Stereoselectivity in Complexation of Primary Alkylammonium Cations by the Diastereotopic Faces of Chiral Asymmetric Crowns

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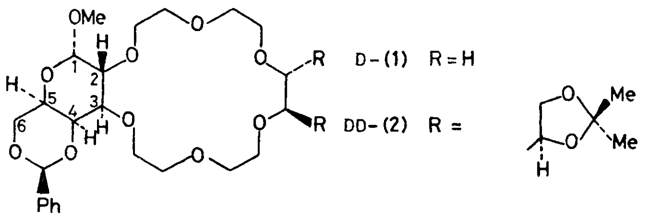
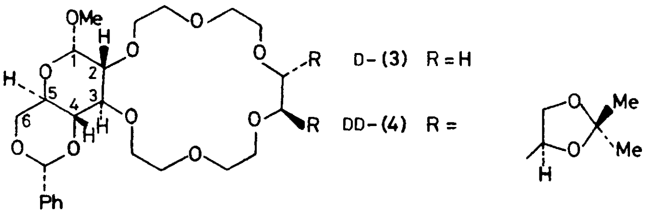
Summary The temperature-dependent ^{1}H n.m.r. spectra of the 1:1 complexes formed between crowns D-(**1**), DD-(**2**), D-(**3**), and DD-(**4**) and primary alkylammonium cations in solution are interpreted in terms of equilibria involving diastereoisomeric complexes of (i) similar strengths in the case of the *galacto*-crowns D-(**1**) and DD-(**2**) and (ii) dissimilar strengths in the case of the *gluco*-crowns D-(**3**) and DD-(**4**) where a secondary interaction of a dipole-induced dipole type appears to be responsible for the stereoselectivity.

Recently, we reported[1] on the synthesis of the chiral asymmetric crowns D-(**1**), DD-(**2**), D-(**3**), and DD-(**4**) incorporating either D-glucose or D-galactose residues as the source of their asymmetry. We now discuss the ability of these crowns to form diastereoisomeric complexes with primary alkylammonium salts in more detail.

The values of the stability constants (K_a) for complexation of $Bu^tNH_3^+SCN^-$ (**5**).HSCN and $PhCH_2NH_3^+SCN^-$ (**6**).HSCN with D-(**1**), DD-(**2**), D-(**3**), and DD-(**4**) in $CDCl_3$ are recorded in the Table. We have already commented[1] on the expected decrease in the strengths of the complexes which arise from disubstitution of D-(**1**) and D-(**3**) with bulky 2,2-dimethyl-1,3-dioxolanyl groups affording DD-(**2**) and DD-(**4**), respectively. Also, the formation of stronger complexes between all four crowns and the less sterically demanding $PhCH_2NH_3^+$ cations was not unexpected on the basis of previous comparisons[2–5] between the complexing powers of $Bu^tNH_3^+SCN^-$ and $PhCH_2NH_3^+SCN^-$ with chiral symmetrical crowns. However, two features in relation to the K_a values in the Table were surprising. (i) All four crowns form much weaker complexes with $Bu^tNH_3^+SCN^-$ than does 18-crown-6 (K_a, 750,000)[6] itself. While ring inversion can occur in the symmetrical 'all-*gauche*-OCH_2-CH_2O' conformation of 18-crown-6 in the complex, this conformational change is denied to complexes involving D-(**1**), DD-(**2**), D-(**3**), and DD-(**4**) as a result of the *trans*-fusions of the macrocyclic polyether rings to C-2 and C-3 of the pyranosidic rings. Thus, it would appear that 'rigid' 18-crown-6 derivatives form weak complexes, whereas 'flexible' 18-crown-6 derivatives form more dynamic and apparently stronger complexes. (ii) Despite the fact that one face of the *galacto*-crowns is more sterically hindered on account of the *cis* ring junction at C-4 and C-5 between the pyranosidic and 2-phenyl-1,3-dioxanyl rings, D-(**1**) and DD-(**2**) form much stronger complexes than do the *gluco*-crowns D-(**3**) and DD-(**4**). The clue to the reasons for this unexpected observation comes from an investigation of the chemical shift changes experienced by protons in the *galacto* and *gluco* portions of the crowns on stepwise additions of salts (*cf.* ref. 7). For example, the chemical shifts of H-1, H-4, and PhC*H* in D-(**1**) attain their limiting values (see Figure 1) at a 1 : 1 molar ratio of D-(**1**) : $Bu^tNH_3^+SCN^-$. Not only is this evidence for 1 : 1 complex formation, but it also suggests that O-1 and O-4 participate with the ether oxygens of the macrocycle in hydrogen bonding and/or electrostatic stabilisation with the ammonium hydrogens of the $Bu^tNH_3^+$ cations in distorted face-to-face complexes (see Figure 1).





Crowns D-(**1**), DD-(**2**), D-(**3**), and DD-(**4**) all have diastereotopic faces and hence can form diastereoisomeric α- and β-complexes [*cf.* the α-D-(**1**)–(**5**).HSCN and β-D-(**1**)–(**5**).HSCN complexes in Figure 1] with both achiral and chiral salts. We have examined (see Table) the temperature dependences of the ^1H n.m.r. spectra of the 1 : 1 complexes formed between D-(**1**), DD-(**2**), D-(**3**), and DD-(**4**) and selected $RNH_3^+SCN^-$ salts in CD_2Cl_2. The following observations can be made. (i) The temperature dependences of both crown and salt signals in the ^1H n.m.r. spectra are interpretable in terms of equilibrations between diastereoisomeric α- and β-complexes. (ii) Dissociation of the complexes is the slow rate-determining step in the complexation–decomplexation process (*cf.* ref. 3). In accordance with K_a values, complexes involving $Bu^tNH_3^+$ cations dissociate faster than complexes involving $PhCH_2NH_3^+$ cations. (iii) The rate of association of the complexes is fast and, in some instances, is characteristic of a diffusion-controlled process (*cf.* ref. 3). (iv) Reorganisation of the bonding pattern (hydrogen and electrostatic) within diastereoisomeric complexes is fast on the ^1H n.m.r. time scale even at −75 °C. (v) At low temperatures, the *gluco*-crowns D-(**3**) and DD-(**4**) bind all the salts examined stereoselectively (2 : 1, or better) to one of their diastereotopic faces. In the

TABLE

Thermodynamic parameters for complexation of primary alkylammonium thiocyanates (**5**).HSCN, (**6**).HSCN, (*S*)-(**7**).HSCN, and (*R*)-(**7**).HSCN by the chiral asymmetric crowns D-(**1**), DD-(**2**), D-(**3**), and DD-(**4**).

Crown	$RNH_3^+SCN^-$	R	K_a[a] /l mol^{-1}	$\Delta G°$ /kcal mol^{-1}	^1H N.m.r. probes[c]	Isomer ratio (T/°C) Major : minor	$\Delta G^\ddagger_d$[c,e] /kcal mol^{-1}	$\Delta G^\ddagger_a$[c,h] /kcal mol^{-1}
D-(**1**)	(**5**).HSCN	Bu^t	22,000[b]	5·9	*H*-4, –O*Me*, –C*Me*$_3$	55 : 45 (−85)	10·3[f]	**4·4**
	(**6**).HSCN	$PhCH_2$	>10^7	>9·5	PhC*H*<, *H*-1, –O*Me*	55 : 45 (−70)	11·9[f]	<2·4
	(*S*)-(**7**).HSCN	(*S*)-PhCHMe	—	—	PhC*H*<, Ph(*Me*)CH–	57 : 43 (−70)	12·1[f]	—
DD-(**2**)	(**5**).HSCN	Bu^t	1,100[b]	4·1	—[d]	—[d]	[d]	—
	(**6**).HSCN	$PhCH_2$	>10^7	>9·5	PhC*H*<, *H*-4, –O*Me*	50 : 50 (−70)	12·0[f]	<2·5
	(*S*)-(**7**).HSCN	(*S*)-PhCHMe	—	—	PhC*H*<, –O*Me*,	50 : 50 (−75)	11·7[f]	—
					Ph(*Me*)CH–	50 : 50 (−75)	11·7[f]	—
D-(**3**)	(**5**).HSCN	Bu^t	300[b]	3·4	—[d]	—[d]	—[d]	—
	(**6**).HSCN	$PhCH_2$	>10^7	>9·5	PhC*H*<, *H*-1	67 : 33 (−75)	11·4[g]	<1·9
	(*S*)-(**7**).HSCN	(*S*)-PhCHMe	—	—	PhC*H*<, *H*-1	80 : 20 (−75)	11·8[g]	—
DD-(**4**)	(**5**).HSCN	Bu^t	87[b]	2·6	—[d]	—[d]	—[d]	—
	(**6**).HSCN	$PhCH_2$	2,300	4·6	*H*-1	75 : 25 (−75)	12·1[g]	7·5
	(*S*)-(**7**).HSCN	(*S*)-PhCHMe	—	—	*H*-1	>97 : <3 (−60)	12·1[g]	—
	(*R*)-(**7**).HSCN	(*R*)-PhCHMe	—	—	*H*-1	72 : 28 (−75)	11·8[g]	—

[a] Obtained for the equilibrium, $RNH_3^+SCN^- + \text{Crown} \rightleftharpoons RNH_3\text{Crown}^+SCN^-$, in $CDCl_3$ at 20—25 °C by a ^1H n.m.r. spectroscopic method (ref. 6). [b] Ref. 1. [c] Temperature-dependent ^1H n.m.r. spectra were recorded in CD_2Cl_2 at 220 MHz on a Perkin Elmer R34 spectrometer with Me_4Si as 'lock' and internal standard. Signals for all protons listed separated into signals at low temperatures. Note that in a few instances, probes were available in both the crown and the primary alkylammonium cations. [d] No spectral changes other than line-broadening down to −90 °C. [e] The free energies of activation for dissociation of the major complexes. [f] Calculated from the rate constants. Error of ±0·3 kcal mol^{-1}. [g] From line-shape analysis. Error of ±0·3 kcal mol^{-1}. [h] The free energies of activation for association of the major complexes calculated from the expression, $\Delta G^\ddagger_a = \Delta G^\ddagger_d - \Delta G°$.

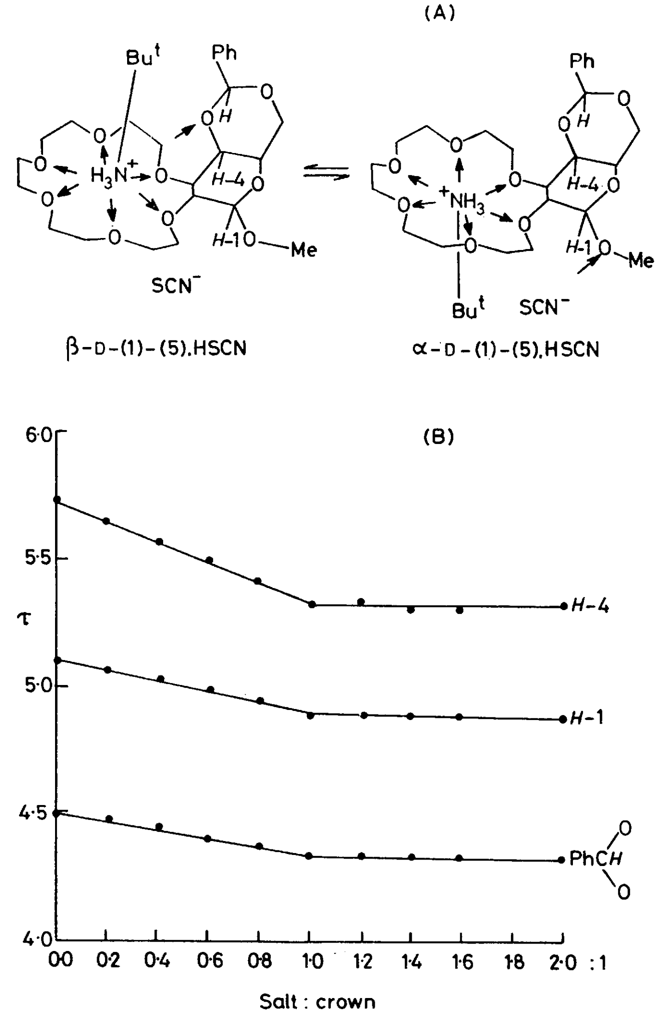
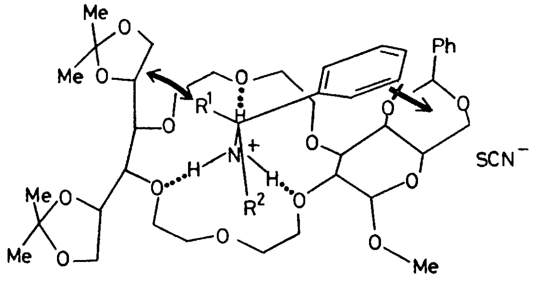


FIGURE 1. (A) The diastereoisomeric α- and β-D-(**1**)—(**5**).HSCN complexes. Oxygens believed to be involved in hydrogen bonding and/or electrostatic stabilisation with the ammonium hydrogens of the Bu^{t}NH$_3^+$ cations are indicated by means of arrows (→). (B) Change in chemical shifts of the indicated protons with change in salt: crown ratio.

case of DD-(**4**) and (*S*)-PhCHMeNH$_3^+$SCN$^-$ (*S*)-(**7**).HSCN, formation of one of the diastereoisomeric complexes is nearly stereospecific (>97 : <3) at −70 °C. We believe that complexation occurs preferentially at the β-face because of the similarities in the chemical shifts of the signals for H-1 in DD-(**4**) (τ 5·21) and in the complex DD-(**4**)–(*S*)-(**7**).HSCN (τ 5·17) at low temperatures. This observation suggests that O-1, and hence the α-face, is involved with the minor, and the β-face with the major, diastereoisomer. Recalling the weak 1 : 1 complexes formed[8,9] between 1,3-dioxans and benzene in CCl$_4$, we are tempted to ascribe the high stereoselectivity of binding to the β-face to a dipole-induced dipole type of interaction (see Figure 2) between the 2-phenyl-1,3-dioxan ring in DD-(**4**) and the phenyl group† of (*S*)-PhCHMeNH$_3^+$SCN$^-$. Supporting this proposal is the observation (see Figure 2) that when (*R*)-PhCHMeNH$_3^+$SCN$^-$ replaces (*S*)-PhCHMeNH$_3^+$SCN$^-$ in the β-DD-(**4**)–(*S*)-(**7**).HSCN complex, the steroselectivity of binding to the β-face is reduced to 72 : 28 in accordance with the steric interaction in the β-DD-(**4**)–(*R*)-(**7**).HSCN complex of the methyl group in the cation with a 2,2-dimethyl-1,3-dioxolanyl group in the crown.



β-DD-(4)-(S)-(7).HSCN $R^1 = H, R^2 = Me$
β-DD-(4)-(R)-(7).HSCN $R^1 = Me, R^2 = H$

FIGURE 2. Idealised (*cf*. I. Goldberg, *Acta Cryst.*, 1977, **B33**, 472) three-point binding models for the diastereoisomeric complexes β-DD-(**4**)–(*S*)-(**7**).HSCN and β-DD-(**4**)–(*R*)-(**7**).HSCN showing the dipole-induced dipole interaction between the 2-phenyl-1,3-dioxan rings and the phenyl group. Note that only crown oxygens are involved in complexation to the β-face of DD-(**4**).

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† We also believe (ref. 5) that attractive π-lone pair interactions involving the phenyl group in salts and the oxygens in 2,2-dimethyl-1,3-dioxolanyl groups (*cf*. ref. 9) of crowns can contribute to the stabilisation of complexes.

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