Tetrahedron Letters No. 24, pp 2279 - 2282.
©Pergamon Press Ltd. 1979. Printed in Great Britain.

0040-4039/79/0608-2279$02.00/0

# THE COMPLEXING PROPERTIES OF A CHIRAL 18-CROWN-6 DERIVATIVE INCORPORATING A 2,5-ANHYDRO-D-MANNITOL RESIDUE. A CONSTITUTIONAL AND STEREOCHEMICAL MEANS OF ENHANCING COMPLEXATION

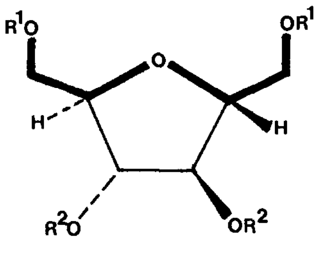
J. Anthony Haslegrave and J. Fraser Stoddart[1]
Department of Chemistry, The University, Sheffield S3 7HF

David J. Thompson
Organics Division, Imperial Chemical Industries Ltd.,
P.O. Box No. 42, Hexagon House, Blackley, Manchester M9 3BA

*Measurements of both a thermodynamic and kinetic nature establish that an 18-crown-6 derivative incorporating a 'chiral diethyleneglycol' unit in the shape of a 2,5-anhydro-D-mannitol residue forms extremely strong complexes with alkali metal, $NH_4^+$, and $RNH_3^+$ ions.*

Our appreciation[2-4] that the stereochemistry of noncovalent interactions in metal and organic cationic complexes of crown compounds plays a crucial role in determining their stabilities has prompted us to try and optimise the complexing ability of chiral 18-crown-6 derivatives containing carbohydrate residues. Examination of framework molecular models indicates that incorporation of a constrained 'diethyleneglycol' fragment in the form of either a *cis*- or *trans*-fused tetrahydrofuranyl-2,5-dimethylyl unit into the 18-crown-6 constitution can lead to improved orientations of oxygen atoms with respect to the bound cation—metal or primary alkylammonium—compared with those observed for complexes of 18-crown-6. Indeed, there is evidence[5] that tetrahydrofurano-18-crown-6 compounds containing one, two, and three fused 5-membered rings—usually obtained and evaluated as diastereoisomeric mixtures—form slightly stronger complexes with $Bu^tNH_3^+SCN^-$ in $CDCl_3$ than does 18-crown-6 itself.[6] Fortunately, there is a readily available source[7] of a 'chiral diethyleneglycol' unit[8] in 2,5-anhydro-D-mannitol D-(1), which can be obtained[9] in two steps from D-glucosamine hydrochloride. In this communication, we describe *(i)* the preparation of the 18-crown-6 derivative D-(2) and report on *(ii)* a preliminary assessment of the binding properties of D-2 towards alkali metal, $NH_4^+$, and $RNH_3^+$ ions.

Treatment (*cf.* ref. 10) of D-1[11] in $Me_2NCHO$ with 2.2 molar equivs. of $Bu^tMe_2SiCl$ in the presence of imidazole (5 molar equivs.) led[12] to a good yield (62%) of the bis-*t*-butyldimethylsilyl ether D-(3), m.p. 40-42°, $[\alpha]_D$ + 19.0° (*c* 0.4, $CHCl_3$) after medium pressure liquid chromatography ($Et_2O$:light petroleum, b.p. 60-80°, 2:1) on $SiO_2$. Methylation



| | $R^1$ | $R^2$ |
|---|---|---|
| D-1 | H | H |
| D-3 | $SiMe_2Bu^t$ | H |
| D-4 | $SiMe_2Bu^t$ | Me |
| D-5 | H | Me |

D-2

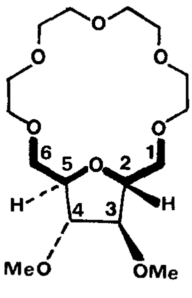


Table 1. The association constants $(K_a)^a$ and derived free energies of complexation $(\Delta G)$ for the formation of 1:1 complexes between D-2 and some selected picrate salts in $CDCl_3$ at 25°C.

| Cation | $Li^+$ | $Na^+$ | $K^+$ | $Rb^+$ | $NH_4^+$ | $MeNH_3^+$ | $Bu^tNH_3^+$ |
|---|---|---|---|---|---|---|---|
| $K_a \times 10^{-6}(M^{-1})$ | 0.075 | 1.30 | 110.0 | 4.90 | 12.0 | 1.60 | 0.25 |
| $\Delta G$(kcal mol$^{-1}$) | -6.6 | -8.3 | -11 | -9.1 | -9.7 | -8.5 | -7.4 |

[a] The $K_a$ values were determined by a u.v. spectroscopic method following extraction of aqueous picrate solutions with $CDCl_3$ solutions of D-2 (see K.E. Koenig, R.C. Helgeson, and D.J. Cram, *J.Amer.Chem.Soc.*, 98, 4018 (1976) and S.S. Moore, T.L. Tarnowski, M. Newcomb, and D.J. Cram, *ibid.*, 99, 6398 (1977)).

(MeI/NaH/THF) of the secondary hydroxyl groups of D-3 gave D-4, $[\alpha]_D$ + 1.0° ($c$ 1.0, $CHCl_3$), as a pure oil in 96% yield after column chromatography (light petroleum, b.p. 60-80° : $Et_2O$, 2:1) on $SiO_2$. The silyl ether protecting groups in D-4 were hydrolysed ($AcOH:H_2O:THF$,3:1:1)[13] affording (95%) 2,5-anhydro-3,4-di-*O*-methyl-D-mannitol D-(5), $[\alpha]_D$ + 55.7° ($c$ 1.0, $CHCl_3$) as an oil after column chromatography (EtOAc) on $SiO_2$. Condensation (NaH/$Me_2SO$) of D-5 with tetraethyleneglycol bistosylate[14] at 45°C gave (19%) the 18-crown-6 derivative D-(2), b.p. 120-122° (0.03 mm), $[\alpha]_D$ + 35.8° ($c$ 0.5, $CHCl_3$), $^1H$ n.m.r. data : $\delta$ ($CD_2Cl_2$) 3.32 (s, 6H, 2 x OMe), 3.45-3.70 (m, all other protons other than the bridgehead protons), and 4.03 (bs, 2H, bridgehead protons).

The association constants $(K_a)$ for 1:1 complex formation between D-2 and selected picrate salts are listed in Table 1. The derived free energies of complexation $(\Delta G)$ indicate that, although the 'all-*gauche*-O-C-C-O' conformation[2] is denied to the macrocyclic ring, D-2 still forms very strong complexes[15] with alkali metal, $NH_4^+$, and $RNH_3^+$ ions. At least two factors—one constitutional and the other stereochemical—probably contribute to this observation. They are *(i)* the increased basicity of tetrahydrofuranyl oxygen atoms[16] over 'ordinary' crown ether oxygen atoms and *(ii)* the increased cooperativity of binding sites—indicated from inspection of molecular models—brought about by incorporation of a *trans*-fused tetrahydrofuranyl residue into the 18-crown-6 constitution. The $C_2$ symmetry which characterises D-2 means that dynamic $^1H$ n.m.r. spectroscopy can be employed[17] to study the kinetics of exchange of $RNH_3^+$ cations between opposite faces of isometric 1:1 complexes.[18] The results of these investigations, which rely upon the temperature dependent behaviour of the signals for H-2 and H-5—and in some cases, for the OMe protons—of D-2-$RNH_3^+X^-$ complexes in $CD_2Cl_2$ are recorded in Table 2. Since the 18-membered ring of D-2 cannot undergo ring inversion, the $\Delta G_c^\ddagger$ values can be equated with the free energies of activation $(\Delta G_d^\ddagger)$ for dissociation of the isometric complexes. Reference to the data listed in Tables 1 and 2 allows the following observations to be made: *(i)* The order of stabilities for the alkali metal cations as their picrate salts is $K^+ > Rb^+ > Na^+ > Li^+$ as expected for an 18-crown-6 derivative. *(ii)* The picrate salts of $RNH_3^+$ cations decrease in stability in the order for R of H > Me > $Bu^t$, a trend which probably reflects the decreasing stabilisation of the complexes through pole pole interactions and hydrogen bonding with the anion as much as the increasing steric bulk of the R group across the series. *(iii)* The kinetic stabilities

Table 2. Temperature dependent $^1$H n.m.r. spectral data and kinetic and thermodynamic parameters for the 1:1 complexes formed between selected $RNH_3^+X^-$ salts and **D**-**2**[a]

| R | X | $^1$H N.m.r. probes | ($\delta$ at 30°) | $T_c$, °C[b] ± 3 | $\Delta\nu$(°C), ±2°[b] | $k_c$ $s^{-1}$ | $\Delta G_c^{\ddagger}$, ±0.3[b] kcal $mol^{-1}$ |
|---|---|---|---|---|---|---|---|
| Me | SCN | H-2,5 | (4.12) | -80 | 59 (-95) | 131 | 9.3 |
| Me | $ClO_4$ | H-2,5 | (4.10) | -82 | 58 (-95) | 129 | 9.2 |
| Et | $ClO_4$ | H-2,5 | (4.11) | -62 | 53 (-80) | 118 | 10.2 |
| $Pr^i$ | SCN | H-2,5 | (4.05) | -55 | 54 (-90) | 120 | 10.5 |
| | | 2 x OMe | (3.33) | -75 | 8 (-85) | 18 | 9.9 |
| $Pr^i$ | $ClO_4$ | H-2,5 | (4.12) | 0 | 40 (-28) | 89 | 13.5 |
| | | 2 x OMe | (3.36) | -25 | 9 (-30) | 20 | 13.1 |
| $Bu^t$ | SCN | H-2,5 | (4.15) | -35 | 66 (-60) | 147 | 11.5 |
| | | 2 x OMe | (3.38) | -50 | 13 (-60) | 29 | 11.4 |
| $Bu^t$ | $ClO_4$ | H-2,5 | (4.15) | -15 | 61 (-70) | 135 | 12.5 |
| | | 2 x OMe | (3.38) | -40 | 10 (-50) | 22 | 12.1 |
| $PhCH_2$ | SCN | H-2,5 | (4.06) | -50 | 81 (-80) | 179 | 10.6 |
| $PhCH_2$ | $ClO_4$ | H-2,5 | (4.08) | -20 | 52 (-40) | 116 | 12.3 |
| *(R)*-PhCHMe | SCN | H-2,5 | (4.10) | -50 | 66 (-80) | 147 | 10.0 |
| *(R)*-PhCHMe | $ClO_4$ | H-2,5 | (4.10) | -54 | 62 (-80) | 138 | 10.5 |
| *(S)*-PhCHMe | SCN | H-2,5 | (4.08) | -54 | 57 (-70) | 126 | 10.6 |
| *(S)*-PhCHMe | $ClO_4$ | H-2,5 | (4.05) | -55 | 61 (-90) | 135 | 10.5 |

[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] Abbreviations used are: $T_c$, coalescence temperature; $\Delta\nu$, 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 $k_c = \pi\Delta\nu/2^{\frac{1}{2}}$; $\Delta G_c^{\ddagger}$, free energy of activation calculated from the Eyring equation.

of the $SCN^-$ and $ClO_4^-$ salts depend upon the nature of the cation and the sequence for R of $Pr^i > Bu^t > PhCH_2 >$ *(R)*-PhCHMe $\simeq$ *(S)*-PhCHMe $\simeq$ Et > Me holds more or less in accordance with previous observations[19-21] on other crown compounds. *(iv)* Complexes involving $ClO_4^-$ salts are generally[20,21] more stable kinetically than those involving $SCN^-$ salts, although $MeNH_3^+X^-$ and *(S)*-$PhCHMeNH_3^+X^-$ provide exceptions.[22]

The following conclusions can be drawn: *(i)* Complexation of cations by 18-crown-6 derivatives can be enhanced by constitutional and stereochemical means. *(ii)* Differences in $\Delta G$ values are *not* necessarily reflected in differences in $\Delta G_d^{\ddagger}$ values, *i.e.* the free energies of association can vary depending upon the nature of the crown (*cf.* ref. 3) *and* the cation.[23] *(iii)* The nature of the cation *can* influence the relative kinetic complexing strengths of complexes associated with different anions.[22]

## 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. Amer Chem. Soc.*, **100**, 8260 (1978)
3. R.B. Pettman and J.F. Stoddart, *Tetrahedron Lett.*, 461 (1979).
4. D.A. Laidler, J.F. Stoddart, and J.B. Wolstenholme, *Tetrahedron Lett.*, 465 (1979).
5. J.M. Timko, S.S. Moore, D.M. Walba, P.C. Hiberty, and D.J. Cram, *J. Amer Chem. Soc.*, **99**, 4207 (1977).

6. It has not escaped our attention that tetrahydrofuranyl units are encountered commonly in naturally-occurring ionophores.

7. Dr. R.A. Wall of Edinburgh University extolled the virtues of this source of chirality to us in April, 1977.

8. The 'chiral diethyleneglycol' unit in D-1 to D-5 is indicated by means of thickened bonds in the formulae.

9. B.C. Bera, A.B. Foster, and M. Stacey, *J. Chem. Soc.*, 4531 (1956).

10. E.J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, 94, 6190 (1972).

11. D-1 is most readily purified by converting ($Ac_2O$/pyridine) it to its tetraacetate, $[\alpha]_D$ + 33.0° (*c* 1.12, $CHCl_3$) (R.U. Lemieux and B. Fraser-Reid, *Canad. J. Chem.*, 42, 547 (1964) report $[\alpha]_D$ + 27.3 (*c* 4.2, $CHCl_3$)) and subjecting it to medium pressure liquid chromatography (light petroleum, b.p. 60-80° : EtOAc, 3:1) on $SiO_2$ before regenerating (NaOMe/MeOH) D-1.

12. The compositions of all new compounds were confirmed by elemental analysis. Structural assignments were based upon the results of mass spectrometry and $^1H$ n.m.r. spectroscopic evidence.

13. See footnote 9 in ref. 10.

14. J. Dale and P.O. Kristiansen, *Acta. Chem. Scand.*, 26, 1471 (1972).

15. By way of comparison, the $K_a \times 10^{-6}$ values for the 1:1 complexes formed between methyl 4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido[2,3-*b*][1,4,7,10,13,16]hexaoxacyclooctadecane (R.B. Pettman and J.F. Stoddart, *Tetrahedron Lett.*, 457 (1979)) and the picrates of $Li^+$, $Na^+$, $K^+$, $Rb^+$, $NH_4^+$, $MeNH_3^+$, and $Bu^tNH_3^+$ in $CDCl_3$ are (R.B. Pettman and J.F. Stoddart, unpublished results) 0.073, 0.13, 0.53, 0.22, 0.24, 0.011, and 0.002 $M^{-1}$ respectively.

16. E.M. Arnett, *Prog. Phys. Org. Chem.*, 1, 223 (1963); S. Searles Jr. and M. Tamres, "The Chemistry of the Ether Linkage", ed. S. Patai, Wiley-Interscience, London, 1967, Chapter 6, p. 243; A.H. Haines, "Cyclic Ethers" in Barton and Ollis's Comprehensive Organic Chemistry, Volume 1, ed. J.F. Stoddart, Pergamon Press, Oxford, 1979, Part 4.4, p. 853.

17. J.F. Stoddart, *Chem. Soc. Revs.*, in press.

18. K. Mislow, *Bull. Soc. Chim. Belg.*, 86, 595 (1977).

19. L.C. Hodgkinson, S.J. Leigh, and I.O. Sutherland, *J.C.S. Chem. Comm.*, 639 (1976).

20. J.C. Metcalfe, J.F. Stoddart, and G. Jones, *J. Amer Chem. Soc.*, 99, 8317 (1977); D.A. Laidler and J.F. Stoddart, *Tetrahedron Lett.*, 453 (1979).

21. F. de Jong, D.N. Reinhoudt, and G.J. Torny, *Tetrahedron Lett.*, 911 (1979).

22. In the case of the D-2-$MeNH_3^+X^-$ complexes, it is conceivable that $X^-$ ions—and $SCN^-$ ions in particular—can hydrogen bond to the acidic Me group rather than compete with the crown ether oxygens for hydrogen bonding to the $NH_3^+$ centre. Thus, we caution against any generality for the recent claim (see ref. 21) that 'the structure of the cation has little effect on the relative complex stabilities for different anions.'

23. Inspection of the relevant data in Tables 1 and 2 reveals that although the $MeNH_3^+$ cation forms a stronger complex with D-2 under equilibrium conditions than does the $Bu^tNH_3^+$ cation, the $MeNH_3^+$ cationic complexes are kinetically much less stable than the $Bu^tNH_3^+$ cationic complexes. Despite the fact that an anion effect cannot be discounted as the source of at least a partial explanation for this observation, it seems likely that the *differences* in $\Delta G$ values are not always reflected (*cf.* ref. 21) in *differences* in $\Delta G^{\ddagger}_{d}$ values when the cations are markedly *different* in constitution.

(Received in UK 30 March 1979)