Chiral Crowns Incorporating Pyridyl Units and Tertiary Amine Functions

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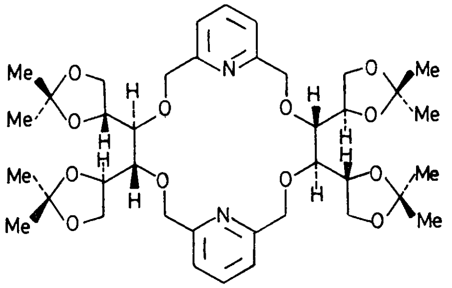
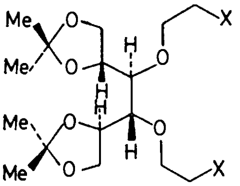
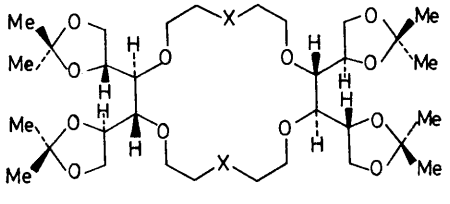
Summary The chiral hosts DD-(**1**) and DD-(**7**) have been synthesised and the temperature dependence of the ^1H n.m.r. spectrum of the 1 : 1 complex between DD-(**1**) and benzylammonium thiocyanate in solution has been interpreted in terms of slow dissociation of the complex.

Chiral macrocyclic polyethers derived from (*R*)- and (*S*)-binaphthol,[1,2] L-tartaric acid,[3,4] and D-mannitol[3] as sources of chirality have been shown (i) to complex with primary alkyl ammonium salts[1–7] and (ii) to exhibit chiral recognition when the salt is racemic.[1,2,5–7] Incorporation into achiral macrocycles of nitrogen atoms in the form of either pyridyl units[6,7] or tertiary amine functions[8] can lead to increased stabilities for the complexes formed with RNH_3^+ cations partly as a result of stronger hydrogen bond formation involving the nitrogen atoms in the macrocycles. We now report on the kinetic and thermodynamic consequences for complexation of introducing nitrogen atoms into chiral macrocycles.


DD-(1)


D-(2) X = OTs
D-(3) X = N_3
D-(4) X = NH_2
D-(5) X = $NHCO_2Et$


DD-(6) X = NCO_2Et
DD-(7) X = NMe
DD-(8) X = O

Condensation of 1,2 : 5,6-di-*O*-isopropylidene-D-mannitol[9] with 2,6-bis(bromomethyl)pyridine[10] in Me_2SO at 50 °C for 50 h with NaH as base gave (7·5%) the dipyridyl-18-crown-6 derivative DD-(**1**), m.p. 147—149 °C, $[\alpha]_D - 22°$ (*c* 0·55, $CHCl_3$). Chirality and two tertiary amine functions were introduced diametrically into the 18-crown-6 constitution by utilising the previously reported[2,3] 1,2 : 5,6-di-*O*-isopropylidene-3,4-di-*O*-(2-toluene-*p*-sulphonyloxyethyl)-D-mannitol D-(**2**) as starting material. Azide displacement of the tosyloxy groups in D-(**2**) proceeded smoothly with NaN_3 in Me_2NCHO at 110 °C for 2 h to give the bisazide D-(**3**) as an oil, $[\alpha]_D + 20·8°$ (*c* 1·0, $CHCl_3$), in 86% yield after chromatography (Et_2O) on silica. Hydrogenolysis (Pt–C) of D-(**3**) in Et_2O afforded (90%) the non-crystalline diamine D-(**4**), which on reaction at 0 °C for 3 h with $ClCO_2Et$ and NaOH in H_2O–Et_2O gave the bisurethane D-(**5**), $[\alpha]_D + 6·8°$ (*c* 0·31, $CHCl_3$) as an oil in 75% yield. Condensation of D-(**5**) with the bistosylate D-(**2**) in Me_2SO at 50 °C for 15 h afforded (33%) the bisurethane DD-(**6**), $[\alpha]_D - 11·9°$ (*c* 0·57, $CHCl_3$), which was reduced with $LiAlH_4$ in Et_2O (86%) to the *NN*-dimethyl-diaza-18-crown-6 derivative DD-(**7**), m.p. 106—108 °C, $[\alpha]_D + 38·8°$ (*c* 2·02, MeOH), ^1H n.m.r. spectrum ($CDCl_3$): τ 5·55—6·58 and 7·12—7·65 (32H, m, CH_2 and CH protons), 7·75 (6H, s, 2 × NMe), and 8·60 and 8·66 (24H, 2 × s, 8 × Me).

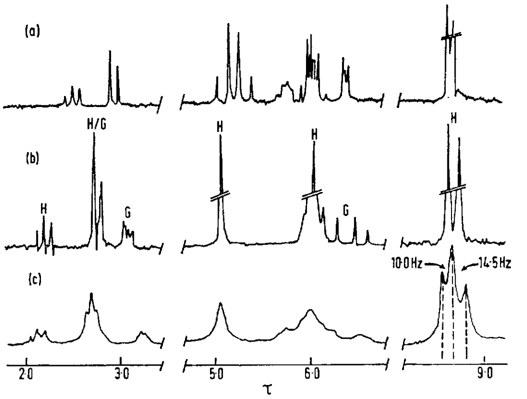


Figure. The ^1H n.m.r. spectra of host DD-(**1**) (a) in CD_2Cl_2 at ambient temperature, and in CD_2Cl_2 with 1 equiv. of $PhCH_2NH_3^+$-SCN^- added at (b) ambient temperature and at (c) −60 °C. The letters G and H indicate the guest and host signals respectively in (b).

Dynamic ^1H n.m.r. spectroscopy is a valuable technique for investigating the kinetics of complexation of hosts with metal[11] and RNH_3^+[8,12] guest salts. We have examined the temperature dependences of the ^1H n.m.r. spectra of the 1 : 1 complexes formed between DD-(**1**), DD-(**7**), and DD-(**8**)[3,5] and $PhCH_2NH_3^+SCN^-$ in CD_2Cl_2. In the case of the all-oxygen host DD-(**8**), complexation-decomplexation is fast on the ^1H n.m.r. time scale even at −70 °C. However, the hosts DD-(**1**) and DD-(**7**) form complexes which show considerable temperature dependences in their ^1H n.m.r. spectra which are not evident in the spectra of the pure hosts. The Figure summarises our results for DD-(**1**). The spectrum of pure DD-(**1**) shows (Figure, a) an AB_2 system with $J_{AB} = 7·7$ Hz at τ 2·51 and 2·94 for the pyridyl protons, an AB system with J_{AB} = 13·0 Hz at τ 5·11 and 5·31 for the pyridyl CH_2 protons, a series of multiplets between τ 5·62 and 6·48 for the other CH_2 and CH protons, and two singlets at τ 8·64 and 8·70 for the Me protons. Addition of 1 equiv. of $PhCH_2NH_3^+SCN^-$ causes significant changes in the chemical shifts of the signals observed for the host and gives rise to supplementary peaks in the aromatic region between τ 2·69 and 3·20 for the phenyl protons of the guest and an AB system with J_{AB} = 13 Hz at τ 6·24 and 6·54 for the benzylic CH_2 protons of the guest (see Figure, b). On decreasing the probe temperature, all signals are found to broaden considerably below 0 °C before becoming slightly better resolved again at −60 °C (see Figure, c). In particular, the signals for the Me protons of the isopropylidene groups appear as three singlets at τ 8·58, 8·68, and 8·82 in the approximate ratio of 1:2:1 and coalesce at −35 °C to give the two signals observed at higher temperatures. We associate these spectral characteristics with slow dissociation of the complex rendering the isopropylidene groups on one side of the host diastereotopic in relation to those on the other side in a face-to-face complex. Provided the breaking and making of individual hydrogen bonds between the host and guest within the complex is still fast on the ^1H n.m.r. time scale, isopropylidene groups on the same face of the host will remain homotopic. Even if reorganisation of hydrogen bonds is slow on the ^1H n.m.r. time scale isochronous behaviour of the diastereotopic isopropylidene groups on each face could be observed. Either way, four singlets should be observed for the Me protons of the isopropylidene groups under conditions of slow complex dissociation. On the assumption that the middle two singlets overlap, we have calculated rate constants, k_c of 22 and 32 s^{-1}, at the coalescence temperature (T_c −35 °C) for peak separations of 10·0 and 14·5 Hz respectively (see Figure, c) from the approximate expression $k_c = \pi(\nu_A - \nu_B)/\sqrt{2}$ for two-site exchange between groups of diastereotopic Me protons resonating at ν_A and ν_B. The derived free energy of activation for dissociation ($\Delta G_d^\ddagger$) of the complex is *ca.* 12·2 kcal mol^{-1}.

Stability constants defined as equilibrium constants (K_a in l mol^{-1}) for the equilibrium (1) were measured by an

$$\mathrm{RNH_3^+SCN^- + Host \overset{K_a}{\rightleftharpoons} RNH_3{\cdot}Host^+SCN^-} \qquad (1)$$

^1H n.m.r. spectroscopic method[6] in $CDCl_3$. Values of K_a for DD-(**1**) ($Bu^tNH_3^+$, 2·3 × 10^2; $PhCH_2NH_3^+$, > 2·0 × 10^7) and DD-(**7**) ($Bu^tNH_3^+$, 9·4 × 10^2) indicate that these diaza-crowns form much stronger complexes than the all-oxygen-crown DD-(**8**) ($Bu^tNH_3^+$, < 30; $PhCH_2NH_3^+$, 2·1 × 10^5). Comparison of the derived free energy difference of *ca.* 9·9 kcal mol^{-1} for complex formation between host DD-(**1**) and guest $PhCH_2NH_3^+SCN^-$ with the $\Delta G_d^\ddagger$ value of *ca.* 12·2 kcal mol^{-1} suggests that the free energy of association ($\Delta G_a^\ddagger$) of the guest with the host is small (*ca.* 2·3 kcal mol^{-1}). This means that the association rate constant is *ca.* 10^{10} l mol^{-1} s^{-1} which is characteristic of a diffusion-controlled process and compatible with face-to-face complexation.

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