_d^\ddagger$) for dissociation of the 1:1 complexes correspond to values calculated from the Eyring equation using rate constants determined by line shape analysis of the PhCH signal at a temperature close to coalescence in each case.
[c] Partial [1]H n.m.r. data (CD$_2$Cl$_2$) at +30° : δ 5.51 (s, 2H, 2 x PhC*H*), 4.78 (d, J = 3.5 Hz, 2H, H-1,1'), and 3.37 (s, 6H, 2 x OCH$_3$).
[d] Partial [1]H n.m.r. data (CD$_2$Cl$_2$) at +30° : δ 5.50 (s, 2H, 2 x PhC*H*), 4.88 (d, J = 2.6 Hz, 2H, H-1,1'), 4.30 (m, 2H, H-4,4'), and 3.40 (s, 6H, 2 x OCH$_3$).

Table 2.   Temperature dependent [1]H n.m.r. spectral data[a] and kinetic and thermodynamic parameters for the 1:1 complexes formed between $RNH_3^+ClO_4^-$ salts <u>11</u>.HClO$_4$, (R)-<u>12</u>.HClO$_4$, and (S)-<u>12</u>.HClO$_4$ and the crowns 2,3:3',2'-αα-<u>DD</u>-<u>4</u> and 2,3:3',2'-αα-<u>DD</u>-<u>6</u> with *homotopic* faces.

Crown	R	[1]H N.m.r. probes (δ at 30°)	T_c,°C [b] ±3°	Δυ(°C), ±2° [b]	k_c [b] s^{-1}	$\Delta G_c^\ddagger$, ±0.3 [b,c] kcal mol$^-$
2,3:3',2'-αα-<u>DD</u>-<u>4</u> [d]	PhCH$_2$	H-1,1' (4.88)	-75	86 (-90)	191	9.4
		2 x OCH$_3$ (3.41)	-80	32 (-90)	71	9.4
	(R)-PhCHMe	H-1,1' (4.90)	-77	55 (-90)	122	9.4
		2 x OCH$_3$ (3.42)	-88	18 (-100)	40	9.3
	(S)-PhCHMe	H-1,1' (4.88)	-85	51 (-100)	113	9.1
		2 x OCH$_3$ (3.38)	-92	13 (-100)	29	9.2
2,3:3',2'-αα-<u>DD</u>-<u>6</u> [e]	PhCH$_2$	2 x PhC*H* (5.60)	-34	26 (-90)	58	12.0
		H-1,1' (5.30)	-32	43 (-90)	96	11.8
		H-4,4' (4.48)	-32	37 (-90)	82	11.9
		2 x OCH$_3$ (3.44)	-36	23 (-90)	51	11.9
	(R)-PhCHMe	2 x PhC*H* (5.60)	-73	22 (-90)	49	10.0
		H-1,1' (5.03)	-70	24 (-90)	53	10.1
		H-4,4' (4.48)	-70	26 (-90)	58	10.1
		2 x OCH$_3$ (3.44)	-73	21 (-90)	47	10.0
	(S)-PhCHMe	2 x PhC*H* (5.60)	-78	11.3 (-90)	25	10.0

[a] See footnote a in Table 1.
[b] Abbreviations used are: T_c, coalescence temperature; Δυ, frequency separation of the appropriate [1]H n.m.r. probe with the temperature at which it was measured indicated in parenthesis; k_c, exchange rate constant at T_c calculated from the expression $k_c = \pi\Delta\upsilon/2^{\frac{1}{2}}$; $\Delta G_c^\ddagger$, free energy of activation calculated from the Eyring equation.
[c] The value for $\Delta G_c^\ddagger$ can be equated directly with the free energy of activation ($\Delta G_d^\ddagger$) for dissociation of the 1:1 complexes.
[d] Partial [1]H n.m.r. data (CD$_2$Cl$_2$) at +30° : δ 5.50 (s, 2H, 2 x PhC*H*), 4.79 (d, J = 3.5 Hz, 2H, H-1,1'), and 3.39 (s, 6H, 2 x OCH).
[e] Partial [1]H n.m.r. data (CD$_2$Cl$_2$) at +30° : δ 5.50 (s, 2H, 2 x PhC*H*, 4.89 (d, J = 2.6 Hz, 2H, H-1,1'), 4.26 (m, 2H, H-4,4'), and 3.39 (s, 6H, 2 x OCH$_3$).

Finally and significantly, the K_a values for complexation of 2,3:2',3'-$\alpha\alpha$-DD-3, 2,3:3',2'-$\alpha\alpha$-DD-4, 2,3:2',3'-$\alpha\alpha$-DD-5, and 2,3:3',2'-$\alpha\alpha$-DD-6 by $Me_3CNH_3^+SCN^-$ in $CDCl_3$ were estimated[15] to be <50, <50, 4650, and 5750 M^{-1}, respectively. These results demonstrate convincingly that the configurational constraint— which leads to poor cooperativity of noncovalent bonds at the primary binding site— imposed upon all these crowns has a drastic effect upon their complexing ability towards organic cations. Since $\Delta G_d^\ddagger$ values remain (*cf.* ref. 13) "unchanged" in the 9.1 to 12.5 kcal mol^{-1} range, this observation can only be explained in terms of *very much slower* rates of association of organic cations with 18-crown-6 derivatives when their conformational characteristics are "wrong" for complex formation. The message is clear. The formation of noncovalent bonds is a *highly directional* process.

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.C. Coxon, D.A. Laidler, R.B. Pettman, and J.F. Stoddart, *J.Am.Chem.Soc.*, in press.

3. It has been suggested (P.A.S. Smith, *Aldrichimica Acta*, 10, 30 (1977) that this "more correct trivial" name replaces the older usage of dicyclohexyl-18-crown-6. In addition, IUPAC have recommended (*Pure Appl. Chem.*, 45, 13 (1976)) that the relative configurational descriptors *cisoid* and *transoid* should be employed rather than *syn* and *anti*, respectively, with tricyclic systems such as dicyclohexano-18-crown-6.

4. The "all-*gauche*-OCH_2CH_2O" conformation is illustrated in 1 by a dot and circle notation: the dot (●) indicates "up" oxygens and the circle (o) "down" oxygens.

5. Our earlier observation (A.C. Coxon and J.F. Stoddart, *J.C.S. Perkin 1*, 767 (1977)) that 20-crown-6 derivatives and synthetically-related macrobicyclic polyethers with bridgehead carbon atoms form weak complexes with Na^+, K^+, Rb^+, and Cs^+ chlorides in MeOH can also be explained by lack of cooperativity of binding sites.

6. I.J. Burden, A.C. Coxon, J.F. Stoddart, and C.M. Wheatley, *J.C.S. Perkin 1*, 220 (1977).

7. W. Hain, R. Lehnert, H. Röttele, and G. Schröder, *Tetrahedron Lett.*, 625 (1978).

8. We differentiate isomers as having 2,3:2',3' or 2,3:3',2' *constitutions* depending upon the nature of the two ring junctions with respect to the numbering of the pyranosidic ring proceeding in an anticlockwise fashion around the macroring.

9. D.A. Laidler and J.F. Stoddart, *Carbohydr. Res.*, 55, C1 (1977).

10. The ditosylate α-D-(8) has m.p. 37-41° and $[\alpha]_D$ + 25.6°(c 1.5, $CHCl_3$); the ditosylate α-D-(10) has m.p. 40-42° and $[\alpha]_D$ + 68.1° (c 1.2, $CHCl_3$).

11. The melting points and specific optical rotations agree reasonably well with those in the literature.

12. The "definition" of the terms anisometric and isometric is discussed by K. Mislow, *Bull.Soc.Chim.Belg.*, 86, 595 (1977).

13. Our designation of complexes as α and β has been discussed elsewhere (D.A. Laidler and J.F. Stoddart, *J.C.S. Chem.Comm.*, 481 (1977)).

14. In the case of the bisgalactoside crown 2,3:2',3'-$\alpha\alpha$-DD-5 the chemical shift behaviour of H-4,4' also supports the belief that the β-complex predominates.

15. For the method employed, see J.M. Timko, S.S. Moore, D.M. Walba, P.C. Hibberty, and D.J. Cram, *J.Am.Chem.Soc.*, 99, 4207 (1977).

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