Formation of Inclusion Complexes by Tricyclic Hosts

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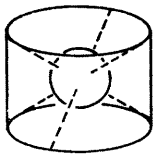
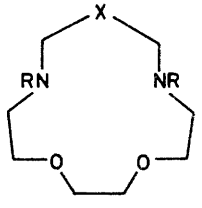
Summary The tricyclic host molecules (**4a**) and (**4b**) form inclusion complexes (cryptates) with appropriate bis primary alkylammonium thiocyanates (**7**).

ALTHOUGH inclusion complexes, shown diagramatically as (**1**), are formed by many biological systems the simplest well established examples involving relatively small organic host molecules and organic guest molecules are provided by cyclodextrin complexes.[1] Recently vancomycin[2] and related antibiotics have also been shown to form inclusion complexes with derivatives of D-Ala-D-Ala. Examples of inclusion complexes formed by synthetic host molecules are rarer. The cryptates[3] formed between synthetic polymacrocyclic systems and metal cations, the ammonium cation, protons, and certain anions have been described but analogous complexes involving organic guest molecules have not been well characterised.† The known ability of diaza 15-crown-5 host macrocycles (**2**) to form *cis,cis*-complexes [*e.g.* (**3**)] with guest primary alkylammonium salts,[4] together with the results described in the previous communication,[5] suggested that hosts having the general structure (**4**) would form inclusion complexes with bis primary alkylammonium salts (**7**), provided that the host cavity was of an appropriate size to accommodate the guest dication.

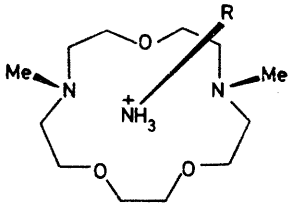


(1)



(2)

a; R = Me, X = CH_2OCH_2
b; R = H, X = *m*-$CH_2C_6H_4CH_2$
c; R = H, X = CH_2OCH_2



(3)

The host molecule (**4a**) was synthesised in 18% yield by the reaction of diaza 15-crown-5 (**2c**) with 2,7-bisbromomethylnaphthalene. The n.m.r. spectrum of (**4a**) at 25 °C in CD_2Cl_2 was consistent with rapid interconversion of the two conformations (**5a**) and (**5b**) and inversion of the conformation of the 15-membered macrocycles; at low temperatures (< −85 °C) both processes become slow on the n.m.r. time scale with appropriate changes in the n.m.r. spectrum. The n.m.r. spectrum of a mixture of (**4a**) with 2 equiv. of methylammonium thiocyanate in CD_2Cl_2‡ showed two NMe signals at low temperature (δ 1·73 and 2·00 at −20 °C) corresponding to the two 2:1 complexes (**6a**) and (**6b**). The line shape changes in the n.m.r. spectrum of the host macrocycles indicated that the inversion of each host macrocycle was also slow on the n.m.r. time scale at these temperatures as required for the structures (**6a**) and (**6b**). At lower temperatures (< −60 °C) further line shape changes in each of the NMe signals indicated that each complex (**6a**) and (**6b**) consists of a mixture of rapidly interconverting conformational isomers, but the relationship between these isomers was not defined by the spectral changes. The spectrum of (**4a**) in the presence of excess of methylammonium thiocyanate (4:1, G:H ratio) showed NMe signals below *ca.* 0 °C corresponding to free methylammonium thiocyanate (δ 2·56) and the two complexes (**6a**) and (**6b**). The high field chemical shift of the guest NMe groups in the complex as compared with free methylammonium thiocyanate is consistent with the formation of the 2:1 inclusion complexes shown in (**6a**) and (**6b**).

The n.m.r. spectrum of a 1:1 mixture of the host (**4a**) and the salt (**7**, $n=6$) in $CDCl_3$ showed very broad lines at 25 °C for all but the aryl hydrogens, but at 60 °C reasonably sharp n.m.r. lines were observable for both the host and guest components. The high field chemical shifts of the methylene groups of the guest cation suggested strongly that an inclusion complex (**8**) had been formed. At lower temperatures (<0 °C) the n.m.r. spectrum of a CD_2Cl_2 solution of the complex was well resolved and consistent with slow inversion, on the n.m.r. time scale, of the conformation of the 15-membered macrocycles as required by the structure (**8**). The spectrum at low temperatures was only interpretable in terms of a single type of complex, but did not distinguish between the possibilities (**8a**) or (**8b**). The n.m.r. spectrum of a 2:1 mixture

† Inclusion complexes of a chiral polymacrocyclic host are probably involved in some examples of chiral recognition reported recently (ref. 3).

‡ All n.m.r. spectra were run at 220 MHz for 0·1 M solutions using a Perkin Elmer R34 spectrometer. A few drops of CD_3OD were added to solutions of the complexes to prevent crystallisation of the salt.

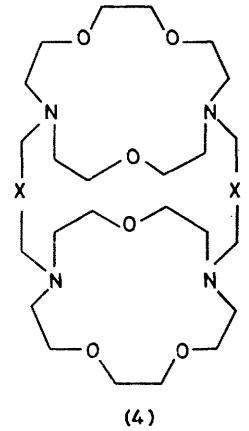
(G:H ratio) of salt (**7**, $n = 6$) and host (**4a**) indicated very clearly the presence of free and complexed guest cations (Figure, signals marked F and C), with the signals of the free cation (Table) at significantly lower field than those of the complexed cation, as expected for the complex (**8**). The complex described above. In this case, however, there was evidence for a major complex, similar to (**8a**) or (**8b**), together with a minor complex. The proportion of this second complex increased on addition of more of the guest dication and it is probably a complex in which each

TABLE. Chemical shifts of guest cations (**7**) in inclusion complexes (**8**) with hosts (**4a**) and (**4b**).

Host	Guest	Temp/°C	N.m.r. spectrum of guest[a] α-CH_2	β-CH_2	γ-CH_2
(**4a**)	(**7**, $n = 5$)	−30	2·00 (2·90)	0·83 (1·65)	0·40 (1·40)
(**4a**)	(**7**, $n = 6$)	−25	1·91 (2·90)	0·75 (1·66)	0·40 (1·40)
(**4b**)	(**7**, $n = 3$)	−40	1·00 (2·97)	1·40 (~2·0)	

[a] Guest methylene groups labelled as $H_3N^+CH_2$ (α)CH_2(β)CH_2(γ). Chemical shifts in parentheses refer to uncomplexed guests.

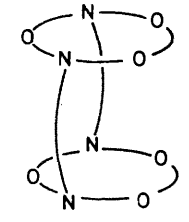
exchange of free and complexed guest cations involves a relatively high energy barrier ($\Delta G^{\ddagger}$ 14·0 kcal mol^{-1}) comparable with the energy barrier for the inversion of the host macrocycle in the complex ($\Delta G^{\ddagger}$ 14·3 kcal mol^{-1}). This is consistent with a guest exchange process involving consecutive dissociation and recombination at each macrocycle of the host in turn.



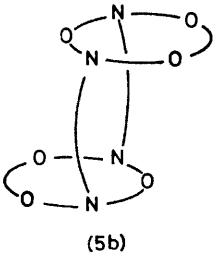
(4)

a, X =

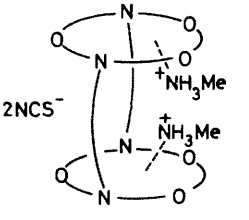
b, X =



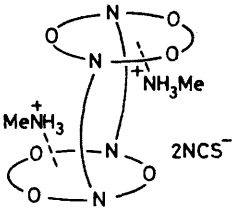
(5a)



(5b)

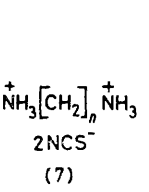


(6a)

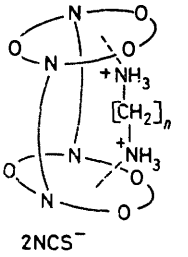


(6b)

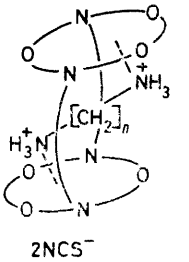
The n.m.r. spectrum of the inclusion complex formed by a 1:1 mixture of the host (**4a**) and the guest salt (**7**, $n = 5$) showed rather similar temperature dependence to that of



(7)



(8a)



(8b)

host molecule is associated with two molecules of guest. The host (**4b**) was formed in 16% yield by the reaction of the diamine (**2c**) with 1,4-bisbromomethylbenzene. This host formed a 1:1 inclusion complex [*cf.* (**8**)] with the guest (**7**, $n = 3$). In both of these cases the high field chemical shifts of the methylene groups of the guest cations indicated that an inclusion complex had been formed (Table).

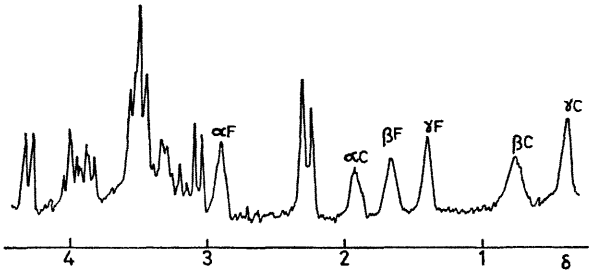


FIGURE. N.m.r. spectrum (220 MHz) of host OCH_2 and NCH_2 protons and guest $[CH_2]_n$ protons for complex of (**4a**) with bis primary alkylammonium salt (**7**, $n = 6$) in the presence of an excess of the guest salt at −50 °C. The labels F and C refer to the $[CH_2]_n$ signals from free and complexed guest, respectively.

The results described here establish the feasibility of forming inclusion complexes (cryptates[3]) between relatively simple polycyclic crown ether systems and organic guest molecules. The success of this investigation is a consequence of (a) a stereoselective binding site that directs the guest molecule into the cavity of the host, (b) a polyfunctional guest with a host binding site for each functional

group, and (c) a host cavity of appropriate size. These considerations, together with other important factors which have recently been listed,[6] indicate the possibility of designing host molecules for a wide range of polyfunctional guests.

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