Cyclophanes as synthetic receptors

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Abstract - Strategies for improving guest recognition are discussed. The bis crown ethers (14), with well defined separation between the two macrocyclic receptors, form complexes with bis-alkyl ammonium cations $H_3\overset{+}{N}(CH_2)_n\overset{+}{N}H_3$ and show a high selectivity for guest chain length. The bis zinc porphyrin (18) is a selective host for 4,4'-dipyridyl and forms complexes rather less readily with the diamines $H_2N(CH_2)_nNH_2$ without showing a high selectivity for chain length. The behaviour of synthetic ditopic receptors of the cyclophane type evidently depends upon the separation and rigidity of the bridges linking the two receptor systems and also upon the rigidity of di-functional guest molecules and the separation and orientation of the two functional groups.

INTRODUCTION

The discovery of crown ethers by Pedersen[1] opened up a new era in organic chemistry since, for the first time, it became possible to design synthetic organic compounds that would form selective, electrostatically bound complexes with cations. Other work on the complexation of organic molecules had originally been inspired by cyclodextrin complexes,[2] and synthetic cyclophanes[3] had been shown to function in a similar way to cyclodextrins; in these cases binding energy was primarily derived from hydrophobic interactions. The complexes that play a major role in biology, and in many cases involve recognition of a substrate or drug molecule by a protein, are held together by a combination of electrostatic and hydrophobic interactions and the key to designed molecular recognition by synthetic host molecules lies in understanding and controlling these two types of binding interaction. This requires an accurate knowledge of the geometry of the large host molecule and the smaller guest molecule together with at least a good qualitative evaluation of the binding forces between them. Progress towards this objective will be described in this paper which will concentrate upon host molecules which bind primarily through electrostatic interactions.

Crown ethers (1) bind metal cations with a moderate level of selectivity but they show rather little distinction between different groups R in the complexes, such as (2), of

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m,n = 1, 2, 3, etc.

X, Y = O, NR, etc.

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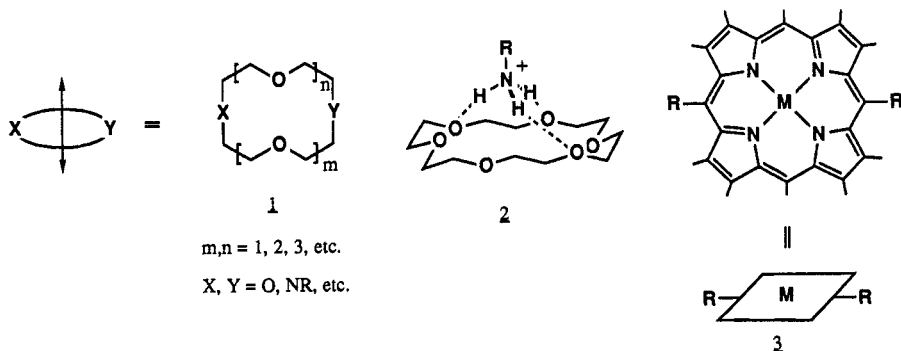
primary alkylammonium cations, $R\overset{+}{N}H_3$.[4] Development of crown ethers for better recognition of guest cation has been achieved[5,6] through polycyclic structures such as the cryptands,

the introduction of steric barriers into monocyclic systems, and modification of the crown ether structure to give less flexible hosts (preorganisation) with predictable geometry. Synthetic hosts for anions[7] have been developed to a lesser extent, protonated aza crown ethers have pH dependent properties and work at Liverpool has been focused upon metallo-porphyrins (3) which bind both anions and electron rich ligands, but have not been developed for guest recognition other than as haemoglobin analogues[8] which bind oxygen and carbon monoxide.

MONOTOPIC RECEPTORS

Crown ethers (1) are flexible molecules which can adopt a large number of conformations, a limited number of these are found in crystal structures of both free and complexed crown ethers, but a complete examination requires an extensive search for low energy conform-ations by a combination of molecular graphics and molecular mechanics calculations.   This is not a simple procedure due to (i) the large number of conformations which may be generated by the use of facilities such as MULTIC in the MACROMODEL molecular modelling package,[9] (ii) the inaccuracy of molecular mechanics calculations for polar molecules such as crown ethers, and (iii) the absence of a simple procedure for including solvent effects in molecular mechanics calculations.   For example, rotation about 9 bonds of 12-crown-4 in 120° steps and ring closure at a single bond restricted to distances of 1 - 4 Å generates several thousand conformations.   These are reduced considerably by structural refinement and recognition of identical conformers, but there are still many non-identical conformations of low energy (use of the AMBER force field generates 16 conformers with steric energies 55 - 60 KJ mol^{-1} from the first 150 conformations).   Conformations form-ing complexes with cations can probably be further restricted to those with gauche XC-CY bonds, but this still leaves difficulty in selecting the complexing conformation.   Never-theless, the well known 18-crown-6·RNH$_3$ complexes have only been found in crystal struc-tures with the conformation shown in (2) and this is also consistent with a DNMR study of the complexes in CD$_2$Cl$_2$.[10]

    The conformational ambiguity of the crown ethers may be reduced by restricting rota-tion about single bonds in the crown ether macrocycle either by fusion of an aromatic ring as in dibenzo-18-crown-6 (4) or by insertion of a 2,6-bridged phenolic ring into the crown ether as in (5).   The latter strategy has been used most effectively by D.J. Cram[6] and his co-workers in the increasingly pre-organised hemispherand (6) and spherand (7) systems.   Alternatively the calix[4]arenes (8) are also excellent examples of hosts for cations that are largely pre-organised.[11]

Similar conformational uncertainty is attached to protonated polyazacrown ethers as hosts for anions but metalloporphyrin hosts (3) are conformationally well-defined and the pre-dictability of their structures may be extended by using aryl substituents in the meso-positions as in the diarylporphyrin (9).   In general, both crown ethers and metallopor-phyrins can form complexes such as (2) with RNH$_3$ at both faces as indicated by the arrows in (3) and (9).   This uncertainty can be removed by using 12- and 15-membered aza-crown ethers[12] which form only syn- (10) or syn,syn- (11) complexes with alkylammonium cations or by using hemispherands (6) which form only the complex (12).

Selective complexation, even by a conformationally well defined monocyclic receptor which binds at a single face such as (12), requires contact between the group R in the guest cation and substituents on the host macrocycle.   Such contact can be introduced into monocyclic hosts by the introduction of steric barriers,[5,13] preferably at both faces of the macrocycle, but a high level of guest recognition is not easy to achieve by this strategy.   Complexation within the cavity of a polycyclic host (13) offers a much better opportunity for achieving guest recognition but inclusion complexation tends to be avoided, in the absence of hydrophobic forces, unless a bridged, face selective receptor such as (10) - (12) is used.   A rather simpler method for enforcing inclusion complex-ation is through the use of ditopic receptors which contain a pair of binding sites which are complementary to two functional groups X and Y in the guest molecule.   This strategy has been used to examine guest recognition in inclusion complexation as described below.

INCLUSION COMPLEXES OF DITOPIC RECEPTORS

The face-to-face crown ethers (14) have been shown[14] to be highly selective hosts for di-cations H$_3$N(CH$_2$)$_n$NH$_3$ in organic solvents such as CHCl$_3$ and CH$_2$Cl$_2$.   The aromatic systems are inserted into the bridges to ensure (i) a predictable separation d of the nitrogen atoms in the two crown ether macrocycles, and (ii) induced high field shifts of the ^{1}H nmr

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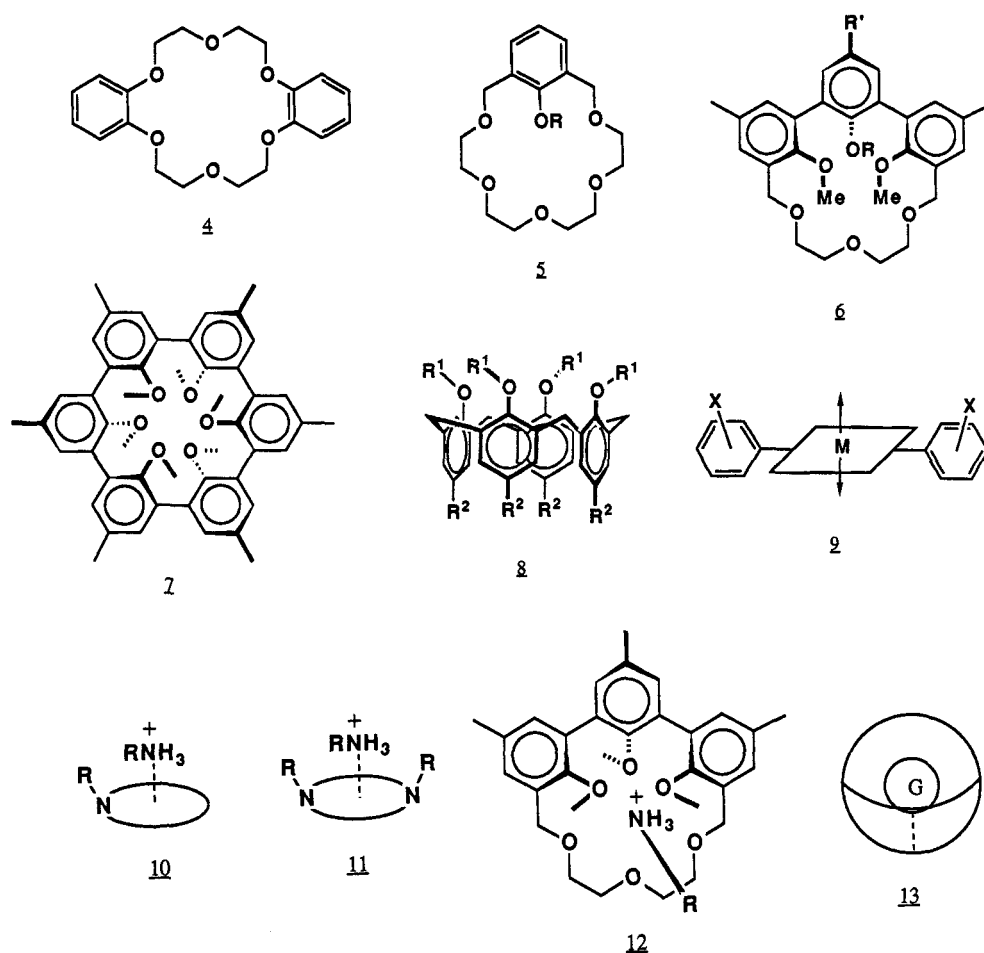
spectrum of the enclosed guest CH_2 groups to provide evidence for the formation of the inclusion complex (15). The complexes (15) are readily studied by ^1H nmr spectroscopy and information on the free energy barriers (ranging from 10 - 15 kcal.mol^{-1}) for exchange of guest cations can be obtained from the temperature dependence of the nmr signals. The signals from the CH_2 groups of the guest are shifted 2 - 4 ppm to high field of their normal chemical shifts by the induced ring currents of the aromatic rings included in the bridges. In the presence of a pair of competing cations $H_3\overset{+}{N}(CH_2)_n\overset{+}{N}H_3$ and $H_3\overset{+}{N}(CH_2)_{n+1}\overset{+}{N}H_3$ the hosts (14) usually select, within the sensitivity of the nmr spectrometer, only one cation from the pair so that guest selection may be determined for all host molecules of this type. The results of this study are consistent with the geometry of complexation indicated in Figure 1. The calculated contact distances, $\underline{x}$ and $\underline{y}$, between the $-\overset{+}{N}H_3$ centres and the crown ether macrocycles are consistent with molecular models of diaza crown ether $R\overset{+}{N}H_3$ complexes. The hosts (14) are far from pre-organised for complexation. The diaza-crown ether macrocycles can adopt many conformations of similar energy and detailed ^1H and ^{13}C nmr studies have shown that in solution they may not be conformationally homogeneous. Thus the crystal structure of the meta-xylylene bridged crown ether (16) shows[15] a centrosymmetric conformation in which the 15-membered rings adopt a conformation with one anti- NC-CO bond which is unsuitable for complexation. The conformations of the complexes of (16) with the guest dications $H_3\overset{+}{N}(CH_2)_n\overset{+}{N}H_3$, n = 2 or 3 are unknown but their high field ^1H nmr spectra suggest that they are conformationally homogeneous in solution.[16] However, in spite of this lack of pre-organisation the hosts (15) show a high degree of selectivity, which is probably partially a consequence of the enforced all anti- conformation of the guest dication and hence sharply defined guest geometry.

The crowned metalloporphyrin (17) is a heteroditopic receptor which was designed[17] as a host for functionalised ammonium cations $H_3\overset{+}{N}(CH_2)_n X$, where X is an electron rich group.
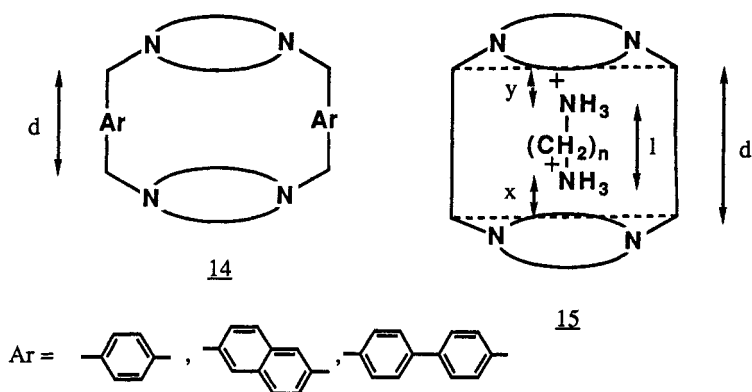
Fig. 1. Selection of guest bis-cations by face-to-face crown ethers (14).   In (15) $\underline{d}$ is the fixed separation between the two methylene carbons in the CH_2ArCH_2 bridge, $\underline{\ell}$ is the distance between the two nitrogen atoms in the all anti-conformation of the bis-cation, $\underline{x}$ and $\underline{y}$ are distances which represent optimum contact of the $-\overset{+}{N}H_3$ groups with the crown ether macrocycles.   For optimum complexation $d = \ell + X + y$.
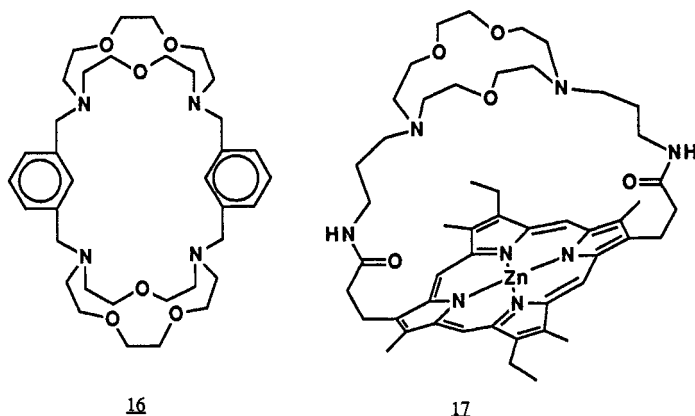
Although this host can probably complex both components of metal salts and $R\overset{+}{N}H_3 \cdot ClO_4^-$ the complexation is not accompanied by guest recognition.   Complexation of a functionalised ammonium cation at both the crown ether ($-\overset{+}{N}H_3$ receptor) and the zinc atom ($-NH_2$ the receptor) could not be demonstrated.   The host (17) has flexible bridges which do not necessarily enforce the separation of the two mutually attractive receptor sites and these bridges, which are attached to the nitrogen atoms of the diaza crown ether, may also interfere with complexation at the crown ether site.

The third type of ditopic receptor, the face-to-face zinc porphyrin (18), has a rather more rigid bridge between the two porphyrin systems but because this bridge is able to adopt a number of different conformations (18 a - c) the separation of the two zinc atoms is not sharply defined and can vary from 10.8 to 12.8 Å.   The calculated steric energies of the three conformations (18 a - c) [with metal free porphyrin units] are similar.   This bis zinc-porphyrin is a good host for diamines such as 4,4'-dipyridyl and the diamines $H_2N(CH_2)_nNH_2$.   Association constants for these guests may be measured from the change in the Soret band in the absorption spectrum (λ_{max}, 407 nm in the free zinc porphyrin and 418 nm in an amine complex] as increased amounts of guest are added to a methylene chloride solution of the host (10^{-6} M).   These association constants for diamines may be compared with those for analogous monodentate guests (pyridine and butylamine) to determine the enhancement due to the second functional group in the guest (Table).

The results of this study show that host (18) is selective for 4,4'-dipyridyl where the second pyridine ring gives an enhancement factor that is slightly greater than the assoc-iation constant for the complex with pyridine itself.   In contrast, the diamines $H_2N(CH_2)_nNH_2$ show enhancement factors for the second amino group that are significantly smaller than the association constant for butylamine.   Furthermore host (18) shows much less distinction between diamines of different length than the bis-crown ethers (14) show for the analogous bis-ammonium cations $H_3\overset{+}{N}(CH_2)_2\overset{+}{N}H_3$.

TABLE.   Complexes of face-to-face zinc porphyrin (18)

Moderate Guest	$K_a(M^{-1})^{a,b}$	Bidenate Guest	$K_a(M^{-1})^{a,b}$			Enhancement	
pyridine	$1.4 \pm 0.1 \times 10^3$	4,4'-dipyridyl	3	±1	$\times10^7$	2	$\times 10^4$
		$H_2N(CH_2)_2NH_2$	6	±2	$\times10^5$	1.2	$\times 10^2$
		$H_2N(CH_2)_4NH_2$	6	±2	$\times10^5$	1.2	$\times 10^2$
BuNH$_2$	$5 \pm 0.5 \times 10^3$	$H_2N(CH_2)_5NH_2$	1	±0.2	$\times10^6$	2	$\times 10^2$
		$H_2N(CH_2)_6NH_2$	3	±0.5	$\times10^6$	6	$\times 10^2$
		$H_2N(CH_2)_7NH_2$	1.2	±0.2	$\times10^6$	2.4	$\times 10^2$
		$H_2N(CH_2)_8NH_2$	3	±0.5	$\times10^5$	0.6	$\times 10^2$

[a]Guest added to host (18) at 10^{-6}M in CH_2Cl_2 at 25°C. K_a determined
by measurements of absorbance at 407 and 418 nm as guest concentra-
tion increased.   For a monodentate guest it is assumed that the two
zinc porphyrin systems act independently.
[b]Error limits are based upon fit of observed and calculated absorb-
ance.

A rather similar picture comes from a comparison of K_a for diamine guests for the bis-zinc
porphyrin (18) and the simple zinc porphyrin (19), once again 4,4'-dipyridyl shows a much
greater enhancement in K_a due to the second zinc-porphyrin receptor site than the diamines
$H_2N(CH_2)_nNH_2$ show.   This selectivity appears to be a function of the separation and rela-
tive orientation of the two functional groups in the guest and also the rigidity of the
guest molecule (see Figure 2).   4,4'-Dipyridyl is an ideal guest because it adopts a
single rigid conformation with a N $\cdots$ N separation (7.20 Å) that fits the Zn $\cdots$ Zn
distance in (18a) or (18b).   The diamines $H_2N(CH_2)_nNH_2$ can exist in a number of conform-
ations of comparable energy and therefore have a variable N $\cdots$ N separation, furthermore
the lone pair orientation is less appropriate for the relationship between the two zinc
atoms in the bis-porphyrin (18).   The distal bridges of (18) enclose a broad cavity which
can accept conformations of the diamines containing gauche bands, in contrast with the
narrow cavity enclosed by the aromatic systems of the bis-crown ethers (14), this accounts
for the much lower degree of recognition of chain length by the bis-porphyrin.

18a
0 kJ mol⁻¹

18b
+5 kJ mol⁻¹
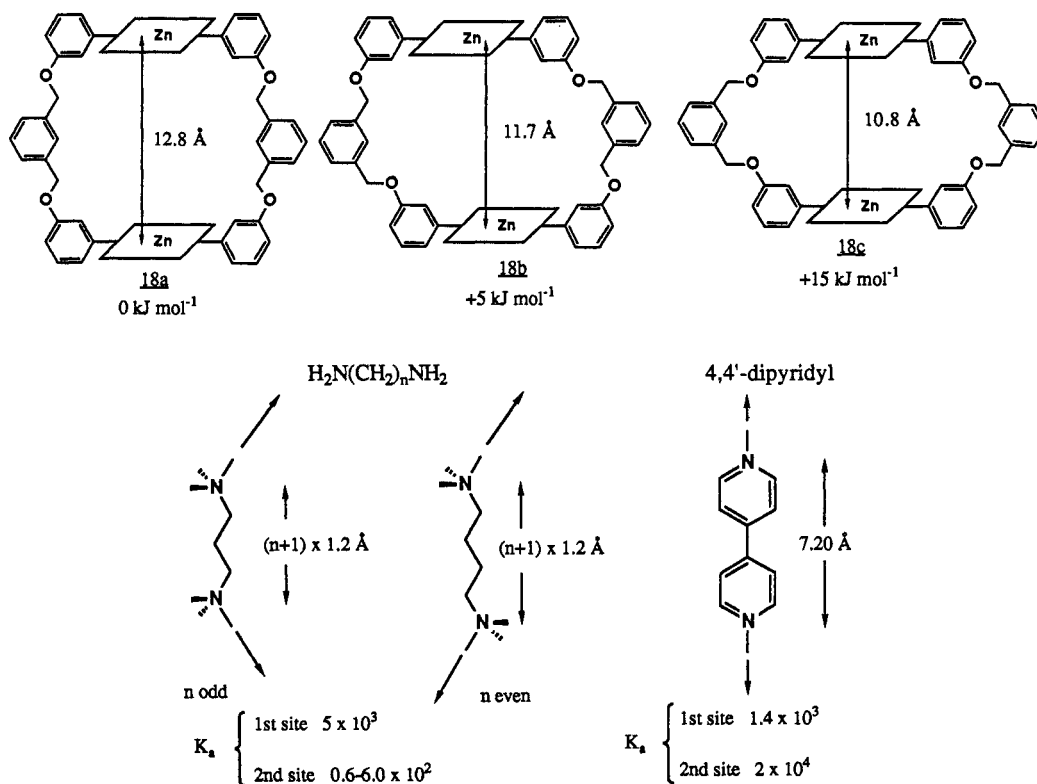
18c
+15 kJ mol⁻¹

Fig. 2. Separation of nitrogen atoms and lone pair orientation in guests of host
bis-porphyrin (18).   Diaminoalkanes   are   considered   in   the   extended   (all
anti-conformation) and lone pair directions are indicated by arrows.   The values for K_a
refer to binding of the analogous monodentate ligand and the enhancement in K_a's recorded
in the Table for bidentate ligands.

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