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Molecular Recognition by Macropolycyclic Hosts

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Abstract. The formation of complexes between crown ethers and aklylammonium cations may, to some extent, be modelled using standard molecular mechanics methods and an appropriate charge distribution scheme. Monocyclic crown ethers may be developed to give chromoionophores suitable for use in optical fibre based ion sensors. The incorporation of two crown ether systems into polycyclic host molecules which show highly selective complexation of guest bis-alkylammonium cations is described. The scope of these ditopic receptors may be extended by using metalloporphyrins in place of one or both of the crown ether binding sites.

Key words. Aza crown ethers, ditopic hosts, metalloporphyrins, molecular modelling, chromoionophores.

The formation of molecular complexes in solution by protein host molecules (Equation 1) has long been recognised as an essential feature of many biological processes [1]. The current wide interest in synthetic host molecules dates from the discovery of the crown ethers by C. J. Pedersen in 1967 [2], their development by the pioneering work of D. J. Cram and his coworkers [3], and the invention of cryptand host molecules by J.-M. Lehn [4].[1]

$$\text{Host} + \text{Guest} \overset{K_s}{\rightleftharpoons} \text{Host} \cdot \text{Guest} \qquad (1)$$

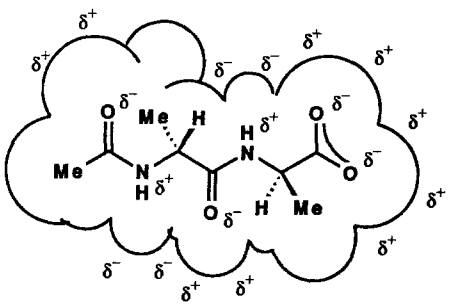
These early studies led to our initial interest in cyclophanes and macropolycyclic compounds of the aza-crown ether type [5] which has developed into the research described in this paper.

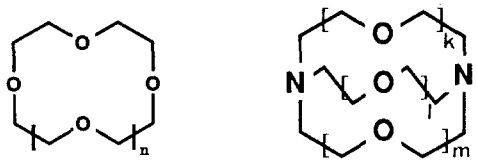
The relative importance of the different types of non-covalent binding forces between guest and host molecules that can lead to an appropriate value for the association constant for complexation (K_s of Equation 1) depends upon the solvent [6]. For most of the examples that will be discussed in this paper complexation takes place in organic solvents ($CHCl_3$, CH_2Cl_2 and their perdeuterated derivatives) and is based upon electrostatic attraction between the two components, in some cases this is manifested as hydrogen bonding.

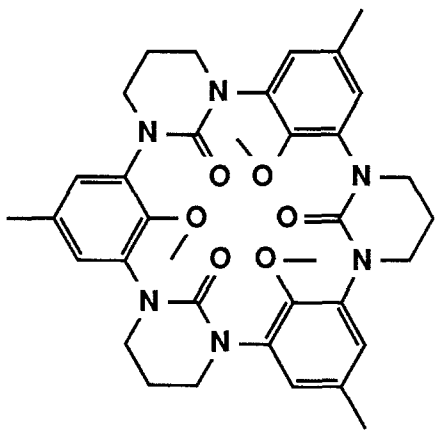
Hydrophobic interactions, which are of major importance for complexation in aqueous solvents [7], are not available in organic solvents so that for most examples involving high binding energies (>6–10 kcal mol^{-1}) one of the components of the complex is either a cation, or less frequently, an anion [8]. For cationic guests the host molecule must contain electron rich atoms, usually N or O, as binding sites. In principle, the ideal host for any particular guest contains a cavity with size, shape and charge distribution complementary to those of the guest as shown

diagrammatically in Figure 1 for guest D-ala–D-ala. The principles of host design are therefore simple but the translation of the curved lines of Figure 1 into a real host molecule for D-ala–D-ala is a formidable problem which to date has been solved only by nature [9] (vancomycim and related antibiotics).

Relatively simple synthetic host molecules, such as coronands [2], cryptands [4], and spherands [3], for example **1–3**, contain circular or spherical cavities which are ideally suited for simple spherical guest metal cations or, in appropriate cases, for alkylammonium cations. Guest recognition for both types of guest can be achieved by careful design of the host molecule for all three structural types.







1 Coronands **2** Cryptands **3** Spherand

Fig. 1.

Host molecules **1–3** have usually been designed by studies of CPK molecular models [3] but, to some extent, these classical models are now being replaced by computer based modelling [10]. This requires a graphics terminal together with software to provide graphical input and output of structures and their three dimensional manipulation, in addition molecular mechanics programs are needed for calculating conformational energies and intermolecular interactions.[2] Molecular mechanics programs will usually locate energy minima with acceptable accuracy but the calculated steric energies and, to a lesser extent, molecular geometries depend upon the parameters of the force field. These parameters include the usual terms for bond lengths, bond angles, torsion angles, and non-bonded interactions, but for calculations involving complexation by electrostatic attraction additional parameterisation for charge distribution is of great importance. For our work we have used the charge scheme developed by R. J. Abraham and his coworkers [11]. This charge scheme, used with the force field [12] contained in the COSMIC package,[3] gives reasonable values for the energetics of inversion of the chair conformations of

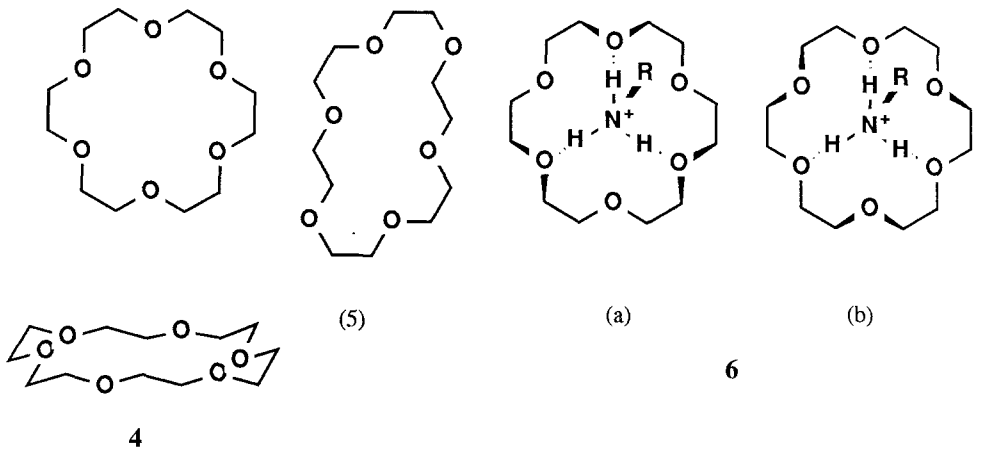


Fig. 2.

six-membered rings (cyclohexane, dioxan, tetrahydropyran and *N*-methylpiperidine) and the relative energies of different conformations of crown ethers. For example it correctly assigns a lower steric energy to the conformation **5** of 18-crown-6 which is found in the crystal structure of the free host as compared with the well known D_{3d} conformation **4** which is found in 18-crown-6 complexes. The difference in these steric energies (ΔE 8.4 kcal mol^{-1}) resides very largely in the different electrostatic energies (ΔE 7.3 kcal mol^{-1}) of the two conformations.

Calculated binding energies of alkylammonium cations by 18-crown-6, using the same charge scheme **8** and the COSMIC force field are much too large (ΔE 50–60 kcal mol^{-1}) but the calculations neglect the effects of the solvent, polarisability of the two interacting molecules, and counter-ion association. The results are in accord with the very limited guest recognition shown [13] in the formation of the complexes 18-crown-6·RN^+H_3 and they also indicate that, although the two possible minimum energy arrangements of guest and host in the complex show well defined N^+—H—O hydrogen bonds, there is little or no distinction in binding energy between hydrogen bonding to the three oxygen atoms on the upper face of the host **6a** as compared with the oxygen atoms on the lower face of the host **6b**.

The most favorable conformations of free crown ethers are those in which the unfavourable O—O interactions associated with *gauche* C—C bonds are avoided as far as possible by the inclusion of one or more *anti* C—C bonds in the ring system. In contrast, the most suitable conformations of crown ethers for complexation of cations are those in which all the C—C bonds are *gauche*. At the present time, computer based molecular modelling provides only a qualitative approach to the design of host molecules for specific guests and the rationalisation of experimental observations. Accurate molecular modelling will require: (i) correct assessment of the effects of solvent, molecular polarisability, and counter ion, (ii) the use of well based schemes for charge distribution and force fields that are appropriate for these charges, and (iii) the identification of global conformational energy minima for both the free host and the complex. Thus many different conformations of comparable steric energy can be found for most macrocycles (>12 members) and although only a limited number have been recognised in crystal structures relating to any particular ring system the situation in solution is not easily defined. For

example, NMR spectroscopy will only define solution conformations within the limitations of signal averaging by molecular motion [14] and other physical data may also represent the average of two or more equilibrating conformations. None of these problems is trivial but, nevertheless, it would be surprising if computer based molecular modelling does not become a reliable procedure for host design and the investigation of guest/host interactions.

Although most of our work has been concerned with complexes of alkylammonium cations [15] we have recently been interested in the development of optical fibre sensors [16] for metal cations.[4] This involves the use of a chromoionophore [17] which can be placed at the end of an optical fibre, the chromoionophore responds to cation complexation with a colour change that can be detected using a suitable light source and detection system at the other end of the optical fibre. Chromoionophores are of two types, neutral and ionisable. The former contain a polarised chromophore, as shown diagrammatically in **7a** and **7b**, which responds to the capture of a cation with a shift in absorption spectrum to shorter wavelength **7a** or longer wavelength **7b**. A number of neutral chromoionophores **8** and **9** of both types were investigated but they were found to be unsuitable due to their limited spectroscopic response and their low sensitivity [18]. The ionisable chromoionophores **10** have proved to be much more suitable. These respond to metal ion complexation by forming the salts **11**, which, for suitable chromophores, gives a very substantial change in the absorption spectrum.

A number of ionisable chromoionophores **12** and **13** have been tested and compound **12b**, which changes colour from yellow to purple on cation complexation, proved suitable for the detection of K^+ (KCl in H_2O) in the pH range 7–9 at concentrations (1–100 mM) similar to those found in blood plasma (blood $K^+ \sim 4.5$ mM). The K^+/Na^+ selectivity ratio (6.4) was too low to determine K^+

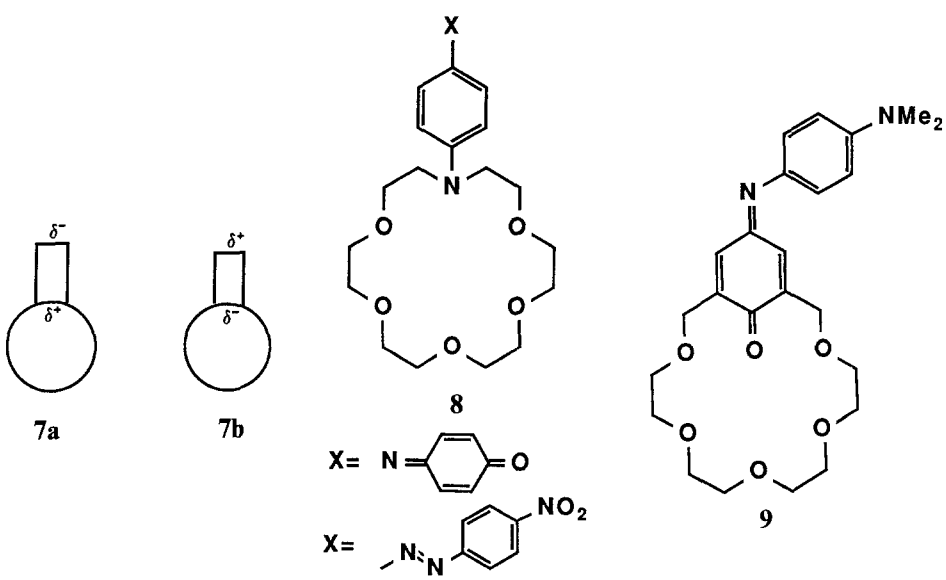


Fig. 3.

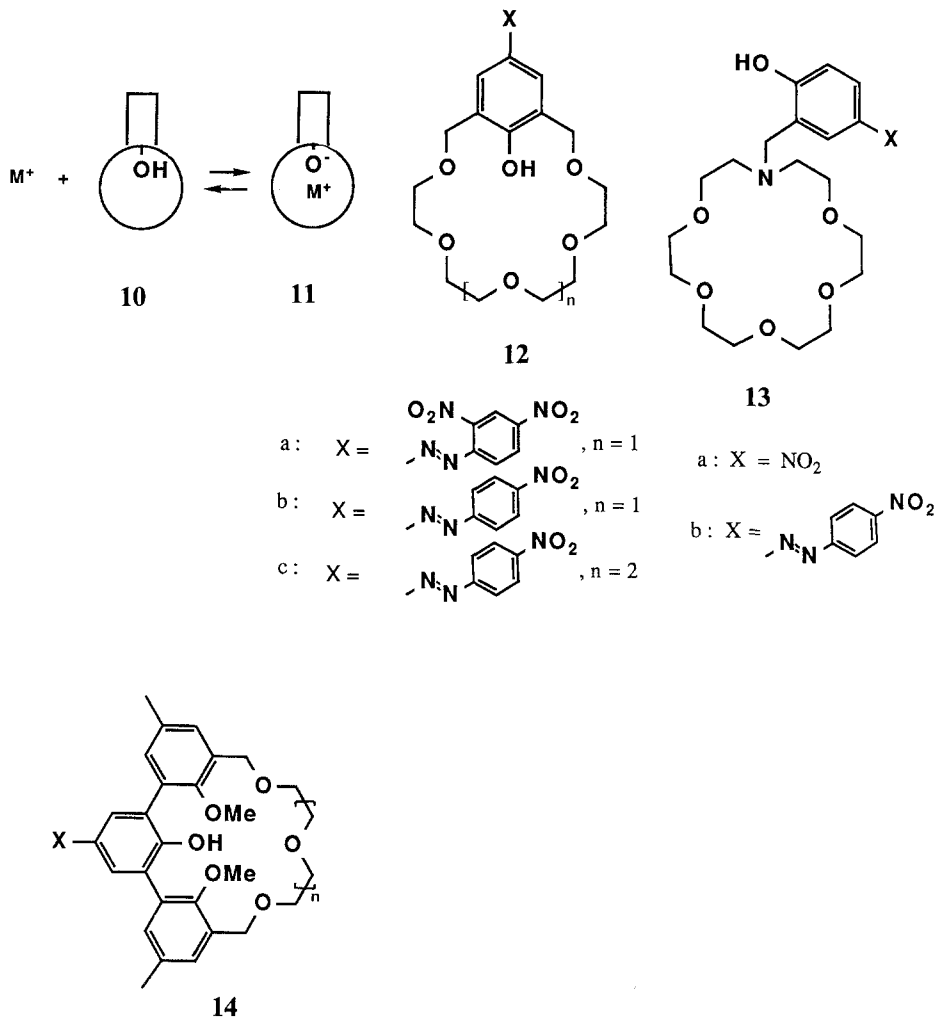


Fig. 4.

levels in blood (Na^+/K^+ ratio ~ 30) and current work is focused upon improving this selectivity by using a suitable modified hemispherand system [19], such as **14**, or a valinomycin mimic [20] such as a suitably modified dibenzo-30-crown-10.

A high level of recognition of guest alkylammonium cations by hosts of the crown ether type was identified as an important objective at the outset of our work. Because complexation of primary alkylammonium cations by simple monocyclic crown ethers, such as 18-crown-6, gives only a very low level of guest recognition [13] our initial studies were directed towards the inclusion of the guest cation in the cavity of a cryptand host [4], as in **15**. Such a molecular inclusion in solution would clearly require the use of a host molecule in which the binding forces are directed towards the centre of the molecular cavity, as indicated by the arrows in **15** to avoid the competitive formation of externally bound complexes such as **16**. Without this stereoselective inward binding exclusion complexes **16** will tend to be formed to

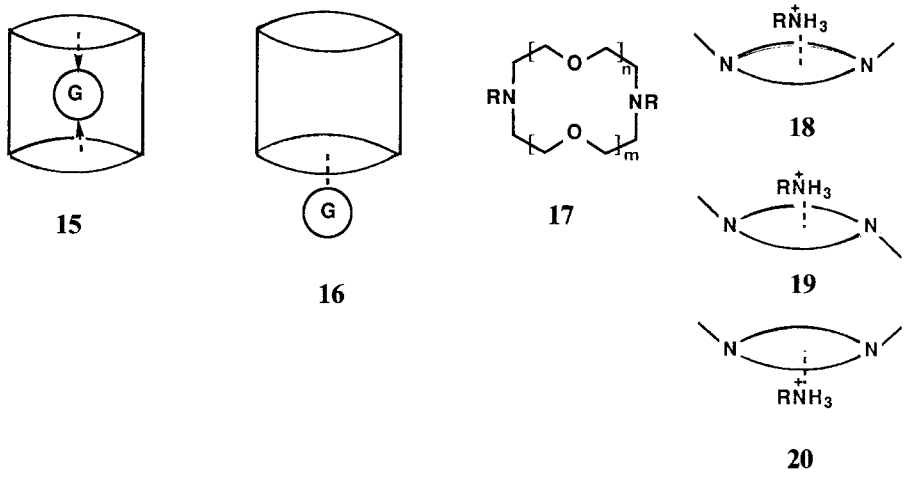
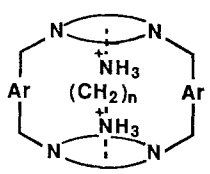


Fig. 5.

avoid unfavourable van der Waals interactions which inevitably result from imperfect design of the host cavity. We were fortunate to find [21] that diaza crown ethers with twelve-membered (**17**, $m = n = 1$) and fifteen-membered (**17**, $m = 1, n = 2$) rings formed only the *cis,cis*-complexes **18** with guest alkylammonium cations RNH_3^+ whereas the larger eighteen-membered diaza-crowns (**17**, $m = n = 2$ or $m = 1, n = 3$) formed mixtures of *cis,cis*-**18**, *cis,trans*-**19** and *trans,trans*-**20** complexes. These studies, based upon ^1H NMR spectroscopy, have been fully described elsewhere.

Following these preliminary studies, it was possible to design host molecules of the type shown in **15**, based upon diaza-12-crown-4 and diaza-15-crown-5 receptors, which would form inclusion complexes with either one bisalkylammonium cation $H_3N^+(CH_2)_nN^+H_3$ **21** or two simple primary alkylammonium cations RN^+H_3 **22**. The use of tricyclic compounds of this type has been described elsewhere [23]. The cryptands **23**, which are based upon two identical diaza-crown ether moieties, were synthesised by the simple one step procedure shown in Scheme 1, whereas it was necessary to use the stepwise procedure [24] summarised in Scheme 2 for the synthesis of analogous cryptands **24** in which the two diaza crown ether moieties are different.

It was found that, in general, the rather rigid tricyclic hosts **23** and **24** selected one or two members from the series of *bis*-cations $H_3N^+(CH_2)_nN^+H_3$ (Table I) and that guest selection could be assessed readily from the ^1H NMR spectra of a 1 : 1 : 1 mixture of the host with a pair of competing guest cations [23]. A clear distinction between the spectra of free and complexed *bis*-cations results from the large induced high field shifts (2–4 ppm) of the guest CH_2 protons because they lie in the shielding zones of the two aromatic systems [Ar in **23** and **24**] of the bridges. The selectivity is summarised in the Table[5] and from the results it can be seen that guest selection depends upon the length of the CH_2ArCH_2 bridge and the size of the aza crown macrocycles. If it is assumed that for the optimum guest $H_3^+N(CH_2)_nN^+H_3$ the $N^+—N^+$ separation in the fully extended (all *anti*) conformation of the guest *l* Å is



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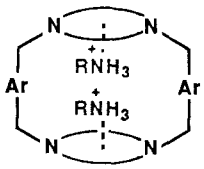

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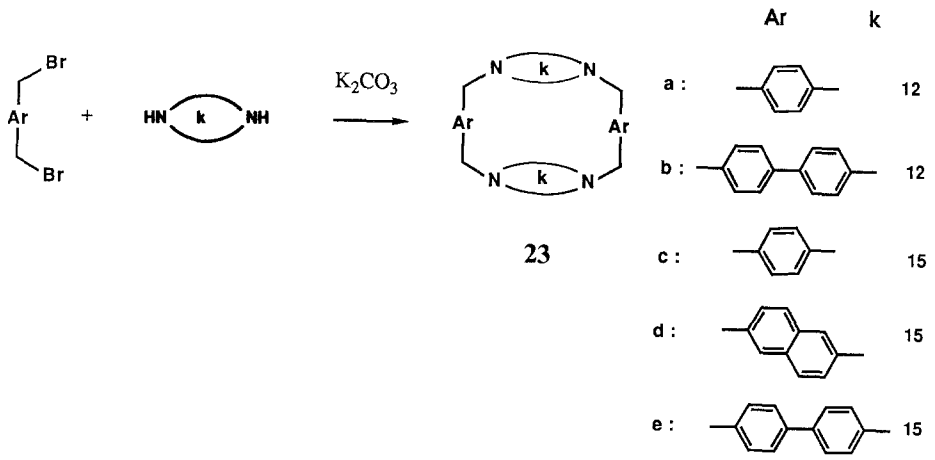

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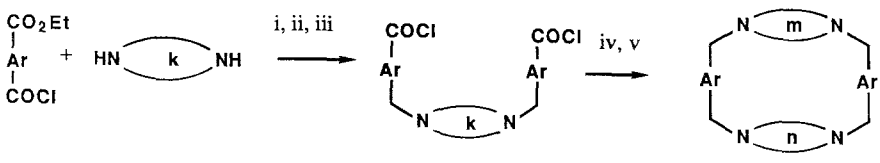
Scheme 1. Synthesis of symmetrical cryptands (**23**).



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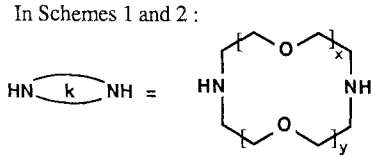
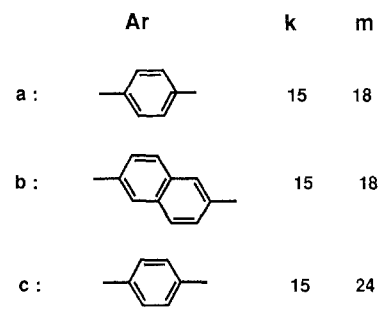
In Schemes 1 and 2 :



for m/k = 12 : x = y = 1

m/k = 15 : x = 1 , y = 2

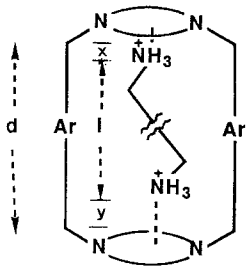
m/k = 18 : x = y = 2



Reagents : i, Et_3N ; ii, NaOH / EtOH , then H^+ ; iii, $(COCl)_2$; iv, HN⌒m⌒NH , Et_3N

v, BH_3 / THF, then H^+ / EtOH

Scheme 2. Synthesis of asymmetrical cryptands.



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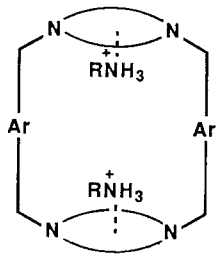

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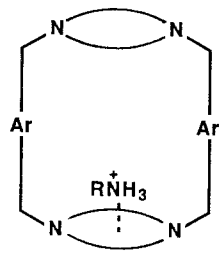

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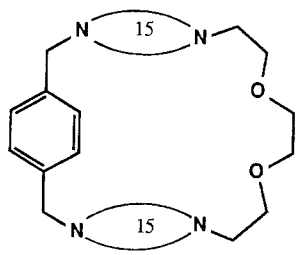


28

Fig. 6.

Table I. Selectivity in complexation of salts $H_3(N^+(CH_2)N^+H_3 \cdot 2\,NCS^-$ by cryptands **23** and **24** in CD_2Cl_2.

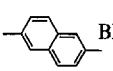
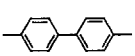
Ar	Host			Guest Selectivity[a]		$d-x-y$[b]
	Ring[c]	Sizes[a]	d/Å[b]	n	l/Å	Å
	12	12	5.8	2	3.7	3.6
	15	15		2	3.7	4.2
B[e]	15	18		3	4.9	4.7
	18	18		3, 4	5.5	5.2[d]
	15	15	7.9	4	6.2	6.3
N	15	18		4, 5	6.7	6.8
	18	18		5	7.3	7.3[d]
	12	12	10.1	5, 6	8.0	7.9
BP	15	15		6	8.6	8.5
	18	18		7	9.8	9.5[d]

[a] The value of n refers to the optimum guest(s) in the series of bis-cations $H_3N^+(CH_2)_nNH_3^+$, the value of l refers to the $N^+—N^+$ distance in the extended conformation of this guest or the average distance for a pair of guests.

[b] For distance d see **25**; x and y are based upon best agreement between experimental values of l and calculated values of $d-x-y$: for $n=12$, $x=1.1$; $n=15$, $x=0.8$; $n=18$, $x=0.3$ Å.

[c] The numbers refer to k and m in formulae **23** and **24**.

[d] The value for n is taken from the work of J. M. Lehn ref. [26].

[e] B =  , N =  BP = 

equal to the distance d (see formula **25**) minus the sum of x and y, the penetration of the $^{+}NH_3$ groups into the diaza-crown ether macrocycles (see formula **25**), then best values for x and y can be obtained from the data in the Table. Calculated values of $d - x - y$ were then compared with values of l for all 10 hosts for which data is available. Agreement between the calculated and observed data is excellent, confirming the general correctness of the structure of the complexes shown diagrammatically in **25** which is also supported by crystal structure data reported by J.-M. Lehn and co-workers [25].

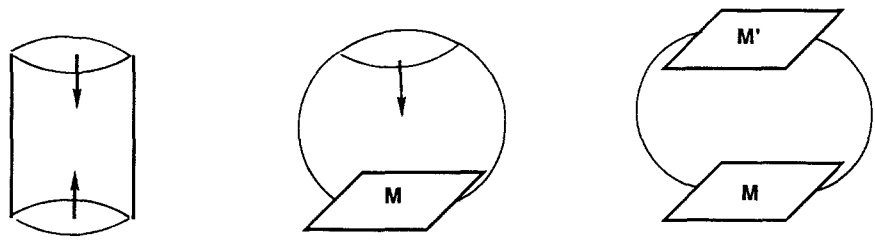
The hosts **23**, based upon 12- and 15-membered diaza-crown ethers are potentially hosts for simple alkylammonium cations $RN^{+}H_3$ and they were expected to form 2:1 **26** and 1:1 **27** complexes of the inclusion type. This was found to be the case for the hosts **23a**, **23b** and **23d** with either $MeN^{+}H_3 \cdot NCS^{-}$ or $MeN^{+}H_3 \cdot ClO_4^{-}$ as the guest salt, but even for low guest to host ratios (1:1) mixtures of 2:1 **26** and 1:1 **27** complexes were formed. Complexation is detectable, and can be analysed for 2:1 and 1:1 complexes, using ^{1}H NMR spectroscopy, individual guest CH_3 signals for the two complexes are resolved at low temperatures ($-90°C$) where guest exchange is slow on the NMR time scale. At higher ratios of guest salts (2:1 and 4:1) the ^{1}H NMR spectra showed that only the 2:1 complex **26** was obtained. There is no difficulty in fitting two $MeN^{+}H_3$ cations into the cavity of hosts **23b** and **23d** but the small cavity of **23a** appears to be barely adequate in size on the basis of CPK molecular models. Subsequently it also proved impossible to construct a computer based model of the complex **23a** · 2 $MeN^{+}H_3$. Nevertheless the ^{1}H and ^{13}C NMR spectra of a 2:1 mixture of host **23a** and $MeN^{+}H_3 \cdot ClO_4^{-}$ showed two guest CH_3 signals at low temperatures ($< -70°C$) shifted to low field (δ 2.9 and 27.9 ppm) and high field (δ 0.2 and 25.5 ppm) relative to the spectrum of the free salt (δ 2.5 and 27.3 ppm) and the ^{1}H NMR spectrum of a 4:1 mixture showed CH_3 signals for the two complexed cations and the free cation in a 1:1:2 ratio. This host **23a** forms a 2:1 complex and, in the absence of other evidence, we conclude that it is an inclusion complex **26** in which the two guest CH_3 groups occupy very different environments because of the limited space within the cavity. Even in this case the formation of the 2:1 complex **26** appears to be more favorable than the formation of a 1:1 complex **27** and we conclude that the entry of the first $MeN^{+}H_3$ cation opens the cavity so that the second cation can enter more easily.

Diaza-12-crown-4 has been shown [27] to form 1:1 complexes with secondary alkylammonium cations $RR'N^{+}H_2$. The ^{1}H NMR spectrum of a 1:1 mixture of host **23a** and $Me_2N^{+}H_2 \cdot ClO_4^{-}$ showed a signal [28] for the guest CH_3 group (δ 1.4 ppm) almost 1.5 ppm to high field of the signal from the free cation. Addition of excess of the guest salt, up to a 4:1 guest to host ratio, gave a CH_3 signal for a 1:1 complex together with a second CH_3 signal corresponding to the excess of the guest salt. Evidently the small cavity of host **23a** can accommodate only one molecule of the larger $Me_2N^{+}H_2$ cation.

Hosts **23** and **24** have rigid CH_2ArCH_2 bridges and consequently show very high selectivity for the *bis*-cations $H_3N^{+}(CH_2)_nN^{+}H_3$. It was of interest to examine the results of introducing less rigid bridges into the tricyclic system, accordingly host **28** was examined [29]. This host selects the bis-cations with $n = 2$ and 3 almost equally readily on the basis of competition experiments of a type similar to those used for the other tricyclic hosts **23** and **24**. The bis-cations with $n = 4$ and 5 are also

complexed equally readily but significantly less readily than the shorter pair of cations ($n = 2$ and 3). We conclude that the shorter cations are complexed by a conformation of the host which has a low energy conformation for the $CH_2(CH_2OCH_2)_2CH_2$ bridge and that the larger cations are complexed by a second conformation of the host which has a higher energy (longer) conformation of this bridge. Such a difference could result from a change in torsion angle about an OC—CO bond from *gauche* to *anti*. Thus hosts such as **28** with flexible bridges may use different conformations of the bridge to form complexes and show selectivity for guest molecules which reflects this flexibility.

Hosts **23**, **24** and **28** are ditopic and contain two electron rich receptor sites; they are therefore suitable hosts for bis-cations or two mono-cations. The development of synthetic receptors for anionic species has been rather slower than the development of synthetic receptors for cations and cryptand species of this type are rather rare, although some interesting examples have been reported. For ditopic hosts, electron deficient receptor sites can be incorporated to give the new cryptand species shown diagrammatically in Scheme 3 in which the ellipses represent electron rich (for example diaza-crown ether) receptor sites and the rectangles represent electron deficient receptor sites. This scheme also indicates possible guest species below each class of ditopic host and clearly the mixed system **29** is of particular interest because it can potentially complex both components of a guest salt.



$H_3N^+ \sim\sim N^+H_3$
2 x RN^+H_3
2 x M^+

$M^+.X^-$
$RN^+H_3.X^-$
$H_3N^+ \sim\sim X^-$
$H_3N^+ \sim\sim X$

29

$X \sim\sim X$
$^-X \sim\sim X^-$
$2X^-$
$2X$

30

Scheme 3. Synthetic ditopic receptors and appropriate guest species.

The electron deficient receptors, indicated by rectangles in the new classes of ditopic host **29** and **30**, are conveniently based upon metalloporphyrins **31** because their coordination chemistry has been extensively investigated [30] and they are readily available synthetically with side chain functionality that permits their incorporation into macropolycyclic systems of types **29** and **30**. Whereas a suitable choice of ring size for the aza-crown ether receptor ensures guest binding only in the inwards direction, as indicated by the arrows in Scheme 3, a metalloporphyrin can

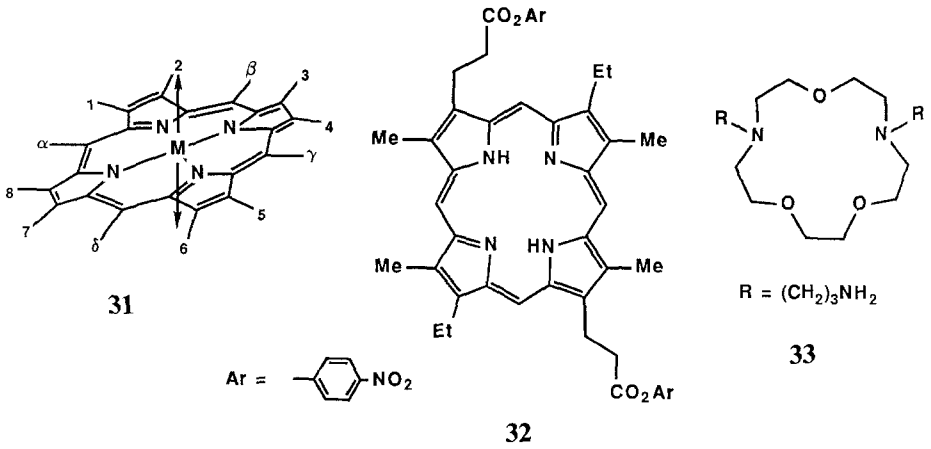
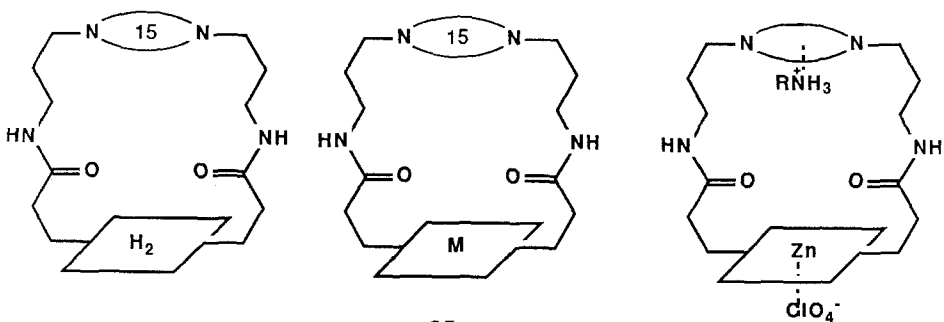


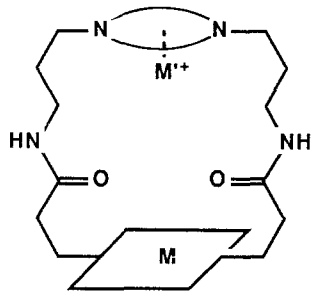
Fig. 7.

usually bind ligands at either face, as indicated by the arrows in **31**. However, for octahedral coordination at the central metal atom of the electron deficient receptor site in **29** and **30** the outer face of the receptor can be blocked by using a bulky ligand which is unable to enter the cavity. Bridges may be constructed using substituents at the β-positions of the pyrrole rings [positions 1–8 in **31**] or the meso-positions [α–δ in **31**] of the porphyrin system. The only ditopic receptors of type **29** that we have studied are derived from the crown capped porphyrin **34**, synthesized by reaction of the bis-*p*-nitrophenyl ester **32** with the diaza-15-crown-5 derivative **33** [31, 32]. The unmetallated capped porphyrin **34** can be metallated readily by reaction with an appropriate metal salt under the usual conditions [30] and a range of metallated systems **35** was prepared, the Zn(II) and Cu(II) derivatives were selected for most studies of complexation.



M = Zn(II), Cu(II), Co(II),
Mn(III), Fe(III)OH, Sn(IV)

Fig. 8.



36 M = Zn ; M' = Cu^{2+}, Fe^{2+}, Fe^{3+}, Mn^{2+}, Co^{2+}, Ni^{2+}

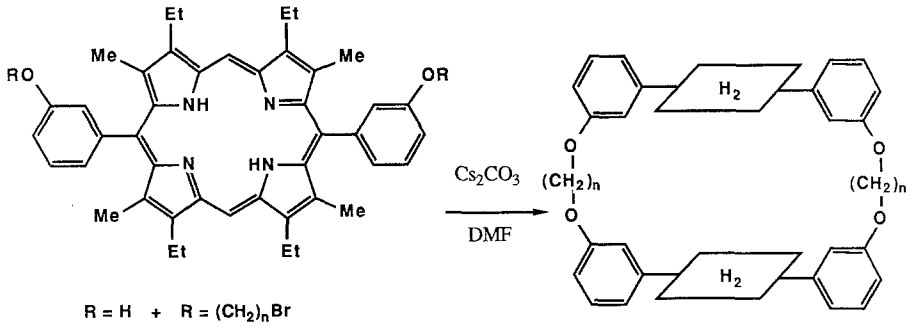
37 M = Cu ; M' = Cu^{2+}, Fe^{3+}, Fe^{2+}, Mn^{2+}

Fig. 9.

The fluorescence spectrum of a methanolic solution of the Zn(II) derivative (**35**, M = Zn) was quenched in the presence of paramagnetic metal salts; from the quenching data it was possible to obtain association constants for the formation of the bimetal complexes **36**. Similar results could be obtained from the analogous Cu(II) derivative (**35**, M = Cu). One or more of the counter ions in these bimetallated complexes, **36** and **37**, are probably bound to the metalloporphyrin moiety but the spectroscopic data does not provide clear evidence for this. Similar treatment of the ditopic receptors (**35**, M = Zn and Cu) with salts of Na^+, Mg^{2+}, Ba^{2+} and Zn^{2+} did not lead to fluorescence quenching although at least some of these cations must be complexed by the diaza-crown ether system. It was concluded [32] that fluorescence quenching was brought about by the magnetic field of a complexed paramagnetic cation rather than through any other effect, but an electron transfer mechanism for fluorescence quenching could not be completely ruled out [33].

The crown capped porphyrin (**35**, M = Zn) proved to be a rather disappointing receptor for alkylammonium salts [22]. The absorption spectrum of the Zn(II) porphyrin was modified in the presence of the salts $RN^+H_3 \cdot ClO_4^-$ and from the spectroscopic data it was possible to obtain association constants for complexation. The host showed little response to changes of R in the guest salt but the ^1H NMR data, together with the changes in the absorption spectrum, suggest that the complexes have the structures shown in **38**. The rather flexible links between the crown ether and porphyrin moieties are presumably one reason for the lack of guest recognition [compare with the semi-flexible ditopic receptor **28**].

Finally, examples of the third type of ditopic receptor **30**, containing two electron deficient metalloporphyrin receptor sites, can be synthesised by the route outlined in Scheme 4 [34]. The properties of these face-to-face porphyrins **39** as selective hosts have not yet been investigated although rather different face-to-face porphyrins have been investigated by Collmann and coworkers in a different context [35]. The diarylpophyrin system of **39** was selected to provide a well defined structural unit and it is hoped that this approach to a largely pre-organised cavity will prove to be effective.



39

Scheme 4. Synthesis of face-to-face porphyrins.

Acknowledgements

The work that has been reported in this paper has been carried out by a number of enthusiastic collaborators; I am grateful to them for their skill, patience and tenacity in working with compounds of high molecular weight which have in many cases demanded a high level of experimental ability.

Notes

[1] It is a pleasure to note the award of the Nobel Prize to Dr. Charles Pedersen and Professors Don Cram and Jean-Marie Lehn for their major contributions to the area of host–guest chemistry.

[2] Many such software packages are available. We have programs from commercial (CHEMX, Molecular Design Ltd), industrial (COSMIC, Dr. J. G. Vinter of Smith, Kline and French) and academic (MACROMODEL, Dr. Clark Still, Columbia University) sources.

[3] We thank Professor R. J. Abraham for making the computer programme CHARGE available and Dr. J. G. Vinter of Smith, Kline and French for a generous gift of the COSMIC package.

[4] This work has been carried out in collaboration with Dr. J. F. Alder (Department of Analytical Science, UMIST). It is a pleasure to acknowledge the important contributions of Dr. Alder's group who have developed all of the instrumentation and optical fibre preparation.

[5] These data also include results obtained by J.-M. Lehn and coworkers reported in Ref. [26].

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