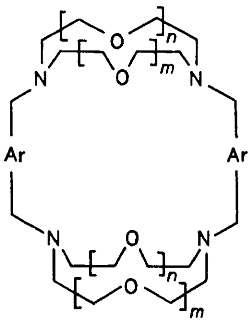
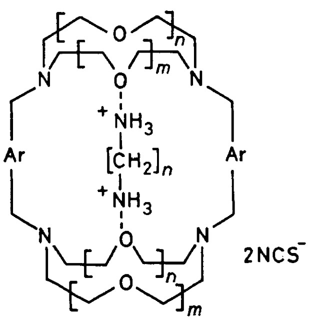
Symmetry and Selectivity in the Formation of Inclusion Complexes by Macrotricyclic Hosts

By NIGEL F. JONES, ASHWANI KUMAR, and IAN O. SUTHERLAND*
(*Department of Organic Chemistry, The Robert Robinson Laboratories, University of Liverpool, P.O. Box* 147, *Liverpool* L69 3BX)

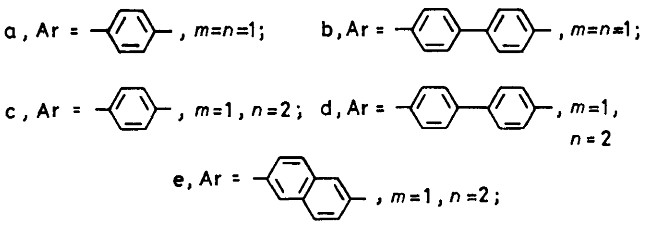
Summary The tricyclic host molecules (**1**) and (**5**) form inclusion complexes with bis-primary-alkylammonium salts (**3**) in which the n.m.r. spectrum of the guest salt reflects the symmetry of the host molecule in the complex; the hosts (**1**) are rigid and highly selective, whereas the host (**5a**) has one flexible bridge and selectivity is modified by this flexibility.



(1)



(2)



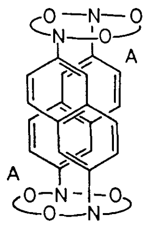
$^{+}HN_3\ [CH_2]_n\ NH_3^{+}\quad 2NCS^{-}$

(3)

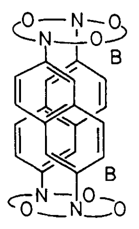
MACROTRICYCLIC host molecules of the general type (**1**) have been shown[1—3] to form inclusion complexes (**2**) with the bis-alkylammonium salts (**3**) and with methylammonium thiocyanate. The hosts (**1a**—**e**), in which the aza-crown macrocycles are 12- or 15-membered, necessarily form inclusion complexes to preserve the *syn*-relationship[4] between the guest cation and the substituents on the nitrogen atoms of the macrocycles. The hosts (**1a**—**d**) have a symmetrical bridge and the n.m.r. spectrum of a guest diamine is not affected by hindered rotation of the aromatic rings of the bridge; evidence for the formation of an inclusion complex is therefore derived solely from the shifts to high field of the CH_2 signals of a guest bis-alkylammonium salt (**3**). The host (**1e**) has lower symmetry and complex formation could be associated with the four conformations shown in (**4a**—**d**).† It was therefore not suprising to find that the complex of host (**1e**) with methylammonium thiocyanate (1 : 2 ratio) showed four ^{+}NMe signals in its n.m.r. spectrum at low temperatures corresponding to 1 : 2 complexes formed by at least three of the four conformations (**4a**—**d**). The

---

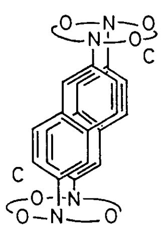
† The macrocycles in these conformations are shown diagramatically to avoid confusion and because the conformational characteristics of the 15-membered ring have not been established. The letters A, B, C, *etc.*, denote the different environments of a guest cation $R\overset{+}{N}H_3$.



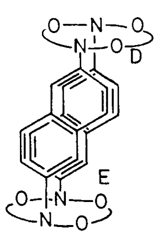
(4a)



(4b)



(4c)



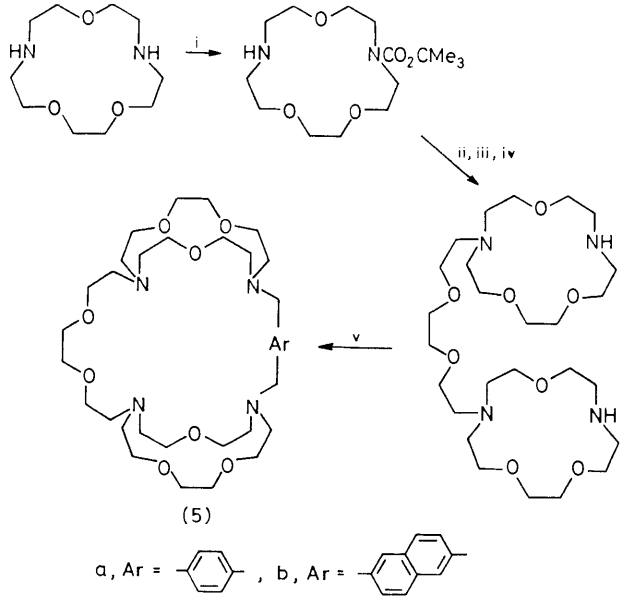
(4d)

n.m.r. spectra of the complexes of host (**1e**) with the bis-alkylammonium salts (**3**, $n = 4$, 5, and 6) (1: 1 ratio) are however consistent with the presence of a single major type of complex in which the host molecule has the conformation (**4d**). This conformation would result in nonequivalence of all of the CH_2 groups in the $[CH_2]_n$ chain of the guest salt (**3**) due to the different environments provided by the two ends of the cavity [see labels D and E in (**4d**)],‡ and this effect is observable in the n.m.r. spectra of the guest salts (**3**) at temperatures where the exchange of CH_2 groups between these two possible environments is slow on the n.m.r. time-scale. Such an exchange process would involve at least partial dissociation and recombination and the activation energies for such a process are evidently substantial for the salts (**3**, $n = 4$) and (**3**, $n = 5$), but considerably lower for the salts (**3**, $n = 3$) and (**3**, $n = 6$) which show averaged spectra for these CH_2 groups at −36 °C. The conformation (**4d**) has an apparent plane of symmetry relating the two sides of the cavity, but this plane is absent if the macrocycles adopt a chiral conformation. The lack of this symmetry plane has been demonstrated for the complex formed between (**1e**) and the salt (**3**, $n = 4$). At very low temperatures the protons of the guest give eight different n.m.r. signals corresponding to a structure for the complex in which the host has C_1 symmetry and the conformations of the macrocycles are determined by the steric requirements for complex formation with the guest bis-cation. The spectroscopic characteristics of the guest cations (**3**) in complexes with the host (**1e**) are summarised in Table 1.

Table 1. N.m.r. spectra[a] (400 MHz) of guests in complexes formed by hosts (**1e**) and (**5**)

Host	Guest	Ratio Host:Guest	Temp. /°C	N.m.r. of guest: δ
(**1e**)	$Me\overset{+}{N}H_3NCS^-$	1:2	37·5	0·97
			−36	0·32 (br), 0·69 (br)
			−90	0·13, 0·36, 0·68, 0·71
(**1e**)	(**3**, $n = 3$)	1:1	−36	0·43 (4H), 0·79 (2H)
(**1e**)	(**3**, $n = 4$)	1:1	37·5	−0·37 (br), 0·94 (br)
			−36	−0·93, −0·22, 0·50, 0·89[b]
			−104	−1·78, −0·85, −0·61, −0·27, −0·06, 0·02, 0·81, 1·12
(**1e**)	(**3**, $n = 5$)	1:1	−36	−0·49, −0·32, 0·18, 0·63, 1·29
(**1e**)	(**3**, $n = 6$)	1:1	−9	−0·55[c], 0·05, 0·98[c]
(**5a**)	(**3**, $n = 2$)	1:0·5	22	2·59
		1:1	−17	2·04[d]
(**5a**)	(**3**, $n = 3$)	1:0·5	25	1·33 (br)[d]
		1:1	−18	2·64 (2H)[e], 2·29 (2H)[e], 1·31, 1·06
	(**3**, $n = 4$)	1:0·5	22	2·53, 1·30
		1:1	−17	2·33[d], 1·27, 1·12
	(**3**, $n = 5$)	1:0·5	22	2·35, 1·39
		1:1	−17	2·41, 1·96, 1·57, 1·21[d]
(**5b**)	(**3**, $n = 4$)	1:0·5	29	2·19, 0·79
		1:1	−48	2·11[d], 1·03 (2H)[e], 0·89, 0·72, 0·47, −0·11[f]
	(**3**, $n = 5$)	1:0·5	29	1·97, 0·83, 0·71
			−48	1·85[d], 1·69, 0·97 (2H)[e], 0·77 (2H)[e], 0·61 (2H)[e], −0·63

[a] All spectra run for solutions *ca.* 0·05 M in host in CD_2Cl_2; chemical shifts in p.p.m. [b] Additional signals due to a minor species at δ −0·49, 0·83. [c] Broad at −36 °C but not resolved as two separate signals. [d] Additional signal(s) obscured by host spectrum. [e] These signals are approximately twice the intensity of the other signals and are assigned to two guest hydrogen atoms. [f] Signals listed are from the major species at −48 °C; at lower temperatures a minor species, δ 1·29, 0·35, 0·07, −1·33, becomes increasingly important.



Scheme. Reagents: i, $(Me_3CO{\cdot}CO)_2O$; ii, $ClCO[CH_2OCH_2]_2COCl$; iii, CF_3CO_2H-H_2O; iv, $LiAlH_4$; v, $BrCH_2ArCH_2Br$

The hosts (**5**) were synthesised using the reaction sequence shown in the Scheme. These hosts also form complexes with the bis-alkylammonium salts (**3**) and the lower symmetry of the hosts is reflected by the spectrum of the guest salt. For example the salt (**3**, $n = 3$) complexed by the host (**5a**) shows two signals for the α-CH_2 groups and two signals for the β-CH_2 group at −18 °C, reflecting the geminal nonequivalence of the CH_2 protons in the complex; as expected these signals coalesce in pairs at temperatures where exchange between these different environments is fast on the n.m.r. time-scale. The n.m.r. spectra of guest salts (**3**) in these complexes with the hosts (**5a**) and (**5b**) are summarised in Table 1.

The hosts (**1**) and (**5**) are highly selective in complex formation with the guest salts (**3**) and this selectivity, based upon the methods described in an earlier paper,[2] is summarised in Table 2. A typical experiment is illustrated in the Figure which shows the results of a competition ex-

---

‡ This interpretation is supported by the ^{13}C n.m.r. spectrum of the complex of (**1e**) with (**3**, $n = 4$) which shows four $^{13}CH_2$ signals at −60 °C and two $^{13}CH_2$ signals at +30 °C.

TABLE 2. Selectivity[a] for guests (**3**) in complexation by hosts (**1**) and (**5**)

Host	Selectivity[a]	Length/Å of cavity (*l*)	Length/Å of preferred guest (*d*)
(**1a**)	$n = 2 \gg 3$	5·8	3·6
(**1b**)	$n = 3 \ll 4 < 5 = 6 > 7 \gg 8$[b]	10·1	7·9[c]
(**1c**)	$n = 2 > 3 > 4$	5·8	3·6
(**1d**)	$n = 4 < 5 < 6 > 7$	10·1	8·5
(**1e**)	$n = 3 \ll 4 > 5 > 6$	7·9	6·1
(**5a**)	$n = 2 = 3 \gg 4 = 5$	variable	

[a] Selectivity for $^{+}NH_3[CH_2]_nNH_3^{+}$ indicated in the table by appropriate values of *n* and inequality or equality signs. [b] Described in ref. 2. [c] Average of (**3**, $n = 5$) and (**3**, $n = 6$).

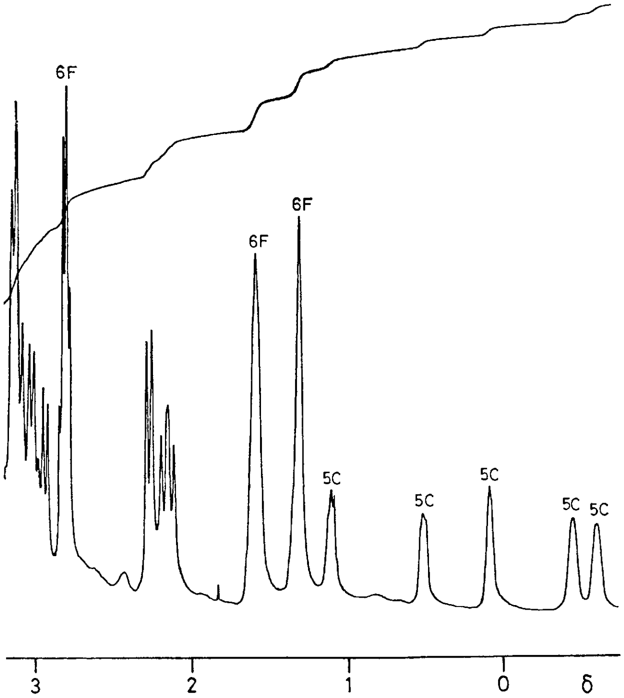
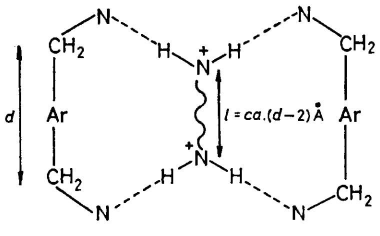


FIGURE. The ^1H n.m.r. spectrum (400 MHz) of a solution of host (**1e**) and guests (**3**, $n = 6$) and (**3**, $n = 5$) in a 1 : 1 : 1 ratio in CD_2Cl_2 containing a little CD_3OD at −35 °C. The signals marked 5C are assignable to the 5-CH_2 groups of the complexed guest (**3**, $n = 5$) and those marked 6F to the α, β, and γ CH_2 groups of the uncomplexed guest (**3**, $n = 6$).

periment involving the host (**1e**) and the guests (**3**, $n = 6$) and (**3**, $n = 5$). It is clear from the n.m.r. spectrum of the guest CH_2 groups that the guest (**3**, $n = 5$) is complexed but the guest (**3**, $n = 6$) is not. The results summarised in Table 2 are based upon similar experiments. The following conclusions follow from the results presented in this paper. (i) The rigid hosts (**1**) detect small differences in the length of the guest cations (**3**) and for optimum host fit the extended guest should have a length corresponding to *ca.* 2 Å less than the length of the CH_2ArCH_2 bridge, in accord with the attachment of guest to host by the hydrogen bonding indicated diagramatically in (**6**). (ii) The more flexible host (**5a**) shows selectivity in that a long guest (**3**, $n = 4$ or 5) may be rejected in favour of a shorter one (**3**, $n = 2$ or 3) but the length of the host cavity is evidently adjustable by conformational changes in the flexible bridge, and this host shows equal ability to complex the two shorter guests (**3**, $n = 2$ and 3), and reduced but equal ability to complex the two longer guests (**3**, $n = 4$ and 5). (iii) Host asymmetry is reflected in the different environments of atoms (or groups) in a complexed guest which may have identical environments in a free guest. This phenomenon has an obvious relationship with the distinction made by enzymes between enantiotopic groups and faces of substrates.



(6)

We thank the S.R.C. 400 MHz n.m.r. service at Sheffield for running n.m.r. spectra.

(*Received*, 17*th June* 1981; *Com.* 709.)

---

[1] M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 309.

[2] R. Mageswaran, S. Mageswaran, and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1979, 722.

[3] F. Kotzyba-Hibert, J. M. Lehn, and P. Vierling, *Tetrahedron Lett.*, 1980, 941.

[4] L. C. Hodgkinson, M. R. Johnson, S. J. Leigh, N. Spencer, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2193.