

TILDEN LECTURE*

Molecular Recognition by Synthetic Receptors

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Molecular recognition is the basis of many biochemical processes but it is only relatively recently that the attention of organic chemists has turned towards the design and synthesis of molecules¹ that can recognize other molecules. This type of recognition is normally achieved through the reversible formation of a complex between a large organic molecule (the host) and a smaller chemical species (the guest), the distinction between any pair of guests being based upon different association constants for complexation (Figure 1). Biological host molecules are usually based upon high molecular weight protein (enzymes, receptors, and antibodies) but the selective binding of oligonucleotides to an appropriate complementary polynucleotide sequence in high molecular weight DNA or RNA is a further well known and important example. A few natural products also act as selective host molecules, particularly the ionophoric antibiotics² and members of the vancomycin group of antibiotics such as ristocetin (1).³ The latter are particularly relevant to this article since the binding between ristocetin and the guest species, acetyl-D-Ala-D-Ala, is based upon the hydrogen bonding and electrostatic interactions summarized in (2); similar interactions will be involved in most of the examples of complex formation that are described below. Such interactions are optimized in solvents with low dielectric constant and are less suitable for host-guest binding in aqueous solution where the major source of binding is usually through hydrophobic interactions. For relatively small organic host molecules hydrophobic binding is difficult to organize and, although the

* Delivered at a Symposium, 'New Aspects of Heterocyclic Chemistry,' at the Scientific Societies' Lecture Theatre, London on 22nd January 1985 and on other occasions in Bristol, Stirling, Guildford, and Aberystwyth.

¹ For reviews see: 'Host Guest Complex Chemistry,' ed. F. Vögtle, Springer, Berlin and Heidelberg, Vol. I, 1981, Vol. II, 1982, Vol. III (ed. F. Vögtle and E. Weber), 1984; F. Vögtle, W. M. Muller, and W. H. Watson in 'Stereochemistry,' ed. F. Vögtle and E. Weber, Springer, Berlin and Heidelberg, 1984, p. 131; I. O. Sutherland in 'Cyclophanes Vol. II,' ed. P. M. Kechn and S. M. Rosenfeld, Academic Press, New York, 1983, p. 679.

² M. Dobler 'Ionophores and their Structures', Wiley, New York, 1981.

³ J. R. Kalman and D. H. Williams, *J. Am. Chem. Soc.*, 1980, **102**, 897, 906; C. M. Harris and T. M. Harris, *J. Am. Chem. Soc.*, 1982, **104**, 363; D. H. Williams, M. P. Williamson, D. W. Butcher, and S. J. Hammond, *J. Am. Chem. Soc.*, 1982, **105**, 1332; M. P. Williamson, D. H. Williams, and S. J. Hammond, *Tetrahedron*, 1984, **40**, 569; M. P. Williamson and D. H. Williams, *Eur. J. Biochem.*, 1984, **138**, 345; M. P. Williamson and D. H. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1985, 949; J. C. J. Barna, D. H. Williams, and M. P. Williamson, *J. Chem. Soc., Chem. Commun.*, 1985, 254.

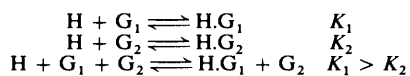
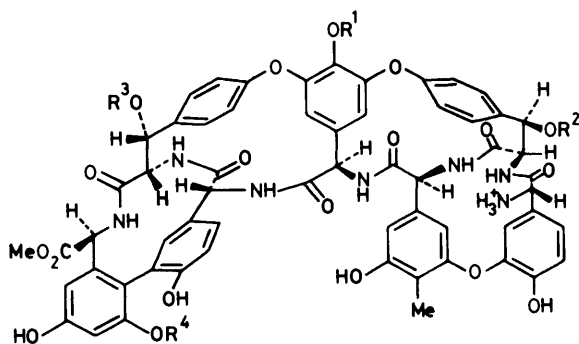
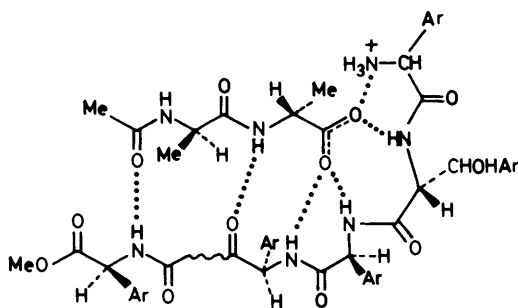


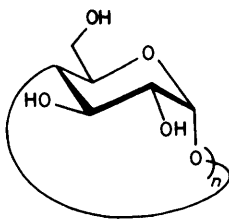
Figure 1 Molecular recognition by a synthetic host molecule H for a pair of guest molecules G₁ and G₂



(1)



(2)



(3)

cyclodextrins (3)⁴ have long been known to function as such hosts, it is only recently that synthetic hosts with hydrophobic cavities have been developed.⁵ Such systems are undoubtedly of importance for future developments in this area of research but will not be discussed further in this review.

Synthetic host molecules are subject to a number of requirements. They should be available through synthesis from simple starting materials by short and simple routes and should not only recognize guest molecules according to their constitution but also according to their configuration, for example they should be able to differentiate enantiomers. Progress towards these objectives will be the major topic of this article.

The discovery of crown ethers by Pedersen⁶ and their subsequent development by others, particularly Cram and his co-workers,⁷ has been well documented. 18-Crown-6 (4) has been shown⁸ to form complexes with metal cations, alkylammonium cations, and a number of other species. Binding to cationic guests is through electrostatic interactions, and although binding to alkylammonium cations is often depicted as involving specific hydrogen bonding as shown in (5) it is perhaps more satisfactory to think of this binding as net attraction⁹ between the

⁴ M. L. Bender and M. Komiyama, 'Cyclodextrin Chemistry', Springer, Berlin and Heidelberg, 1977; G. L. Trainor and R. Breslow, *J. Am. Chem. Soc.*, 1981, **103**, 154; I. Tabushi, T. Nabeshima, and K. Yamamura, *J. Am. Chem. Soc.*, 1982, **104**, 2017; K. A. Connors and D. D. Pendergast, *J. Am. Chem. Soc.*, 1984, **106**, 7607; M. C. Gonzalez, A. R. McIntosh, J. R. Bolton, and A. C. Weedon, *J. Chem. Soc., Chem. Commun.*, 1984, 1138; K. Fujita, S. Ejima, and T. Imoto, *J. Chem. Soc., Chem. Commun.*, 1984, 1277.

⁵ K. Odashima, A. Itai, Y. Iitake, and K. Koga, *J. Am. Chem. Soc.*, 1980, **102**, 2504; I. Tabushi, Y. Kimura, and K. Yamamura, *J. Am. Chem. Soc.*, 1978, **100**, 1304; 1981, **103**, 6486; K. Odashima, T. Soga, and K. Koga, *Tetrahedron Lett.*, 1981, 5311; Y. Murakami in 'Cyclophanes II', ed. F. Vögtle, Springer, Berlin, 1983, p. 107; I. Tabushi and K. Yamamura in 'Cyclophanes I', ed. F. Vögtle, Springer, Berlin, 1983, p. 145; K. Odashima and K. Koga in 'Cyclophanes Vol. II', ed. P. M. Keehn and S. M. Rosenfeld, Academic, New York, 1983, p. 629; R. C. Helgeson, M. Lauer, and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 1983, 101; M. Dhaenens, L. Lacombe, J. M. Lehn, and J. P. Vigneron, *J. Chem. Soc., Chem. Commun.*, 1984, 1097; S. Shinkai, S. Mori, T. Tsubaki, T. Sone, and O. Manabe, *Tetrahedron Lett.*, 1984, **25**, 5315; F. Diederich, *Nachr. Chem. Tech. Lab.*, 1984, **32**, 787; H. J. Schneider, K. Philippi, and J. Pöhlmann, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 908; F. Diederich and K. Dick, *J. Am. Chem. Soc.*, 1984, **106**, 8024, 8037; J. Cancelli, M. Cesario, A. Collet, J. Guilhern, and C. Pascard, *J. Chem. Soc., Chem. Commun.*, 1985, 361; D. J. Cram, K. D. Stewart, I. Goldberg, and K. N. Trueblood, *J. Am. Chem. Soc.*, 1985, **107**, 2574; D. J. Cram, S. Karbach, Y. H. Kim, L. Baczynskyj, and G. W. Kallemeyn, *J. Am. Chem. Soc.*, 1985, **107**, 2575.

⁶ C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 2495, 7017; 1970, **92**, 386, 391; C. J. Pedersen, *J. Org. Chem.*, 1971, **36**, 254, 1690; C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 16.

⁷ D. J. Cram and K. N. Trueblood in 'Host Guest Complex Chemistry I', ed. F. Vögtle, Springer, Berlin and Heidelberg, 1981, p. 43; G. M. Lein and D. J. Cram, *J. Am. Chem. Soc.*, 1985, **107**, 448, and earlier papers in the series 'Host-Guest Complexation'.

⁸ For a review see: I. Goldberg in 'Inclusion Compounds 2', Academic, London, 1984, p. 261; J. M. Timko, S. S. Moore, D. M. Walba, P. C. Hiberty, and D. J. Cram, *J. Am. Chem. Soc.*, 1977, **99**, 4207; O. Nagano, A. Kobayashi, and Y. Sasaki, *Bull. Chem. Soc. Japan*, 1978, **51**, 790; K. N. Trueblood, C. B. Knobler, D. S. Lawrence, and R. V. Stevens, *J. Am. Chem. Soc.*, 1982, **104**, 1355; E. Maverick, P. Seiler, W. B. Schweizer, and J. D. Dunitz, *Acta Crystallogr., Sect. B*, 1980, **36**, 615.

⁹ G. Wipff, P. Weiner, and P. Kollman, *J. Am. Chem. Soc.*, 1982, **104**, 3249; V. J. Thöm, C. C. Fox, J. C. A. Boeyens, and R. D. Hancock, *J. Am. Chem. Soc.*, 1984, **106**, 5947; R. J. Abraham and B. Hudson, *J. Comp. Chem.*, 1985.

array of negative and positive charges presented by the guest cation and the crown-ether as shown diagrammatically in Figure 2. This view has the advantage that it is compatible with computation of binding energy through molecular mechanics calculations,¹⁰ although the status of such calculations is rather uncertain at present due to the difficulty of assigning intramolecular and intermolecular dielectric constants. Unsubstituted 18-crown-6 does not recognize differences¹¹ in the size of group R in the complex (5) because guest-host contact is limited, and in the absence of additional barriers to complexation, such recognition cannot be expected.

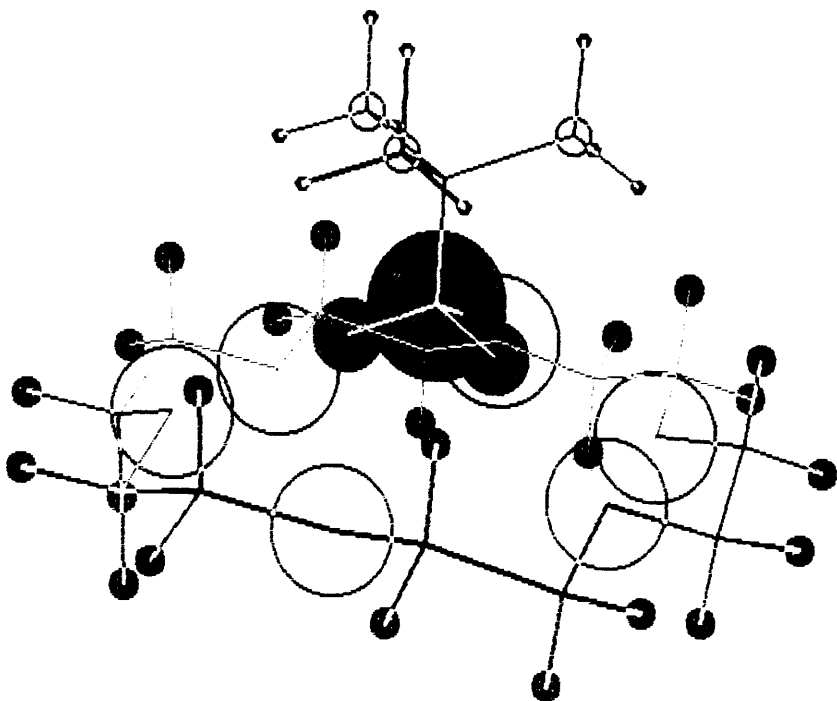


Figure 2 Charge distribution in the complex 18-crown-6. Bu^4NH_3^+ . The open circles represent negative charges and the filled circles represent positive charges, the magnitude of the charge is proportional to the diameter of the circle

¹⁰ M. J. Bovill, D. J. Chadwick, I. O. Sutherland, and D. Watkin, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1529; P. Kollman, *Acc. Chem. Res.*, 1985, **18**, 105; P. Werner, S. Profeta, G. Wipfl, T. Havel, I. D. Kuntz, R. Langridge, and P. A. Kollman, *Tetrahedron*, 1983, **39**, 1113.

¹¹ R. M. Izatt, N. E. Izatt, B. E. Rossiter, J. J. Christensen, and B. L. Haymore, *Science*, 1978, **199**, 994; R. M. Izatt, J. D. Lamb, B. E. Rossiter, N. E. Izatt, J. J. Christensen, and B. L. Haymore, *J. Chem. Soc., Chem. Commun.*, 1978, 386; F. de Jong and D. N. Reinhoudt, 'Stability and Reactivity of Crown Ether Complexes', Academic, London, 1981.

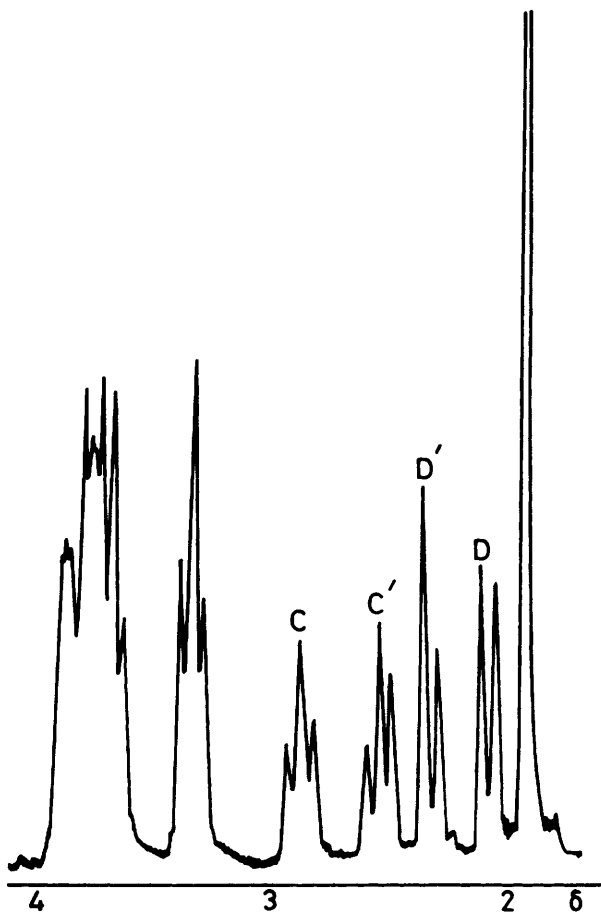
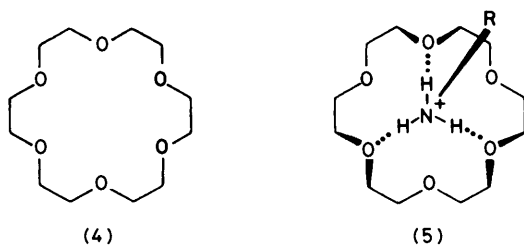


Figure 3 220 MHz ^1H N.m.r. spectrum from δ 1.7–4.1 of a solution of the complex (6a). $\text{PhCH}_2\text{NH}_3^+\text{NCS}^-$ in CD_2Cl_2 at -60°C . The signals labelled C and D and C' and D' are assignable to the groups $\text{OCH}_A\text{H}_B\text{CH}_C\text{H}_D\text{N}$ and $\text{OCH}_A\text{H}_B\text{CH}_C\text{H}_D\text{N}$ of the host macrocycle

This problem of introducing barriers has been tackled in a number of ways and considerable success has been achieved.¹² In our own work we decided that the crown-ether structure was most conveniently modified by replacing one or more of the ether oxygens with a tertiary nitrogen atom. This replacement remains consistent with our requirement for simple synthetic targets and cation binding by nitrogen was expected to be comparable with cation binding by oxygen. The ring nitrogen atoms would also provide convenient points for the attachment of side chains and the bridges required for polycyclic structures since they would not present the stereochemical problems associated with substitution at ring carbon atoms.

The synthesis and some of the properties of aza crown-ethers had been established through the pioneering work of J. M. Lehn and co-workers¹³ and both diaza-15-crown-5 and diaza-18-crown-6 are available commercially. Other aza crown-ethers may be prepared by cyclization reactions involving *N*-acylation, *N*-alkylation, and *O*-alkylation and these methods have been extensively reviewed.¹⁴ Our initial investigations made extensive use of n.m.r. spectroscopy and were centred upon monocyclic aza crown-ethers; the results have been described in detail¹⁵ and only a brief summary will be given here.

The ¹H n.m.r. spectrum of the complex¹⁶ formed in CD₂Cl₂ between equimolecular quantities of *N,N*-dimethyl diaza-15-crown-5 (6a) and benzylammonium thiocyanate is shown in Figure 3. This spectrum shows temperature dependence and at -60 °C the NCH₂ groups are observable as the C and D multiplets of two -OCH_AH_BCH_CH_DN systems, the observed large (*ca.* 12 Hz) couplings in the H_C triplets and the H_D doublets indicates that the host adopts a conformation in which all the NC-CO bonds are *gauche*. The signals of the guest and the host are consistent with the formation of only one type of complex at all temperatures down to -110 °C, in contrast with the complexes¹⁷ of analogous diaza-18-crown-6 systems (6b and 6c). The shift to high field of the host NCH₃ signal for the complex, as compared with the NCH₃ signal of the free host, and the observation of only one NCH₃ at -60 °C suggests that the complex has the *syn,syn*-stereochemistry shown in (7) and we note that similar *syn,syn*-stereochemistry has been found in the solid phase and in solution¹⁸ for the complexes of *N,N*-dimethyl diaza-12-crown-4 (6d) with alkylammonium cations.

¹² D. J. Cram and J. M. Cram, *Acc. Chem. Res.*, 1978, **11**, 8; D. J. Cram and K. N. Trueblood in 'Host Guest Complex Chemistry I', ed. F. Vögtle, Springer, Berlin and Heidelberg, 1981, p. 43.

¹³ J. M. Lehn, *Struct. Bonding (Berlin)*, 1973, **16**; J. M. Lehn, *Pure Appl. Chem.*, 1978, **50**, 871; J. M. Lehn, *Acc. Chem. Res.*, 1978, **11**, 49.

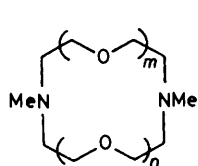
¹⁴ For example see G. W. Gokel and S. H. Korzeniowski, 'Macrocyclic Polyether Syntheses', Springer, Berlin and Heidelberg, 1982.

¹⁵ D. J. Chadwick, I. A. Cliffe, and I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1707, and earlier papers in this series.

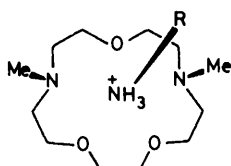
¹⁶ M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1979, 357.

¹⁷ For other examples of stereoselectivity see S. J. Leigh and I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1089; L. C. Hodgkinson and I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1908.

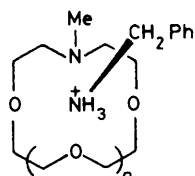
¹⁸ J. C. Metcalfe, J. F. Stoddart, and G. Jones, *J. Am. Chem. Soc.*, 1979, **99**, 8317; J. Krane and O. Aune, *Acta Chem. Scand., Ser. B*, 1980, **34**, 397; J. C. Metcalfe, J. F. Stoddart, G. Jones, W. E. Hull, A. Atkinson, I. S. Kerr, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1980, 540.



(6)



(7)



(8)

a; $m = 1, n = 2$ c; $m = 1, n = 3$

b; $m = n = 2$ d; $m = n = 1$

e; $m = n = 3$

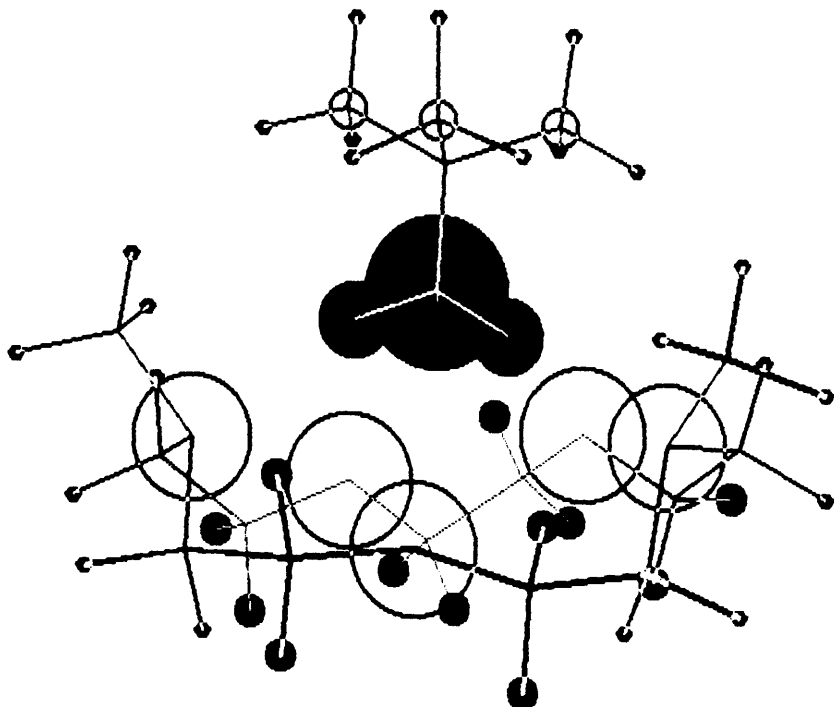


Figure 4 Charge distribution in the complex (7a). Bu^+NH_3^+ . The open circles represent negative charges and the filled circles represent positive charges, the magnitude of the charge is proportional to the diameter of the circle

Although the conformational possibilities for 15-membered rings are extensive,¹⁹ the conformation shown in Figure 4 is supported by Molecular Mechanics calculations and is closely related to the conformation found for the benzylammonium thiocyanate complex of *N*-methyl monoaza-15-crown-5 (8) by *X*-ray crystallography. Simple calculations^{9,20} of electrostatic interactions between charges in the host and guest components of the complex, shown diagrammatically in Figure 4, indicate overall attraction between the two components but, in view of the uncertainties regarding dielectric constant in such calculations, the results must be viewed with caution.

The temperature dependence of the ¹H n.m.r. spectra of aza crown-ethers can be used²¹ to obtain information about the rates of a number of processes by the standard methods of line-shape analysis.²² Such results have been reported and discussed elsewhere and will only be mentioned here where they are relevant to the remainder of this review. Thus conformational inversion (*I*) of a free host macrocycle is usually rapid on the n.m.r. time scale at probe temperatures down to 110 °C so that NCH₂CH₂O systems give rise to AA'BB' multiplets at all temperatures. In contrast with this result the related process (Figure 5a) for a complex of an aza crown-ether involves both conformational inversion of the host macrocycle (*I*) and exchange (*E*) of the guest cation between the two faces of the host macrocycle since only one face of the host is suitable for complexation.* The combined effect of these two requirements is usually associated with a free energy of activation for the overall process (*E* + *I*) (ΔG^\ddagger 9–14 kcal mol⁻¹) which makes it slow on the n.m.r. time scale at temperatures somewhere within the range +25 to –110 °C. Related processes (Figures 5b and 5c) involving exchange of free and complexed guest or of free and complexed host, for solutions containing an excess of guest or host respectively, involve similar free energies of activation and may also be associated with signal collapse and coalescence within the same temperature range. In general, maximum information is obtained from the n.m.r. spectra of complexes under conditions where both processes are slow.²³

The stereochemical homogeneity of the complexes of diaza 15-crown-5 and diaza 12-crown-4 has been mentioned; diaza 18-crown-6 systems gave different results.²⁴ Thus the ¹H n.m.r. spectra of the NH₃⁺ signals of two guests in complexes of the

* This contrasts with the situation for 18-crown-6 RNH₃⁺ complexes in which conformational inversion of the host macrocycle can occur without face-to-face guest exchange because the host macrocycle adopts a conformation in which both faces are identical.

¹⁹ R. Louis, D. Pelissard, and R. Weiss, *Acta Crystallogr., Sect. B*, 1976, **32**, 1480.

²⁰ I. O. Sutherland, unpublished observations.

²¹ For discussions see refs. 16 and 17 and I. O. Sutherland in 'Applications of NMR Spectroscopy to Problems in Stereochemistry and Conformational Analysis', ed. A. P. Marchand, VCH Publishers, Florida, to be published.

²² G. Binsch, *Topics Stereochem.*, 1968, **3**, 97; I. O. Sutherland, *Annu. Rep. NMR Spectrosc.*, 1971, 71.

²³ For recent examples of the application of similar methods for the study of guest–host complexes see: T. Anthonson and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 1983, 1414; T. Alfhheim, J. Dale, P. Groth, and K. D. Krautwurst, *J. Chem. Soc., Chem. Commun.*, 1984, 1502; F. H. Kohnke and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, 1985, 314; B. O. Strasser, K. Hallenge, and A. I. Popov, *J. Am. Chem. Soc.*, 1985, **107**, 789.

²⁴ 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.

diaza 18-crown-6 derivative (6c) are shown in Figure 6. These spectra show very clearly that in both cases three different complexes are formed and we believe that these are the *syn,syn*-, *syn,anti*-, and *anti,anti*-complexes shown diagrammatically in (9). Similar results have been obtained for other diaza 18-crown-6 derivatives, for example (6b), and we have also noted^{16,25} that whereas *N*-methyl monoaza 15-crown-5 appears to form only a *syn*-complex *N*-methyl monoaza 18-crown-6 forms both *syn*- and *anti*-complexes. It is difficult to account for this stereoselectivity shown in complexation by the 12- and 15-membered macrocycles as compared with the 18-membered macrocycle although it is presumably associated with the arrangement of the binding N and O atoms which tend to be sited on one face of the macrocycle in the 12- and 15-membered rings but are available on both faces in the 18-membered and larger rings. The diaza 24-crown-8 derivative (6e) has been shown²⁶ to form the *syn,syn;anti,anti*-complex shown in (10) in which one molecule of the host binds two molecules of the guest alkylammonium cation. All of these diaza crown ethers have been used as binding sites in the polycyclic systems described below but our work has mostly concentrated upon the use of the highly stereoselective 12- and 15-membered rings.

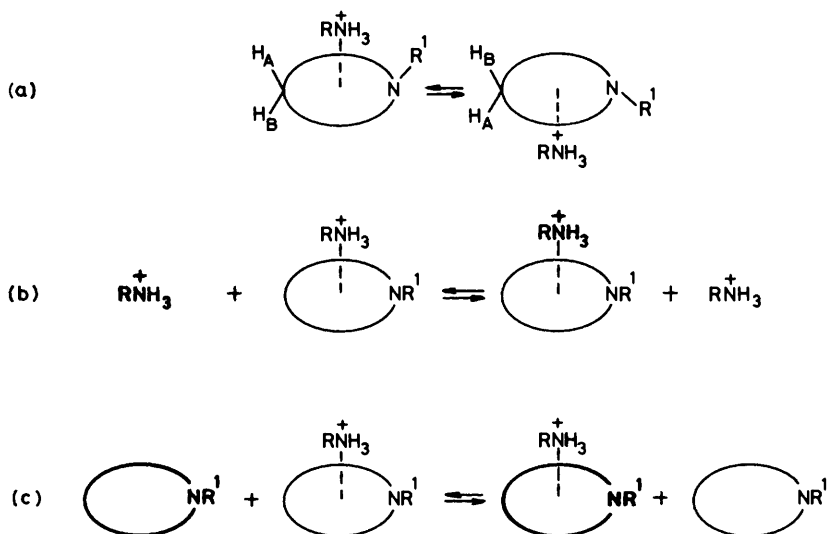


Figure 5 Exchange processes for complexes of aza crown-ethers. In (b) and (c) the two different molecules of guest or host involved in an exchange process are identified by normal and bold printing

²⁵ M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 306; M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1980, 586.

²⁶ M. J. Bovill, D. J. Chadwick, M. R. Johnson, N. F. Jones, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 1065.

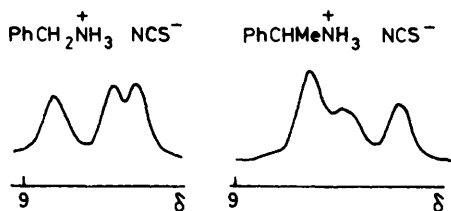
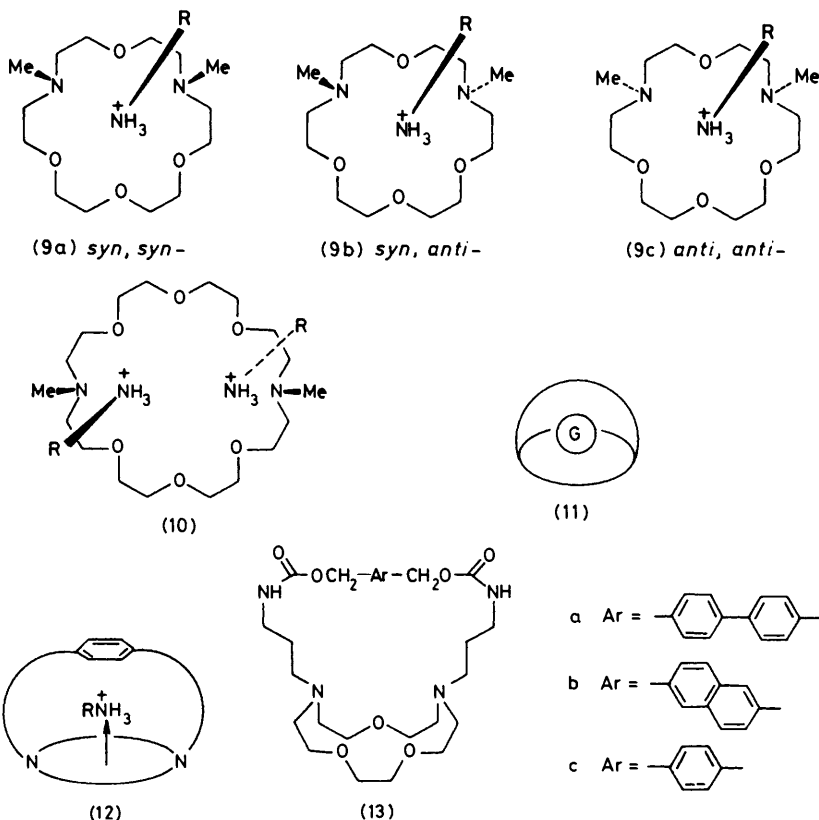


Figure 6 220 MHz ^1H N.m.r. spectrum of $^+\text{NH}_3$ signals in complexes (6c). $^+\text{RNH}_3$ in CD_2Cl_2 at -70°C , the guest salt is indicated above each spectrum

It is clear that a high level of recognition for the guest cation by the host crown-ether requires as much contact as possible between the two components of the complex. This is more easily achieved in an inclusion complex, such as (11), in



which the guest cation lies in a three-dimensional cavity provided by a macropolycyclic host, than in an addition complex in which the guest molecule is attached to a single face of a macromonocyclic host.

The simplest basis for a polycyclic host molecule is a bicyclic system (12) formed by bridging a diaza crown-ether.²⁷ If the diaza crown-ether complexes only in the direction indicated by the arrow in (12) then it will necessarily form an inclusion complex with a guest alkylammonium cation as shown. Such binding properties are shown by diaza-12-crown-4 and diaza 15-crown-5 derivatives and the only other structural feature is the aromatic ring incorporated into the bridge. If the guest molecule lies within the cavity as shown in (12) then it lies in the magnetically shielding zone of the aromatic ring when the n.m.r. spectrum of the complex is measured. The guest protons will therefore show an upfield shift in their n.m.r. spectrum, relative to the spectrum of the free guest, if they lie within the host cavity. These upfield shifts were readily demonstrated²⁸ for a variety of guest alkylammonium cations using the hosts (13a—c). The upfield shifts observable for $CH-N^+$ and $CH-C-N^+$ in the guest cations are summarized in Figure 7. A number of general conclusions can be drawn from these results. Small guest cations show rather larger upfield shifts than large guest cations since they can be situated to a larger extent in the cavity provided by the host. The naphthalene and biphenyl systems of hosts (13a and 13b) are, as expected, rather more effective in inducing upfield shifts than the benzene ring of (13c). The induced shifts are usually rather greater for $CH-N^+$ than for $CH-C-N^+$ since the former is located closer to the complexation site within the cavity of the host. The hosts (13a—c) evidently form inclusion complexes with a range of guest cations but they do not show a high degree of guest recognition, presumably because the cavities are flexible and can open or close to accommodate guest cations of different sizes.

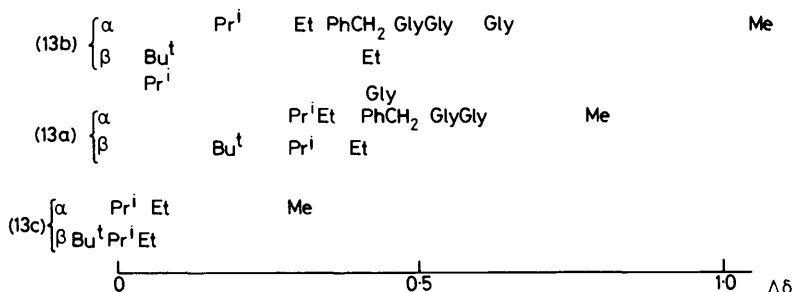
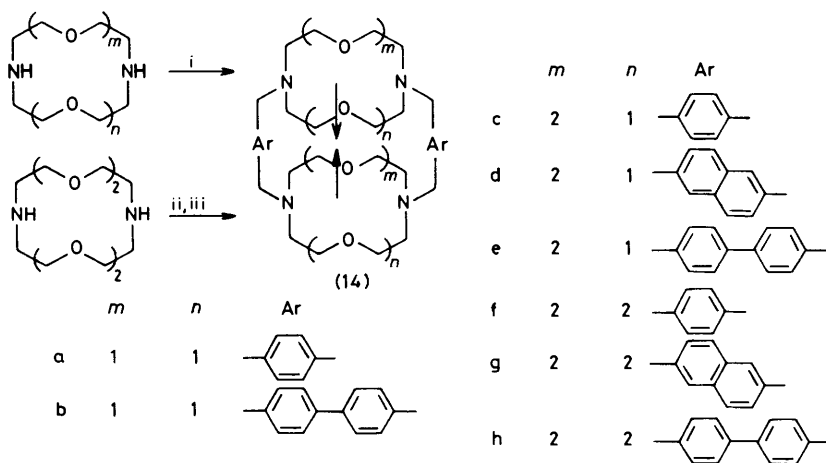


Figure 7 Induced upfield shifts of $(CH-NH_3^+)$ and $(CH-C-NH_3^+)$ protons of guest alkylammonium cations RNH_3^+ in complexes with hosts (13a—c). For each host the upper line refers to α -protons and the lower line to β -protons, the entries Me, Et etc. refer to the group R in RNH_3^+ .

²⁷ Macrobicyclic hosts (cryptands) have been widely used for complexation of metal cations but few reports have appeared in which the guest molecules are organic species, for example see B. L. Allwood, F. H. Kohnke, A. M. Z. Slawin, J. F. Stoddart, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1985, 311.

²⁸ K. A. Owens, Ph.D. Thesis, University of Liverpool, 1985.

The tricyclic hosts shown diagrammatically in (14) are potentially more rigid systems and, because they contain two cation binding sites (ditopic),²⁹ they are suitable host molecules for bis-alkylammonium cations or for two molar equivalents of a simple alkylammonium cation. Provided that the diaza crown-ether rings of (14) are 12- or 15-membered they will complex only in the directions indicated, so that the tricyclic hosts will form only inclusion complexes with guest cations. The links between the two aza crown-ether receptors include aromatic rings as experimental probes for inclusion complexation and to provide a rigid spacing element between the two receptors. The structure (14) also permits a simple one step synthesis³⁰ from diaza-12-crown-4 or diaza-15-crown-5 and a bis-benzyl halide as outlined in Scheme 1.



Reagents: i, $\text{BrCH}_2\text{ArCH}_2\text{Br}$, K_2CO_3 , MeCN; ii, ClCOArCOCl , Et_3N ; iii, B_2H_6

Scheme 1 Synthesis of symmetrical tricyclic hosts

The complexes formed between the tricyclic hosts (14a–e) and a variety of alkylammonium cations were examined^{30,31} by n.m.r. spectroscopy, using for the most part ^1H n.m.r. at frequencies of 220, 250, and 400 MHz. In all cases complexes were examined in CD_2Cl_2 solution at temperatures between -110 and $+45$ °C and the guests were usually thiocyanate salts. A few typical results³² only will be discussed.

The host (14b) has a long narrow cavity of an appropriate shape to take up a bis-

²⁹ J. M. Lehn, *Pure Appl. Chem.*, 1980, **52**, 2441.

³⁰ M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 309.

³¹ R. Mageswaran, S. Mageswaran, and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1979, 722; N. F. Jones, A. Kumar, and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1981, 990.

³² I. O. Sutherland, *Heterocycles*, 1984, **21**, 235.

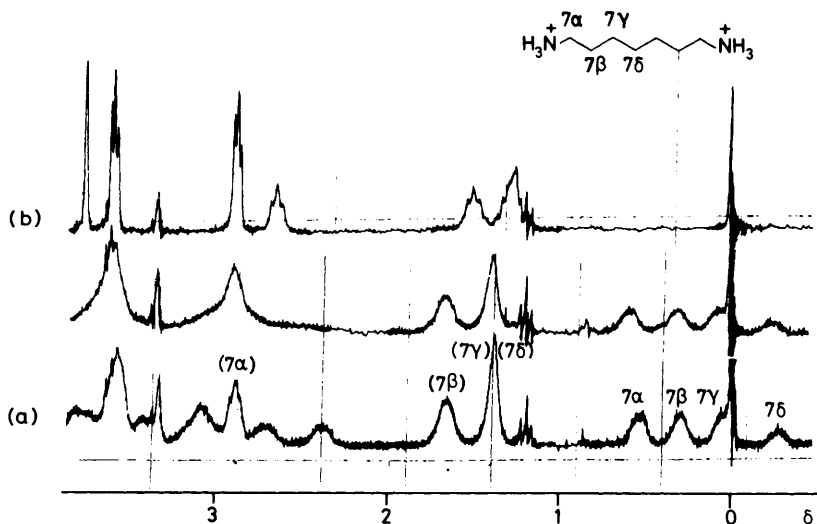


Figure 8 220 MHz ^1H N.m.r. spectrum of a 1:2 mixture of host (14b) and guest $\text{H}_3\text{N}^+(\text{CH}_2)_7\text{NH}_3 \cdot 2\text{NCS}^-$ in CD_2Cl_2 at (a) -60°C and (b) $+45^\circ\text{C}$. The labels $7\alpha, 7\beta$, etc. refer to the indicated CH_2 groups of the guest, entries in parentheses () refer to the free guest cation, other entries refer to the complexed guest cation. This convention is also used in Figures 9–12, 14, 15, and 17–20

alkylammonium cation, $\text{NH}_3^+(\text{CH}_2)_n\text{NH}_3^+$, that can bind to the two crown-ether macrocycles. Thus the ^1H n.m.r. spectrum of a 2:1 mixture of (14b) and $\text{NH}_3^+(\text{CH}_2)_7\text{NH}_3^+$ shows two sets of signals for the guest cation at -60°C (Figure 8a). One set of signals in the range δ 1–3 can be assigned to the methylene groups of the free guest cation while the other set of signals located near the TMS signal can be assigned to the methylene groups of the complexed guest. The upfield chemical shifts of *ca.* 2 p.p.m. for each pair of methylene protons is consistent with the location of the polymethylene chain of the complexed guest cation in the host cavity between the two biphenyl bridges as shown in (15). The observation of two separate sets of signals for the guest cation indicates that the rate of exchange between free and complexed guest is slow on the n.m.r. time scale at low temperatures, but at $+45^\circ\text{C}$ the n.m.r. spectrum shows only one set of averaged signals for the guest (Figure 8b). Thus the tricyclic host (14b) forms the expected inclusion complex (15) with the bis-alkylammonium cation and selectivity for bis-cations of differing length was next investigated. This was achieved through very simple and direct competition experiments. The ^1H n.m.r. spectrum of a 1:1:1 mixture of the host (14b) and the two guest cations $\text{NH}_3^+(\text{CH}_2)_5\text{NH}_3^+$ and $\text{NH}_3^+(\text{CH}_2)_4\text{NH}_3^+$ is shown in Figure 9. The signals from the $(\text{CH}_2)_5$ chain of the longer guest are observable in the high field region of the spectrum whereas the signals from the

$(\text{CH}_2)_4$ group of the shorter guest have chemical shifts identical with those of the free bis-cation. This result shows very clearly that the longer cation is complexed much more readily than the shorter cation.

The results of a similar competition experiment using the pair of cations NH_3^+ - $(\text{CH}_2)_5\text{NH}_3^+$ and $\text{NH}_3^+(\text{CH}_2)_6\text{NH}_3^+$ are shown in Figure 10. In this case the spectrum of a 1:1:1 mixture of the host and the two cations shows very clearly that approximately equal amounts of both cations are complexed. In fact the spectrum of the complexed cations in the high field region ($\delta -1$ to $+1$) is virtually identical with the spectrum obtained using a 1:0.5:0.5 ratio of the host and the two cations, where adequate host is available to complex the whole of the two guests. An extension of this experiment to the pair of guests $\text{NH}_3^+(\text{CH}_2)_6\text{NH}_3^+$ and $\text{NH}_3^+(\text{CH}_2)_7\text{NH}_3^+$ shows that in this case only the shorter cation is complexed (Figure 11) and a similar result is obtained for the pair of cations $\text{NH}_3^+(\text{CH}_2)_7\text{NH}_3^+$ and $\text{NH}_3^+(\text{CH}_2)_8\text{NH}_3^+$ (Figure 12). Thus the selectivity of the host (14b) for the bis-alkylammonium cations $\text{NH}_3^+(\text{CH}_2)_n\text{NH}_3^+$ may be summarized by the sequence

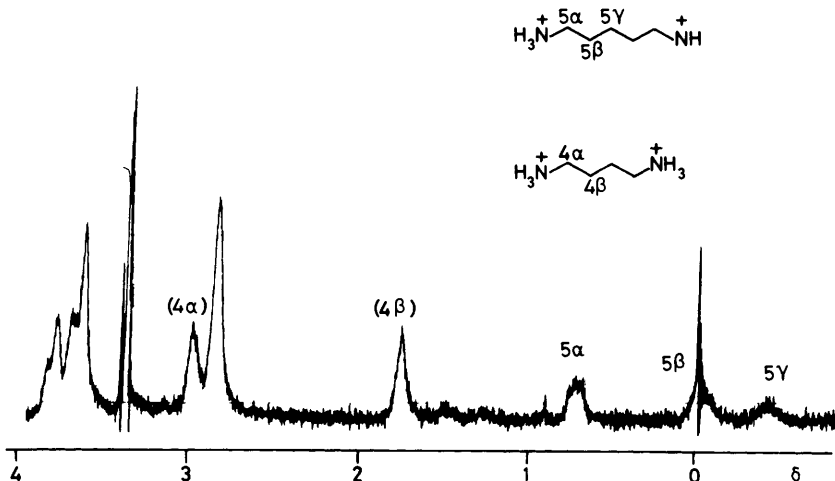
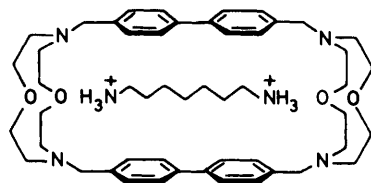


Figure 9 220 MHz ^1H N.m.r. spectrum of a 1:1:1 mixture of host (14b) and guest $\text{H}_3\text{N}^+(\text{CH}_2)_4\text{NH}_3^+ \cdot 2\text{NCS}^-$ and $\text{H}_3\text{N}^+(\text{CH}_2)_5\text{NH}_3^+ \cdot 2\text{NCS}^-$ in CD_2Cl_2 at -60°C

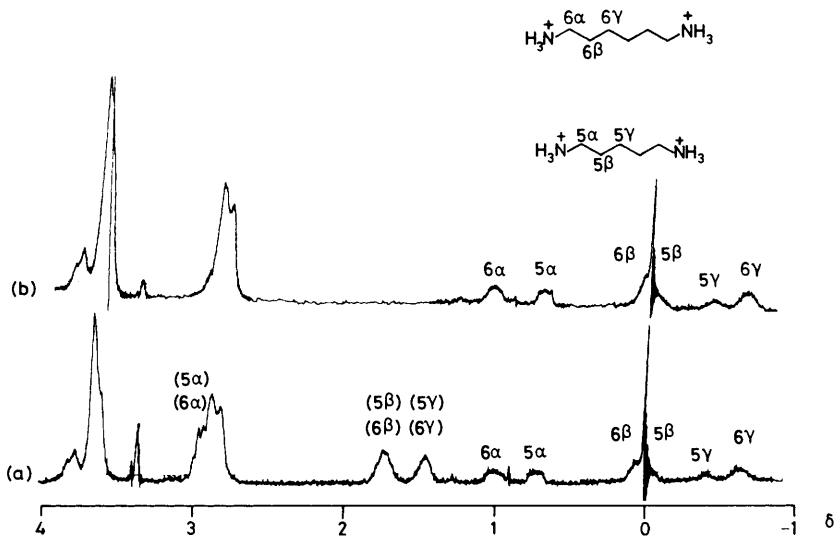


Figure 10 220 MHz ^1H N.m.r. spectrum of host (14b) and guest $\text{H}_3\text{N}^+(\text{CH}_2)_5\text{NH}_3^+\cdot 2\text{NCS}^-$ and $\text{H}_3\text{N}^+(\text{CH}_2)_6\text{NH}_3^+\cdot 2\text{NCS}^-$ in CD_2Cl_2 at $-50\text{ }^\circ\text{C}$ in (a) a 1:1:1 ratio and (b) a 1:0.5:0.5 ratio

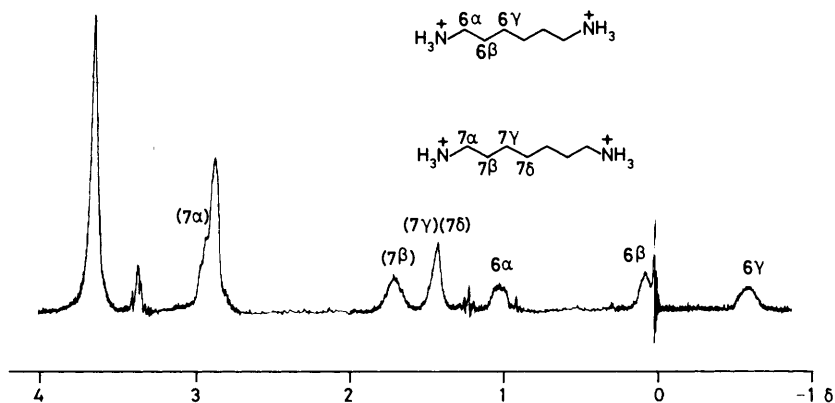


Figure 11 220 MHz ^1H N.m.r. spectrum of a 1:1:1 mixture of host (14b) and guest $\text{H}_3\text{N}^+(\text{CH}_2)_6\text{NH}_3^+\cdot 2\text{NCS}^-$ and $\text{H}_3\text{N}^+(\text{CH}_2)_7\text{NH}_3^+\cdot 2\text{NCS}^-$ in CD_2Cl_2 at $-40\text{ }^\circ\text{C}$

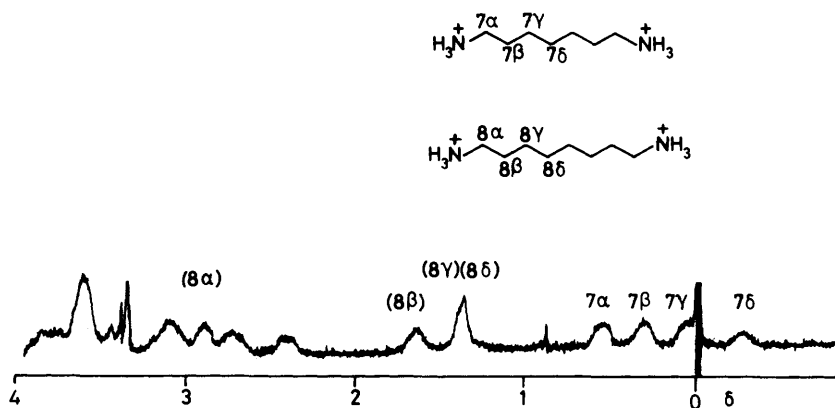


Figure 12 220 MHz ^1H N.m.r. spectrum of a 1:1:1 mixture of host (14b) and guest $\text{H}_3\text{N}^+(\text{CH}_2)_7\text{NH}_3 \cdot 2\text{NCS}^-$ and $\text{H}_3\text{N}^+(\text{CH}_2)_8\text{NH}_3 \cdot 2\text{NCS}^-$ in CD_2Cl_2 at -80°C

shown in Table 1, where the inequality signs refer to substantial differences ($> 5:1$) in association constants for pairs of guests differing by just a single methylene group.

Although the host (14b) was designed primarily as a host for bis-alkylammonium cations it will also form 2:1 inclusion complexes with simple guests such as methylammonium thiocyanate. The host shows a slight preference for forming a 2:1 complex, thus at -80°C the spectrum of a 2:1 ratio of guest and host shows a CH_3N^+ singlet for the guest at δ 0.42 (Figure 13a) corresponding to a 2:1 complex, whereas at the same temperature the spectrum of a 1:1 ratio of guest to host shows a signal at δ 0.42 for the 2:1 complex and a signal at δ 0.38 corresponding to a 1:1 complex (Figure 13b). This slight preference for the formation of a 2:1 complex is presumably associated with a difference in conformation of the free and complexed host. If in the free host the cavity is closed it would be opened in the 1:1 complex so that complexation of a second guest cation is easier than complexation of the first guest cation in spite of the electrostatic repulsion between the cations in the 2:1 complex. This effect may also account for the rather unexpected result observed for competition between the methylammonium cation and the bis-alkylammonium cation $\text{H}_3\text{N}^+(\text{CH}_2)_6\text{NH}_3^+$. Thus the n.m.r. spectrum of a 1:2:1 ratio of the host and the two cations at -60°C shows that the two complexes (14b). $\text{H}_3\text{N}^+(\text{CH}_2)_6\text{NH}_3^+$ and (14b). $2\text{CH}_3\text{NH}_3^+$ are formed in approximately equal amounts (Figure 14a). Kinetically the two complexes differ considerably, since at -30°C the exchange between free and complexed CH_3NH_3^+ is fast on the n.m.r. time scale (Figure 14b) whereas exchange between the free and complexed bis-cation is slow.

It is possible, using the methods outlined above, to determine the extent of guest–host recognition for a number of symmetrical tricyclic hosts (14); the results of this study are summarized in Table 1, which also shows results obtained for the related

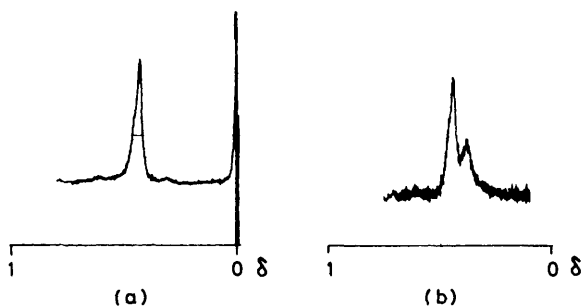


Figure 13 220 MHz ^1H N.m.r. spectrum from δ 0—1 of a mixture of host (14b) and guest $\text{MeNH}_3\cdot\text{NCS}^-$ at -80°C in CD_2Cl_2 in (a) a 1:2 ratio and (b) a 1:1 ratio

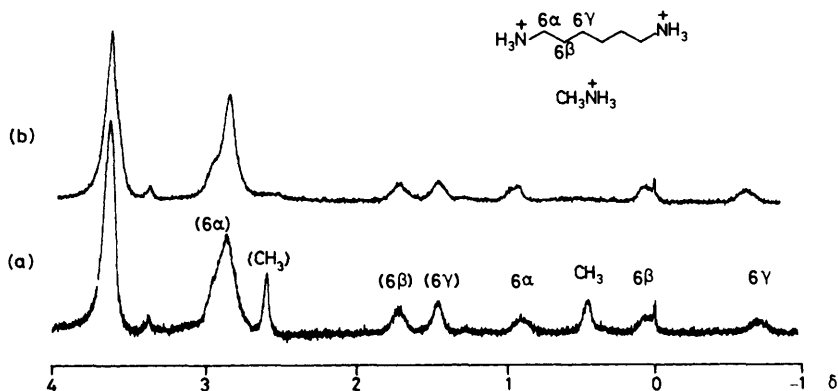


Figure 14 220 MHz ^1H N.m.r. spectrum of a 1:1:2 mixture of host (14b) and guest $\text{H}_3\text{N}^+(\text{CH}_2)_6\text{NH}_3\cdot 2\text{NCS}^-$ and $\text{MeNH}_3\cdot\text{NCS}^-$ in CD_2Cl_2 at (a) -60°C and (b) -30°C

hosts (14f—h) by Lehn and co-workers.³³ It is also possible to use n.m.r. spectroscopy to obtain evidence for the structures of the complexes in solution and one example of this type of study will be discussed. A 1:1:1 mixture of the host (14d) and the two guest cations $\text{H}_3\text{N}^+(\text{CH}_2)_3\text{NH}_3^+$ and $\text{H}_3\text{N}^+(\text{CH}_2)_4\text{NH}_3^+$ at -20°C gives the ^1H n.m.r. spectrum shown in Figure 15a. This spectrum not only clearly indicates preferential complexation of the larger cation but also shows four signals in the range $\delta -1$ to $+1$ which are assignable to four different CH_2 groups in the complexed guest cation. This assignment is confirmed by the ^{13}C n.m.r. spectrum (Figure 15b) which shows four ^{13}C signals for the guest cation at -40°C

³³ F. Kotzyba-Hibert, J. M. Lehn, and P. Vierling, *Tetrahedron Lett.*, 1980, 941; J. P. Kintzinger, F. Kotzyba-Hibert, J. M. Lehn, A. Pagelot, and K. Saigo, *J. Chem. Soc., Chem. Commun.*, 1981, 833; F. Kotzyba-Hibert, J. M. Lehn, and K. Saigo, *J. Am. Chem. Soc.*, 1981, **103**, 4266.

but only two time-averaged signals at +30 °C. Thus the guest cation in the complex must be held in a cavity in which the two ends provide differing environments. The host (14d) can exist in two pairs of conformations, (16a and 16b) and (16c and 16d), which are related by rotation of the naphthalene rings in the bridges. In addition the two conformations within each pair are related by rotation of the macrocycles giving conformations in which the two shorter units ($\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$) are *syn*- and *anti*-related. Consideration of the symmetry of

Table 1 Selectivity in complexation of bis-alkylammonium cations $\text{H}_3\text{N}^+(\text{CH}_2)_n\text{NH}_3^+$ by tricyclic hosts (14) and (17)

| Host | Macrocycles | Bridge ^a | Selectivity ^b |
|-------|-------------|---------------------|--------------------------------|
| (14a) | 12/12 | B | 2 > 3 |
| (14b) | 12/12 | BP | 4 < 5 ~ 6 > 7 > 8 |
| (14c) | 15/15 | B | 2 > 3 > 4 |
| (14d) | 15/15 | N | 3 < 4 > 5 > 6 |
| (14e) | 15/15 | BP | 4 < 5 < 6 > 7 |
| (14f) | 18/18 | B | 3 > 4 ^c |
| (14g) | 18/18 | N | 4 < 5 > 6 > 7 > 8 ^c |
| (14h) | 18/18 | BP | 7 > 8 > 9 ^c |
| (17a) | 15/18 | B | 2 ~ 3 > 4 |
| (17b) | 15/18 | N | 3 < 4 ~ 5 > 6 |
| (17c) | 15/24 | B | 2 < 3 ~ 4 > 5 > 6 |

^a Refers to the Ar unit of (14) and (17), B = benzene, N = naphthalene, and BP = biphenyl. ^b The inequality signs indicate which guest of a pair is complexed in competition experiments. ^c From ref. 33

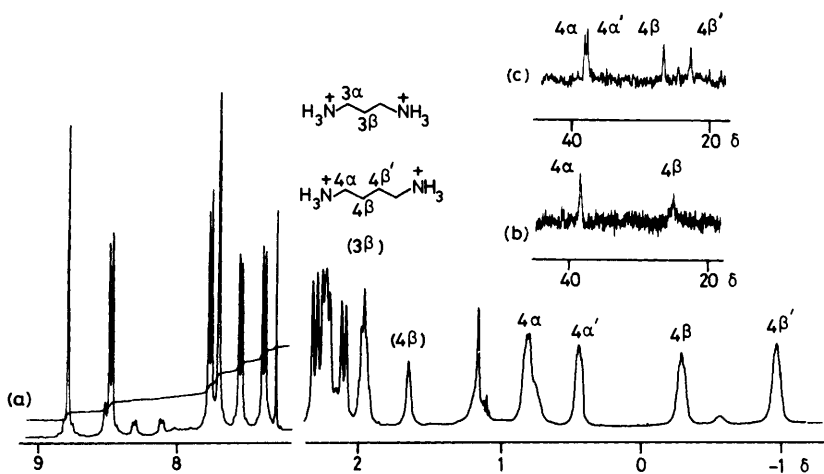


Figure 15 (a) 400 MHz ^1H N.m.r. spectrum of a 1:1:1 mixture of host (14d) and guest $\text{H}_3\text{N}^+(\text{CH}_2)_3\text{NH}_3^+ \cdot 2\text{NCS}^-$ and $\text{H}_3\text{N}^+(\text{CH}_2)_4\text{NH}_3^+ \cdot 2\text{NCS}^-$ in CD_2Cl_2 at -20°C . 90 MHz ^{13}C N.m.r. spectrum from δ 20–40 of a 1:1 mixture of host (14d) and guest $\text{H}_3\text{N}^+(\text{CH}_2)_4\text{NH}_3^+ \cdot 2\text{NCS}^-$ in CD_2Cl_2 at (b) 30°C and (c) -60°C

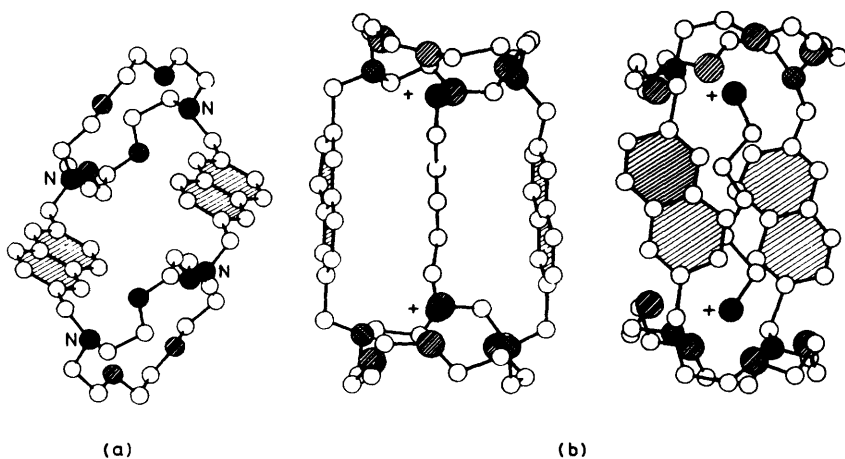


Figure 16 Crystal structure and conformation of (a) host (14g) and (b) complex of host (14g) with guest $\text{H}_3\text{N}^+(\text{CH}_2)_5\text{NH}_3^+$ (taken from ref. 34)

Table 2 Predicted ^1H N.m.r. spectrum for complex (14d). $\text{H}_3\text{N}^+(\text{CH}_2)_4\text{NH}_3^+$

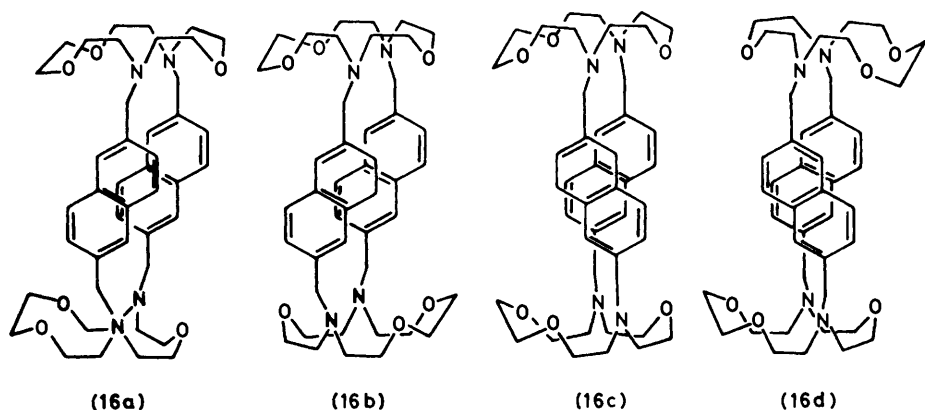
| Host Conformation | Guest Signals | Host Signals | |
|-------------------|------------------------------------|------------------|-------------------|
| | | NCH ^a | Ar-H ^b |
| (16a) | 4 × CH ₂ | 4 doublets | 4 × ABC |
| (16b) | 2 × CH ₂ | 2 doublets | 2 × ABC |
| (16c) | 2 × CH _A H _B | 4 doublets | 4 × ABC |
| (16d) | 2 × CH _A H _B | 4 doublets | 4 × ABC |

^a High field NCH_D doublets of OCH_AH_BCH_CH_DN system. ^b Signals from 2,6-disubstituted naphthalene system

the cavity provided by these four conformations of the host indicates that only one, (16a), would give four guest CH₂ signals in both the ^1H and ^{13}C n.m.r. spectra. Furthermore the complex formed by (16a) would also give six different aromatic proton signals, and four NCH doublet signals as observable in the spectrum (Figure 15a). The predicted appearance of the ^1H n.m.r. spectra of complexes formed by each of the four conformations (16a—d) of host (14d) is summarized in Table 2. Close examination of the ^1H spectrum shown in Figure 15 reveals that a small amount of a second complex, possibly formed by the conformation (16b), is also present.

It is interesting to note that the similar complex (14g). $\text{H}_3\text{N}^+(\text{CH}_2)_5\text{NH}_3^+$ has been examined by X-ray crystallography³⁴ and found to exist in the solid state in a conformation analogous to that found for the complex (14b). $\text{H}_3\text{N}^+(\text{CH}_2)_4\text{NH}_3^+$ in solution. The free host molecule (14g) crystallizes in a conformation (Figure 16a)

³⁴ C. Pascard, C. Riche, M. Cesario, F. Kotzyba-Hibert, and J. M. Lehn, *J. Chem. Soc., Chem. Commun.*, 1982, 357.



in which the cavity is partly filled by the two naphthalene bridges but the conformation of the host (14g) in the crystalline complex (14g). $\text{H}_3\text{N}^+(\text{CH}_2)_5\text{NH}_3^+$ contains a cavity, formed by the two naphthalene bridges and the two crown-ether receptors, into which the guest molecule fits as shown in Figure 16b.

The host (14d) evidently adopts a similar conformation, *cf.* (16a), in its complex with the same bis-cation $\text{H}_3\text{N}^+(\text{CH}_2)_5\text{NH}_3^+$, although this cation is complexed less readily than the shorter cation $\text{H}_3\text{N}^+(\text{CH}_2)_4\text{NH}_3^+$ and much more readily than the longer bis-cation $\text{H}_3\text{N}^+(\text{CH}_2)_6\text{NH}_3^+$ as demonstrated by the spectra shown in Figures 17 and 18.

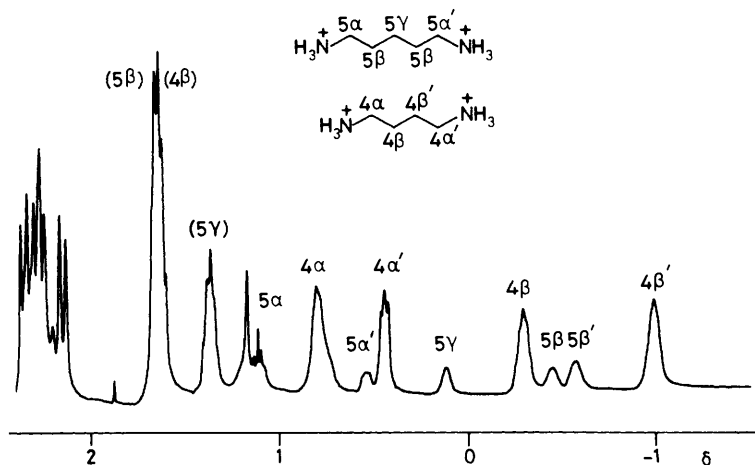


Figure 17 400 MHz ^1H N.m.r. spectrum of a 1:1:1 mixture of host (14d) and guest $\text{H}_3\text{N}^+(\text{CH}_2)_4\text{NH}_3^+\cdot 2\text{NCS}^-$ and $\text{H}_3\text{N}^+(\text{CH}_2)_5\text{NH}_3^+\cdot 2\text{NCS}^-$ at -30°C in CD_2Cl_2

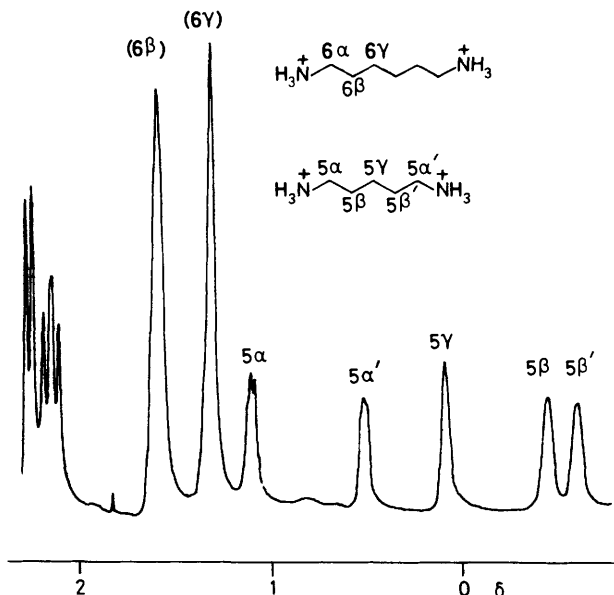


Figure 18 400 MHz ^1H N.m.r. spectrum of a 1:1:1 mixture of host (14d) and guest $\text{H}_3\text{N}^+(\text{CH}_2)_5\text{NH}_3 \cdot 2\text{NCS}^-$ and $\text{H}_3\text{N}^+(\text{CH}_2)_6\text{NH}_3 \cdot 2\text{NCS}^-$ at -20°C in CD_2Cl_2

The selection of a guest bis-cation by the series of symmetrical hosts (14a—e) summarized in Table 1 depends upon the length of the host cavity and upon the size of the crown-ether ring. The adjustment in cavity length obtainable through synthesis is rather coarse, since it is controlled by the length of the aromatic system in the bridge, but it was thought possible that a rather finer adjustment in cavity size might be made through a change in the size of only one of the two crown-ether rings. The series of asymmetrical tricyclic hosts (17a—c) was therefore synthesized³⁵ by the route outlined in Scheme 2 and the selectivity of these hosts in complexation of the same guest bis-cations $\text{H}_3\text{N}^+(\text{CH}_2)_n\text{NH}_3^+$ was examined. The most striking result of this study is the comparison of the selectivity of the closely related hosts (14c) and (17a). Thus the ^1H n.m.r. spectrum of a 1:1:1 mixture of (14c) with the two guests $\text{H}_3\text{N}^+(\text{CH}_2)_2\text{NH}_3^+$ and $\text{H}_3\text{N}^+(\text{CH}_2)_3\text{NH}_3^+$ at 0°C shows clearly that only the shorter guest is complexed (Figure 19), whereas the spectrum of a 1:1:1 mixture of the same two guests and the asymmetrical host (17a) indicates a preference for complexation of the longer guest (Figure 20). Similar changes in selectivity for the related pair of hosts (14d) and (17b) are also observable and in general, from these results and the data summarized in Table 1,

³⁵ K. Lewis, Ph.D. Thesis, University of Liverpool, 1985.

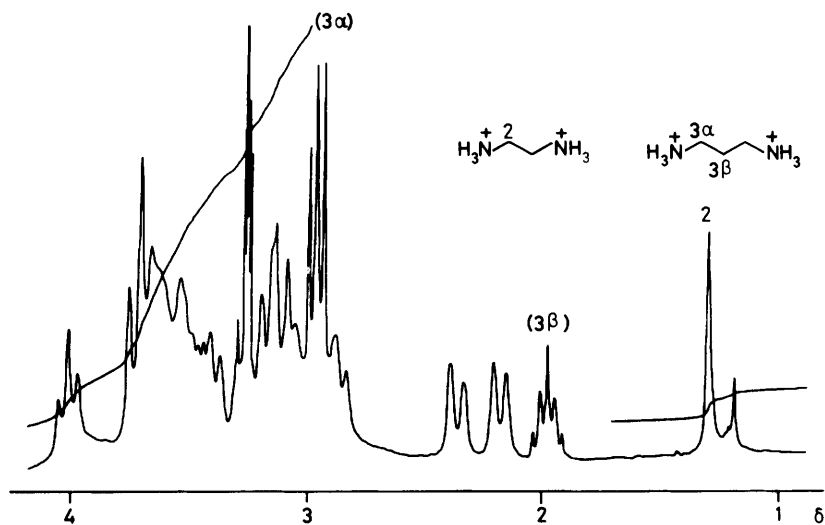


Figure 19 400 MHz ¹H N.m.r. spectrum of a 1:1:1 mixture of host (14c) and guest $\text{H}_3\text{N}^+(\text{CH}_2)_2\text{NH}_3 \cdot 2\text{NCS}^-$ and $\text{H}_3\text{NH}_3^+ \cdot 2\text{NCS}^-$ at 0 °C in CD_2Cl_2

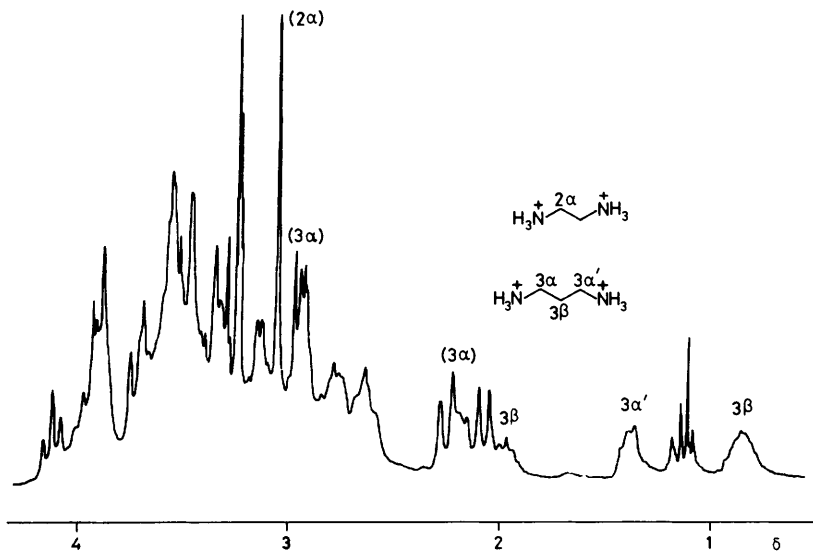


Figure 20 400 MHz ¹H N.m.r. spectrum of a 1:1:1 mixture of host (17a) and guest $\text{H}_3\text{N}^+(\text{CH}_2)_2\text{NH}_3 \cdot 2\text{NCS}^-$ and $\text{H}_3\text{N}^+(\text{CH}_2)_3\text{NH}_3 \cdot 2\text{NCS}^-$ at -21 °C in CD_2Cl_2

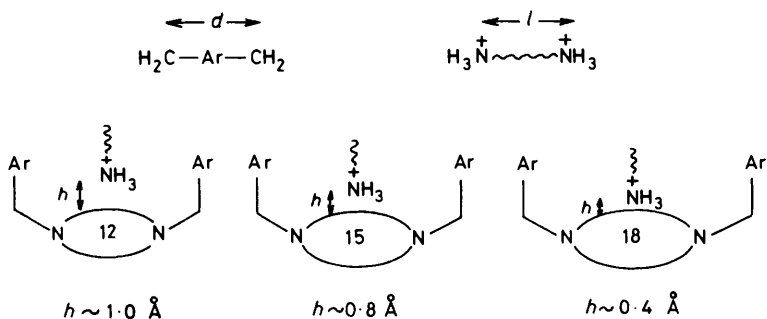


Figure 21 Geometry of complexation of alkylammonium cations by 12-, 15-, and 18-membered diaza crown-ethers. The indicated distance (h) in the complex is based upon the preferred guest length (l) and crown-ether spacing (d) for the selection of bis-alkylammonium cations $\text{H}_3\text{N}^+(\text{CH}_2)_n\text{NH}_3^+$ by the tricyclic hosts (14) and (17) (Table 1)

an increase in size of one or more of the crown macrocycles results in selection of a longer guest bis-cation. A simple explanation of this phenomenon is illustrated diagrammatically in Figure 21, the NH_3^+ group is bound closer to the plane of the macrocycle for the larger macrocycles than for the smaller macrocycles.

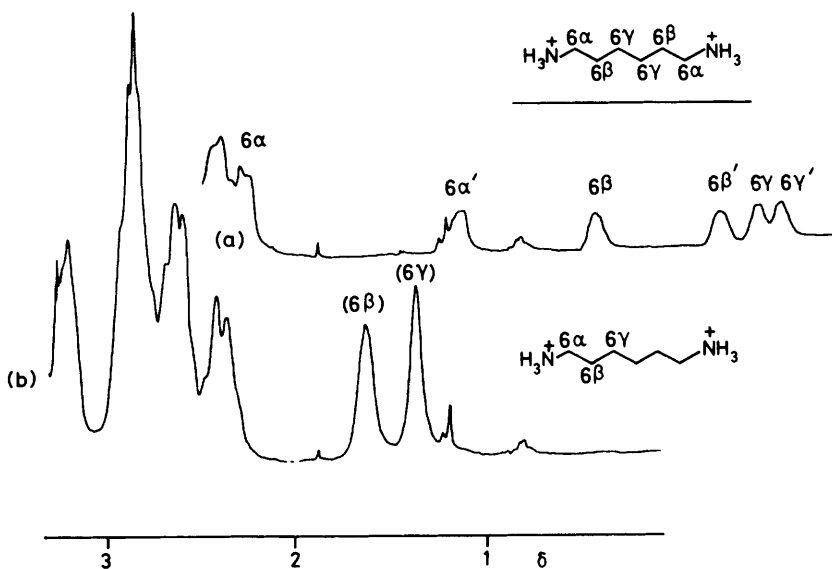
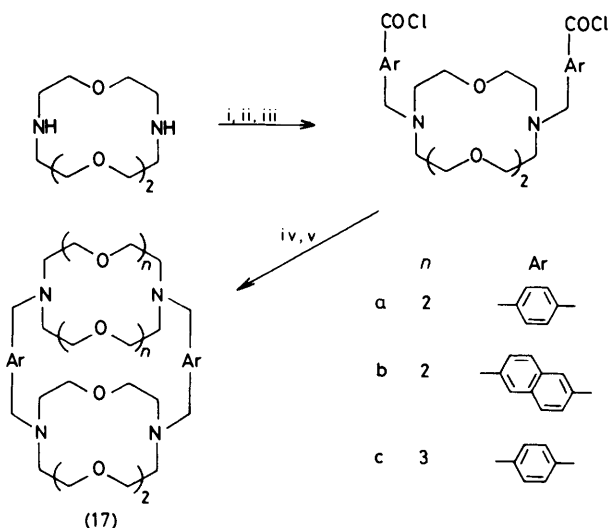


Figure 22 400 MHz ^1H N.m.r. spectrum of host (17b) and guest salt $\text{H}_3\text{N}^+(\text{CH}_2)_6\text{NH}_3^+ \cdot 2\text{NCS}^-$ in CD_2Cl_2 at -23°C for (a) a 1:1 ratio and (b) a 1:2 ratio of host to guest

A further interesting phenomenon was observed for the asymmetrical tricyclic host (17b). This host shows a slight preference for the guest bis-cation $\text{H}_3\text{N}^+(\text{CH}_2)_5\text{NH}_3^+$ as compared with the shorter bis-cation $\text{H}_3\text{N}^+(\text{CH}_2)_4\text{NH}_3^+$ and a strong preference for the former as compared with the longer bis-cation $\text{H}_3\text{N}^+(\text{CH}_2)_6\text{NH}_3^+$. As expected the ^1H n.m.r. spectrum of the complex (17b). $\text{H}_3\text{N}^+(\text{CH}_2)_6\text{NH}_3^+$ shows six different CH_2 signals at high field, assignable as shown in Figure 22a on the basis of spin decoupling experiments. Surprisingly, the addition of an excess of this guest bis-cation apparently destroys the complex and signals assignable to the free bis-cation only are observable (Figure 22b). Thus the bis-cation $\text{H}_3\text{N}^+(\text{CH}_2)_6\text{NH}_3^+$ acts both as a guest and as an inhibitor of complexation when present in excess. The reason for this behaviour is not clear.



Reagents: i, $\text{EtO}_2\text{C-Ar-COCl}$; ii, OH^- ; iii, SOCl_2 ; iv, diaza crown-ether, Et_3N ; v, $\text{B}_2\text{H}_6/\text{THF}$; vi, H^+

Scheme 2 Synthesis of asymmetrical tricyclic hosts

The tricyclic host (17c) is based upon a combination of the relatively rigid 15-crown-5 ring and the much more flexible 24-crown-8 ring. It was therefore of interest to discover whether this host would show reduced selectivity as compared with the hosts (14) and (17a and b). This proved to be the case,³⁵ the host (17c) formed complexes almost equally readily with the three guests $\text{H}_3\text{N}^+(\text{CH}_2)_n\text{NH}_3^+$ ($n = 3-5$), but the longer guest bis-cation $\text{H}_3\text{N}^+(\text{CH}_2)_6\text{NH}_3^+$ was complexed less readily and once again proved to be an inhibitor of complexation when present in an excess.

Selective anion receptors have been examined by Lehn³⁶ and Kimura.³⁷ We wished to discover whether anion binding sites and rigid aromatic bridges could be used in a similar manner to the cation binding sites employed in the tricyclic hosts (14) and (17). Lehn has reported³⁶ that the macrocyclic hosts (18) form strong

complexes with dicarboxylate anions. We therefore synthesized³⁸ the analogous hosts (19) in which each of the polymethylene chains of (18) is replaced by a biphenyl system. The ¹H n.m.r. spectra of a series of potassium salts of dicarboxylic acids, $\text{KO}_2\text{C}(\text{CH}_2)_n\text{CO}_2\text{K}$, are summarized in Table 3 which presents values of $\Delta\delta$, the difference in chemical shift for the various CH_2 groups of the guest in the presence and absence of the host (19). It is noted that for those cases where CPK molecular models suggest that the dicarboxylate anion ($n = 4, 5,$ or 6) fits best into the cavity the values of $\Delta\delta$ are maximized. A change in concentration of both the host and the guest from 10^{-2}M to 10^{-3}M had little or no effect upon the values of $\Delta\delta$ and we conclude that values of K_m must be large.

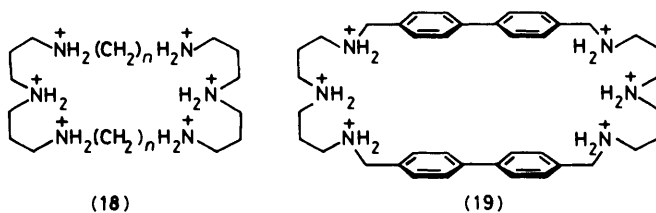


Table 3 Upfield chemical shift ($\Delta\delta$)^a for CH_2 groups of guest dianions $^{-}\text{O}_2\text{C}(\text{CH}_2)_n\text{CO}_2^{-}$ in complexes with cyclophane (19)

| Guest salt <i>n</i> | $\Delta\delta^b$ | | |
|------------------------|------------------|---------|-------------------------------|
| | α | β | $\gamma, \delta, \text{etc.}$ |
| 1 | 0.10 | | |
| 2 | 0.20 | | |
| 3 | 0.31 | 0.32 | |
| 4 | 0.42 | 0.44 | |
| 5 | 0.44 | 0.49 | 0.48 |
| 6 | 0.43 | 0.47 | 0.47 |
| 7 | 0.31 | 0.37 | 0.39 |
| 8 | 0.21 | 0.27 | 0.30 |
| 9 | 0.13 | 0.20 | 0.25 |

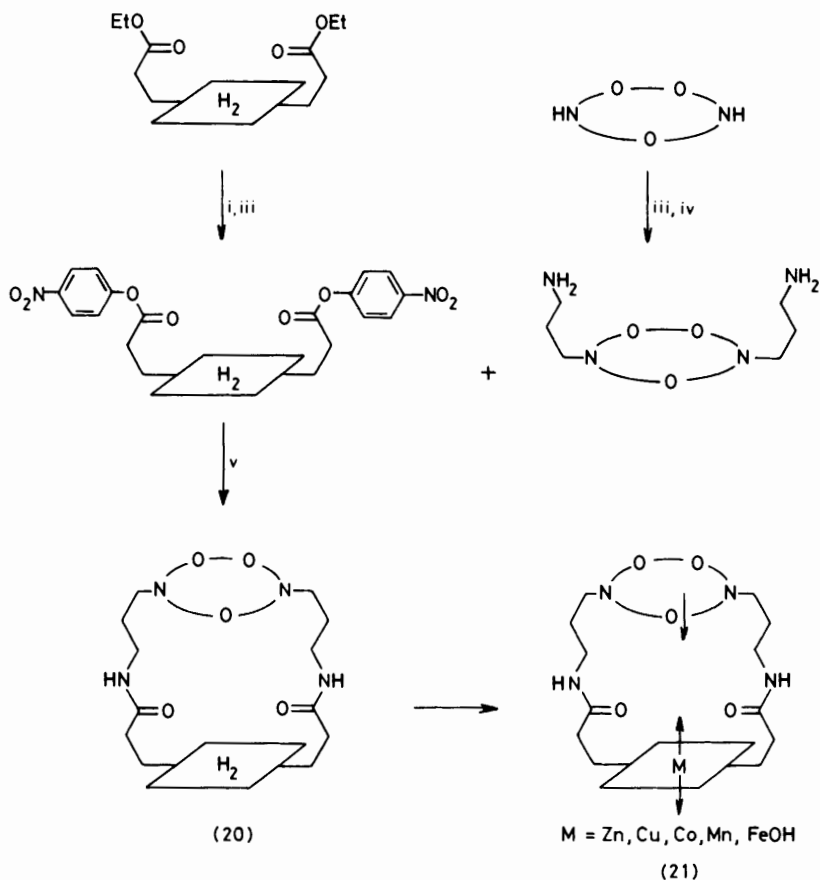
^a 400 MHz ¹H n.m.r. spectra run for 10^{-3}M solutions of a 1:1 ratio of (19).6Br⁻ and guest salt $\text{KO}_2(\text{CH}_2)_n\text{CO}_2\text{K}$ in $\text{H}_2\text{O}-\text{MeCN}$ (80:20). Chemical shifts are not significantly different for 10^{-2}M solutions. ^b The headings $\alpha, \beta, \text{etc.}$ refer to $^{-}\text{O}_2\text{CC}(\alpha)\text{H}_2-\text{C}(\beta)\text{H}_2-$ etc. of the guest dianion




³⁶ F. Vögtle, H. Siger, and W. M. Müller in 'Host Guest Complex Chemistry I', ed. F. Vögtle, Springer, Berlin and Heidelberg, 1981, p. 143; B. Dietrich, M. W. Hosseini, J. M. Lehn, and R. B. Sessions, *J. Am. Chem. Soc.*, 1981, **103**, 1282; F. Peter, M. Gross, M. W. Hosseini, J. M. Lehn, and R. B. Sessions, *J. Chem. Soc., Chem. Commun.*, 1981, 1067; M. W. Hosseini and J. M. Lehn, *J. Am. Chem. Soc.*, 1982, **104**, 3525.

³⁷ E. Kimura, A. Sakonaka, T. Yatsunami, and M. Kodama, *J. Am. Chem. Soc.*, 1981, **103**, 3041; E. Kimura, M. Kodama, and T. Yatsunami, *J. Am. Chem. Soc.*, 1982, **104**, 3182; E. Kimura, A. Sakonaka, and M. Kodama, *J. Am. Chem. Soc.*, 1982, **104**, 4984; E. Kimura, A. Watanabe, and M. Kodama, *J. Am. Chem. Soc.*, 1983, **105**, 2063.

³⁸ J. A. E. Pratt, Ph.D. Thesis, University of Liverpool, 1983.

Having examined complexes of both cationic and anionic guests using hosts with electron-rich and positively charged receptor sites respectively, it was of interest to design a system containing both types of receptor site. We selected³⁹ a diaza 15-crown-5 macrocycle as the electron-rich receptor and a metalloporphyrin as the cationic or electron-deficient receptor, the latter was chosen because of its well defined geometry and because a very wide range of metallated porphyrins has been

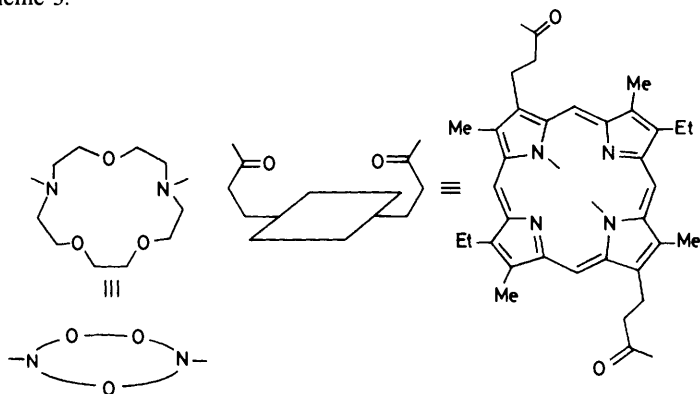


Reagents: i, $\text{CF}_3\text{CO}_2\text{H}$, HCl ; ii, $\text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{O}_2\text{CCF}_3$, ; iii, ;
 iv, $\text{B}_2\text{H}_6/\text{THF}$, HCl ; v, , Δ ; vi, M^{n+} salt

Scheme 3

³⁹ N. M. Richardson, I. O. Sutherland, P. Camilleri, and J. A. Pape, *Tetrahedron Lett.*, 1985, **26**, 3739.

In Scheme 3:



studied.⁴⁰ The two types of receptor must be connected together with suitable covalent links and for this reason the host system was further defined as the metallated diaza 15-crown-5 capped mesoporphyrin II system (21). This was expected to have the ability to bind cations and anions in the directions indicated by the arrows in the structure. It was also expected to be a suitable host for (i) both components of a metal salt $M^+ \cdot X^-$ or all three components of the salt $M^{2+} \cdot 2X^-$, (ii) both components of an ammonium salt $RNH_3^+ \cdot X^-$, (iii) the functionalized ammonium salt $Y \sim NH_3^+ \cdot X^-$, and (iv) of the betaine system $Z^- \sim NH_3^+$. The synthesis of (21) involved the conventional route shown in Scheme 3, based upon the synthesis of an analogous crown-capped porphyrin⁴¹ and also the synthesis of face-to-face porphyrin systems.⁴² The capped porphyrin (20) was readily converted into the monometal complexes (21) by established metallation procedures.⁴⁰

Our first investigation of the capped porphyrin system (21) involved the zinc porphyrin (21, $M = Zn$) and a study of bimetal complexes (22), formed by complexation of a second metal-cation at the crown-ether macrocycle. Although the crown-ether cap has the ability to complex a wide range of metal cations the fluorescence spectrum of the zinc porphyrin system responded to complexation only in cases where a paramagnetic guest cation was involved. No effect was observed for Zn^{II} , Mg^{II} , Ba^{II} , and alkali-metal cations. This contrasts with the behaviour of the anthracene capped crown-ether (23) recently studied by Lehn and co-workers,⁴³ where fluorescence quenching was rather general for cation

⁴⁰ 'Porphyrins and Metalloporphyrins', ed. K. M. Smith, Elsevier, Amsterdam, 1975.

⁴¹ C. K. Chang, *J. Am. Chem. Soc.*, 1977, **99**, 2819.

⁴² J. P. Collman, F. C. Anson, C. E. Barnes, C. S. Berscome, T. Geiger, E. R. Evitt, R. P. Kreh, K. Meier, and R. B. Pettman, *J. Am. Chem. Soc.*, 1983, **105**, 2964.

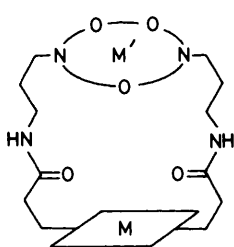
⁴³ J. P. Konopelski, F. Kotzyba-Hibert, J. M. Lehn, J. P. Desvergne, F. Fages, A. Castellan, and H. Bouas-Laurent, *J. Chem. Soc., Chem. Commun.*, 1985, 433.

complexation. By non-linear regression analysis of the relationship between the extent of fluorescence quenching and change in the concentration of the guest cation it was possible to derive the association constants for complexation and the efficiency of fluorescence quenching in the bimetal complexes; these data are reported in Table 4. The degree of fluorescence quenching evidently depends upon the nature of the metal cation in the crown-ether cavity and is only observable for paramagnetic guest metal-cations M^{n+} in (22). It is probably associated with the magnetic effect of the guest cation⁴⁴ although electron transfer⁴⁵ cannot be completely ruled out. Bimetal complexes (22) have also been examined using FAB mass spectrometry;⁴⁶ equimolar mixtures of the capped zinc porphyrin and Cu^{II} , Fe^{II} , and Fe^{III} triflate salts gave peaks in the FAB mass spectrum corresponding to

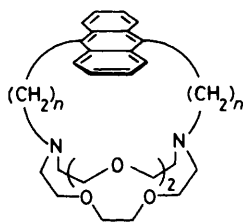
Table 4 Association constants and fluorescence quenching for metal ion complexation by capped porphyrin (21)

| M' salt | K_a/M^{-1} a,c,d | $I_{ML}\%$ b,c,d | K_a/M^{-1} d,e |
|------------------|--------------------|------------------|-------------------|
| $Cu^{II}Cl_2$ | 3.6×10^4 | 86 | |
| $Cu^{II}(OAc)_2$ | 9.3×10^4 | 88 | 1.5×10^4 |
| $Fe^{III}Cl_3$ | 1.1×10^4 | 69 | 8.0×10^3 |
| $Fe^{II}SO_4$ | 4.2×10^4 | 90 | 4.1×10^3 |
| $Mn^{II}(OAc)_2$ | 2.2×10^3 | 83 | 4.5×10^2 |
| $Ni^{II}(OAc)_2$ | 1.4×10^3 | 94 | |
| $Co^{II}(OAc)_2$ | 7.2×10^2 | 83 | |
| | 7.2×10^2 | | |

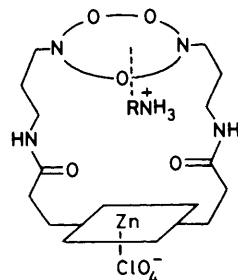
^a Obtained by non-linear regression analysis of fluorescence quenching for different concentration of (21) and M' salt in methanol. ^b Limiting intensity when all the ligand is bound. ^c Data for (21, $M = Zn$). ^d Excitation wavelength 540 nm ($M = Zn$) and 500 nm ($M = Cu$) and emission recorded from 557–700 nm ($M = Zn$) and 525–700 nm ($M = Cu$). Quenching at 567 nm ($M = Zn$) and 531 nm ($M = Cu$). ^e Data for (21, $M = Cu$)



(22)



(23)



(24)

⁴⁴ G. Blandeal, A. Harriman, G. Porter, and A. Wilowska, *J. Chem. Soc., Faraday Trans. 2*, 1984, **80**, 867; G. Porter and M. R. Wright, *Discuss. Farad. Soc.*, 1959, **27**, 18.

⁴⁵ M. C. Gonzalez, A. R. McIntosh, J. R. Bolton, and A. C. Weedon, *J. Chem. Soc., Chem. Commun.*, 1984, 1138; J. K. M. Sanders and P. Leighton, *J. Chem. Soc., Chem. Commun.*, 1984, 854, 856; P. Leighton and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*, 1985, 24.

⁴⁶ R. A. W. Johnstone, I. A. S. Lewis, and M. E. Rose, *Tetrahedron*, 1983, **39**, 1597; R. A. W. Johnstone and M. E. Rose, *J. Chem. Soc., Chem. Commun.*, 1983, 1268.

the bimetal species (22, $M = Zn$). M'^+ ($M' = Cu, Fe$). Other bimetal species have also been observed in this way.

The capped zinc porphyrin (21, $M = Zn$) was also examined as a host for alkylammonium salts, using changes in the porphyrin absorption spectrum to detect complex formation and to determine association constants. The results of this study show little discrimination between the mono- or di-perchlorate salts of the diamines $H_2N(CH_2)_nNH_2$ ($n = 2, 3, \text{ or } 4$) and ethylammonium perchlorate. It appears that the complexes are probably of the type shown in (24), where the perchlorate counterion is attached to the zinc and a cationic species is bound to the crown-ether macrocycle. Other porphyrin crown-ether systems have been described^{47,48} and the complexation of metal ions⁴⁷ and alkylammonium cations⁴⁸ has been studied. These preliminary results indicate that further study of these heteropolytopic receptors of this type should be rewarding.

Conclusions.—The work that has been reported in this article, and the very extensive work on guest–host chemistry that has been reported since 1967, show that substantial progress has been made in the design and synthesis of host molecules that will complex guest molecules selectively. In some cases the efficiency of this selection process is similar to that shown by natural proteins. The potential applications of this new chemistry are indicated by studies of catalysis and transport. The design of synthetic host molecules as selective ligands in ion-selective electrodes and other types of metal-cation sensors has been extensively studied and developed. Application of similar methods in sensors for organic molecules would be a logical extension of the work on metal cations. Finally, the much more difficult area of complexes in aqueous solution has recently been opened up by the use of water-soluble cyclophanes. This impressive amount of progress in a relatively short period suggests that organic chemists will be capable of the design and synthesis of host molecules that have many of the properties of natural proteins. These synthetic host molecules are potentially without the limitations on substrate structure, reaction type, and nature of response that are imposed by biological systems.

Acknowledgements. It is a pleasure to thank my co-workers who are named in the references for their important contributions to the work described in this review. I also wish to acknowledge with thanks our fruitful collaboration with Dr. R. F. Newton of Glaxo Research and Dr. P. Camilleri of Shell Research and the support given by their companies for our work. Finally I wish to record my appreciation for the many excellent 400 MHz spectra run by the SERC n.m.r. service at Sheffield.

⁴⁷ V. Thanabal and V. Krishnan, *J. Am. Chem. Soc.*, 1982, **104**, 3643.

⁴⁸ A. D. Hamilton, J. M. Lehn, and J. L. Sessler, *J. Chem. Soc., Chem. Commun.*, 1984, 311.