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THE COMPLEXING PROPERTIES OF CHIRAL CROWN ETHERS INCORPORATING 1,3:4,6-DI-*O*-METHYLENE-D-MANNITOL RESIDUES. A SECONDARY DIPOLE-INDUCED DIPOLE INTERACTION.

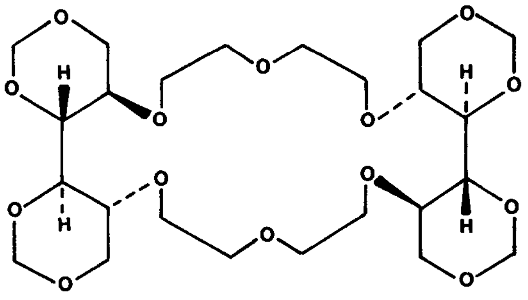
Dale A. Laidler and J. Fraser Stoddart[1]

Department of Chemistry, The University, Sheffield S3 7HF

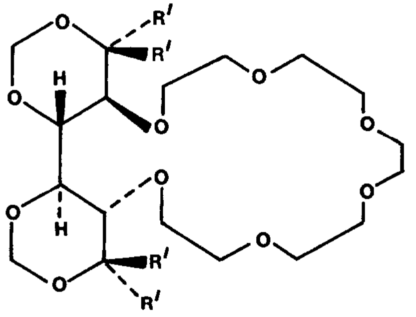
Chiral crown ethers constructed around binaphthol,[2] tartaric acid,[3] and carbohydrates[4] as sources of chirality have been shown to complex with RNH_3^+ ions and, in some cases, to exhibit chiral recognition towards racemic salts. In addition, high stereoselectivity in the complexation of $PhCH_2NH_3^+$ and $PhCHMeNH_3^+$ ions by the diastereotopic faces of chiral asymmetric crown ethers incorporating methyl 4,6-*O*-benzylidene-α-D-glucopyranoside residues has been uncovered.[4b,c] This observation has been ascribed[4c] tentatively to a secondary interaction of a dipole-induced dipole type between the 2-phenyl-1,3-dioxan ring in the crowns and the phenyl groups in the cations. These results suggested to us that the 22-crown-6 DD-(1) and 20-crown-6 D-(2) derivatives derived from 1,3:4,6-di-*O*-methylene-D-mannitol[5] D-(3) might show interesting binding properties with RNH_3^+ ions containing phenyl groups. Moreover, examination of CPK molecular models indicates that DD-1 and D-2 would not be too different topologically from the corresponding *(RR)*-bis(binaphtho)-22-crown-6 and *(R)*-binaphtho-20-crown-6 derivatives synthesized and investigated in considerable detail by Cram.[2a,b]

DD-1, m.p. 192-193°C, $[\alpha]_D$-107.6° (*c* 0.85, $CHCl_3$), was obtained[6] (15%) after chromatography ($CHCl_3$) on Al_2O_3 of the products resulting from reaction between D-3, $Ts(OCH_2CH_2)_2OTs$, and Me_3COK in THF under reflux for 8 h. Condensation between D-3 and $Ts(OCH_2CH_2)_5OTs$ in the presence of NaH in Me_2SO at 50-55°C for 18 h afforded 34% of D-2, b.p. 207°C at 0.01 mm Hg, $[\alpha]_D$-55.4° (*c* 1.46, $CHCl_3$), ^1H n.m.r. data: δ (CD_2Cl_2) : 3.38 (2H, t, *J*=10.5 Hz, H-1a, 6a), 4.30 (2H, q, *J*=5.0, 10.5 Hz, H-1e,6e) and 4.58 and 4.98 (4H, AB system, J_{AB}=6.1 Hz, OCH_2O) after m.p.l.c. (Et_2O:MeOH, 95:5) on SiO_2 of the products isolated from the reaction mixture.

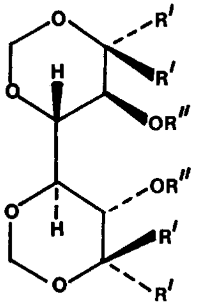
Whereas DD-1 forms exceedingly weak complexes with $RNH_3^+X^-$ salts in $CDCl_3$, D-2 binds[7] reasonably strongly with SCN^- and ClO_4^- salts derived from $MeNH_2$ (4), Me_2CHNH_2 (5), Me_3CNH_2



DD-1

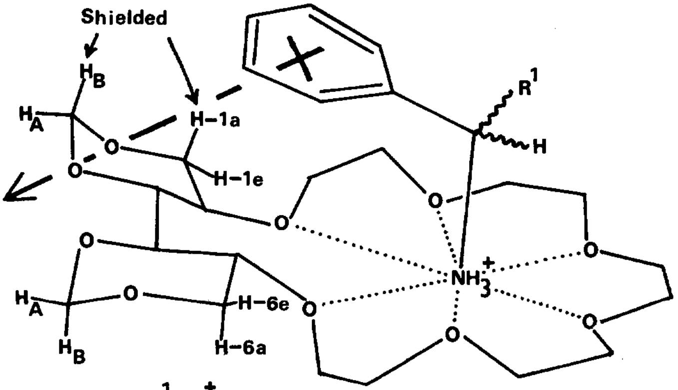


D-2, R'=H   D-2-d$_4$, R'= D



D-3, R' = H, R'' = H

D-3-d$_4$, R' = D, R'' = H



D-2-PhCHR^{1}NH$_3^+$

(6), PhCH$_2$NH$_2$ (7), *(R)*- and *(S)*-PhCHMeNH$_2$ *(R)*- and *(S)*-(8), *(R)*-PhCHCO$_2$MeNH$_2$ *(R)*-(9), and *(R)*- and *(S)*-PhCH$_2$CHCO$_2$MeNH$_2$ *(R)*- and *(S)*-(10). The association constants for complexing of DD-1 and D-2 with Me$_3$CNH$_3^+$SCN$^-$ in CDCl$_3$ were estimated[8] to be <50 and 520 M^{-1}, respectively. In addition, CD$_2$Cl$_2$ solutions of DD-1 were almost incapable of solubilising RNH$_3^+$SCN$^-$ and ClO$_4^-$ salts whereas 1:1 complexes were formed readily between D-2 and salts of 4 to *(S)*-10 as indicated by the substantial changes in the ^{1}H n.m.r. spectra of the crown. The previously enantiotopic methylene protons in 7.HClO$_4$ become[9] diastereotopic in the chiral complex as demonstrated by their appearance as an AB system (δ_A 4.20, δ_B 4.14, J_{AB} = 15 Hz). As the temperature of the CD$_2$Cl$_2$ solution is lowered, all signals exhibit line broadening and the line shape behaviour of the AB system for the OCH$_2$O protons is particularly significant. Below 0°C, the B part—which is assigned[10] to the axial protons—becomes very broad and eventually by -80°C separates out into two signals of equal intensity centered on δ 4.74 and 4.45. The coalescence temperature associated with this spectral change is -55°C. The A part—which is assigned[10] to the equatorial protons—shows a similar kind of behaviour but with a lower coalescence temperature of -65°C and a smaller chemical shift difference (18 Hz) at -80°C. These spectral changes, which are both associated with a value for $\Delta G_c^{\ddagger}$ of 10.5 kcal mol^{-1}, may be interpreted in terms of exchange of cations between the homotopic faces of D-2. The kinetic and thermodynamic data for this and other 1:1 complexes are summarized in the Table. Since the 20-membered ring in the crown cannot undergo ring inversion,[11] the $\Delta G_c^{\ddagger}$ values can be equated with the free energies of activation ($\Delta G_d^{\ddagger}$) for dissociation of the complexes. Four observations[12] can be made: *(i)* Complexes involving MeNH$_3^+$ ions are the weakest of all. This difference could arise from the relative lack of shielding of the RNH$_3^+$ ion, and hence its availability for ion pairing with the anion when the alkyl group is small in a relatively accessible complex. *(ii)* Complexes involving ClO$_4^-$ salts are stronger (0.8-1.8 kcal mol^{-1}) than those involving SCN$^-$ salts. This difference probably reflects the fact that SCN$^-$ ions are more efficient at "de-structuring" complexes than are ClO$_4^-$ ions. *(iii)* The difference (0.5 kcal mol^{-1}) in $\Delta G_d^{\ddagger}$ values for D-2-*(R)*-10.HClO$_4$ and D-2-*(S)*-10.HClO$_4$ indicates modest chiral recognition of *(RS)*-PhCH$_2$CHCO$_2$MeNH$_3^+$ClO$_4^-$ in favour of the *(S)*-isomer by D-2 at low temperatures. *(iv)* Complexes involving cations which contain phenyl groups are stronger (*ca.* 1 kcal mol^{-1}) than those involving cations which lack a phenyl group. This effect is evident in the more highly structured complexes involving ClO$_4^-$ ions. We put forward the hypothesis that this enhanced binding finds its origin in a secondary interaction between the

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

$RNH_3^+X^-$	R	^{1}H N.m.r. probes[b]	T_c, °C ±3°	$\Delta\nu$(°C), ±2 Hz	k_c s^{-1}	$\Delta G_c^\ddagger$, ±0.3 kcal mol^{-1}
4.HSCN	Me	$OC\mathit{H}_A\mathit{H}_BO$	<-110	--	--	<8.2
4.$HClO_4$	Me	$OC\mathit{H}_A\mathit{H}_BO$	<-110	--	--	<8.2
5.HSCN	$CHMe_2$	$OCH_A\mathit{H}_BO$	- 95	22(-100)[c]	49	8.9
5.$HClO_4$	$CHMe_2$	$OCH_A\mathit{H}_BO$	- 80	17(-90)[d]	38	9.7
6.HSCN	CMe_3	$OC\mathit{H}_A\mathit{H}_BO$	<-110	--	--	<8.2
6.$HClO_4$	CMe_3	$OCH_A\mathit{H}_BO$	- 91	15(-100)[e]	33	9.2
7.HSCN	CH_2Ph	$OCH_A\mathit{H}_BO$	- 90	54(-100)[f,m]	120	8.8
7.$HClO_4$	CH_2Ph	$OC\mathit{H}_AH_BO$	- 65	18(-80)[g]	38	10.5
		$OCH_A\mathit{H}_BO$	- 55	64(-80)[h,m]	142	10.5
(R)-8.HSCN	CHMePh	$OC\mathit{H}_A\mathit{H}_BO$	<- 90	--	--	<9.3
(S)-8.HSCN	CHMePh	$OC\mathit{H}_A\mathit{H}_BO$	<-100	--	--	<8.8
(S)-8.$HClO_4$	CHMePh	$OC\mathit{H}_AH_BO$	- 75	20(-90)[i]	44	9.9
		$OCH_A\mathit{H}_BO$	- 65	44(-90)	98	10.1
(R)-9.$HClO_4$	$PhCHCO_2Me$	$OC\mathit{H}_AH_BO$	<- 90	--	--	<9.3
(R)-10.$HClO_4$	$PhCH_2CHCO_2Me$	$OCH_A\mathit{H}_BO$	- 72	32(-90)[k]	71	9.9
(S)-10.$HClO_4$	$PhCH_2CHCO_2Me$	$OCH_A\mathit{H}_BO$	- 60	46(-90)[l]	102	10.4

[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. Abbreviations used are: T_c, coalescence temperature; $\Delta\nu$, frequency separation for 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 $k_c = \pi\Delta\nu/2^{\frac{1}{2}}$ (I.O. Sutherland, *Annu. Rep. NMR Spectrosc.*, 4, 71 (1971)); $\Delta G_c^\ddagger$, free energy of activation at T_c calculated from the Eyring equation.

[b] In all cases exchange of protons (indicated by italics) between two equally populated sites C and D is observed. If the sites that represent two time-averaged signals are designated CD, the spectral changes can all be described as CD → C_2.

[c] δ_C 4.84 and δ_D 4.74. [d] δ_C 4.73 and δ_D 4.65. [e] δ_C 4.71 and δ_D 4.64

[f] δ_C 4.70 and δ_D 4.45 [g] δ_C 4.73 and δ_D 4.94. [h] δ_C 4.74 and δ_D 4.45

[i] δ_C 5.07 and δ_D 4.98 [j] δ_C 4.67 and δ_D 4.47 [k] δ_C 4.81 and δ_D 4.68

[l] δ_C 4.86 and δ_D 4.65

[m] Note that the D signal is shifted to especially high field in these complexes. This suggests a shielding influence by the phenyl group in the cation upon one of the axial OCH_2O protons in D-2.

1,3-dioxan rings in D-2 and a phenyl group in the cation. In the idealized three-point binding model of a face-to-face complex between D-2 and a generalized RNH_3^+ ion of the type $PhCHR^1NH_3^+$ (R^1 = H, Me, or CO_2Me), it is possible for the phenyl group to orient itself over one of the 1,3-dioxan rings of D-2 so as to meet the directional requirements for a dipole-induced dipole interaction[13] as shown in D-2-$PhCHR^1NH_3^+$. Support for this proposal comes from two observations in the low temperature ^{1}H n.m.r. spectra: *(i)* The chemical shift differences ($\Delta\nu$) for H_B are larger for D-2-7.HX and D-2-*(S)*-8.$HClO_4$ which contain a phenyl group, than they are for D-2-5.HX and D-2-6.HX where R is Me_2CH and Me_3C, respectively. Clearly, the anisotropy of a phenyl group is being sensed preferentially by the axial OCH_2O proton on one of the 1,3-dioxan rings. *(ii)* A signal which integrates for *one* proton emerges at high field between δ 2.50 and 3.00 in D-2-7.$HClO_4$, D-2-*(S)*-8.$HClO_4$, and D-2-*(S)*-9.$HClO_4$ - but not in the corresponding SCN^- complexes - and it can be assigned to H-1a on the basis of the following evidence. When the tetradeuterio-20-crown-6 derivative D-2-d_4 was prepared in analogous fashion to that described for D-2 from D-[1,1,6,6-$^2H_4$]mannitol D-3-d_4 and $Ts(OCH_2CH_2)_5OTs$, and the low temperature spectra recorded, this signal was absent in these complexes. Thus, H-1a would appear to fall within the shielding zone of the phenyl group interacting with the 1,3-dioxan ring as shown in D-2-$PhCHR^1NH_3^+$. It is significant that this effect is absent in the less highly structured SCN^- complexes and also in the constitutionally different (one extra CH_2 group) $PhCH_2CHCO_2MeNH_3^+ClO_4^-$ complexes, D-2-*(R)*- and D-2-*(S)*-10.$HClO_4$.

References and Footnotes

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6. Both DD-1 and D-2 and all of the salts derived from the primary alkylamines 4 to *(S)*-8 and the amino acid methyl esters *(S)*-9 and *(R)*- and *(S)*-10 gave satisfactory results (C and H analysis were within 0.3% of theory) for their elemental analyses. Molecular ions were obtained in the mass spectra of DD-1 and D-2 and both compounds were also synthesized by another route.
7. The binaphtho-20-crown-6 (II) also forms (ref.2a) stronger complexes than the bis(binaphtho)-22-crown-6 (I) with $Me_3CNH_3^+SCN^-$ in $CDCl_3$. Somewhat surprisingly, however, the complexes formed by DD-1 and D-2 are less stable than those formed by I and II, respectively. Although more basic oxygens replace aryl ones in DD-1 and D-2 inspection of CPK space filling molecular models of the complexes indicates that the binding sites are less "compact" in DD-1 and D-2 than they are in I and II. This is a consequence of the *stereochemical differences* between the two systems.
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9. Similar behaviour was observed for D-2-5.HSCN and D-2-5.$HClO_4$ where the previously enantiotopic methyl groups in 5.HX become diastereotopic as demonstrated by the appearance of two overlapping doublets in the spectra of the chiral complexes.
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11. Compare with the situation discussed in ref. 4c for rigid 18-crown-6 derivatives.
12. These observations are made on the assumption that the free energies of the transition states for complexes dissociating are characterized largely by the nature of the uncomplexed crown and hence variations in $\Delta G_d^{\ddagger}$ values reflect differences in the ground state free energies of the complexes.
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