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Molecular recognition by synthetic receptors

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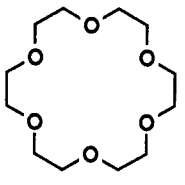
Abstract - Aza crown ethers are effective hosts for primary alkylammonium cations and the stereoselectivity of complexation depends upon the size of the crown ether macrocycle. Metalloporphyrins form complexes with electron rich ligands and anions. Ditopic receptors have been designed which incorporate two of these synthetic receptor molecules in a face-to- face relationship. The rigid face-to-face diaza crown ethers are highly selective hosts for bis-primary alkylammonium cations $H_3\overset{+}{N}(CH_2)_x\overset{+}{N}H_3$ and the selectivity can be rationalised in terms of a simple model. The crown-capped metalloporphyrins are suitable hosts for both components of primary alkylammonium and metal salts, and preliminary experiments show that face-to-face metalloporphyrins will form inclusion complexes with suitable bidentate ligands.

INTRODUCTION

The formation of complexes between large molecules, such as proteins and nucleic acids, and smaller molecules is an essential feature of many biological processes (ref.1). This complex formation, which is often highly selective, involves non-covalent binding forces between the larger host molecule and the smaller guest molecule. Until recently examples of complex formation involving synthetic host molecules were relatively rare but the discovery of crown ethers by C.J. Pedersen in 1967 (ref.2) opened up a new area of chemistry which has been investigated by many groups during the past two decades. The electron rich binding sites in crown ethers, such as 18-crown-6 1, cooperate to bind guest cations which are usually simple metal cations or alkylammonium cations. Synthetic host molecules for anionic species have been less widely studied but either fully protonated aza crown ethers, (ref. 3), such as 2, or the metal atoms of metal coordination complexes, (ref. 4), such as metalloporphyrins 3, bind anions or electron rich ligands. This article will be restricted to studies of host molecules based upon crown ethers and metalloporphyrins but a wide range of synthetic hosts for neutral guests have also been described (ref. 5).



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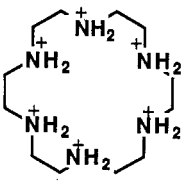

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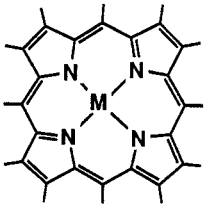

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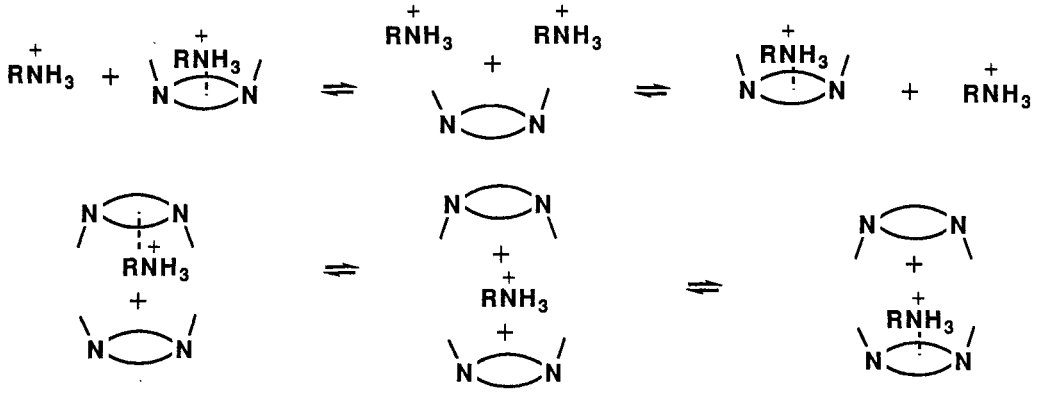
HOST MOLECULES BASED UPON AZA CROWN ETHERS AND METALLOPORPHYRINS

The simple crown ethers, such as 18-crown-6, show relatively little recognition for guest alkylammonium cations. Enhancement of recognition of the guest species may be achieved by constructing steric barriers around the host binding site, as in the classical investigation of binaphthyl based crown ethers by D.J. Cram and his co-workers (ref. 6). Alternatively, the construction of polycyclic host molecules which contain a molecular cavity lined by one or more binding sites has proved to bean effective strategy for enhancing guest recognition and the seminal studies of cryptands by J.M. Lehn (ref. 7) are an excellent illustration of this approach. At an early stage in our own work a

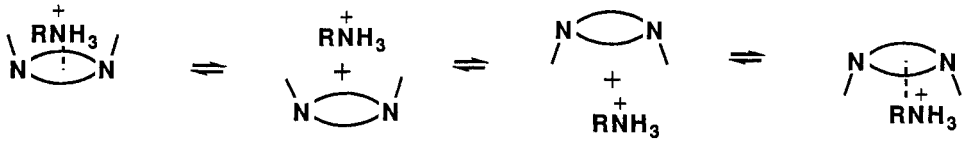
similar approach was adopted and, because cryptands are readily constructed using aza crown ether units, the aza crown ethers were investigated as host molecules for alkylammonium cations (ref. 8).

The formation of complexes between mono- and di-aza crown ethers and primary alkylammonium cations RNH_3^+, usually as thiocyanate salts was investigated largely by using ^1H nmr spectroscopy. Such complexes are formed most readily in organic solvents in which the electrostatic attraction between host and guest is optimised, and $CDCl_3$ and CD_2Cl_2 proved particularly suitable for nmr work. The spectra of complexes examined over the temperature range -110°C to +40°C showed in many cases very extensive temperature dependence which could be interpreted in terms of a number of different rate processes with energy barriers in the range 8 - 14 kcal mol^{-1}. These have been discussed in detail (ref. 9) and the discussion here will be limited to a brief description of the three principal processes, which are summarised for diaza crown ethers in Scheme 1.

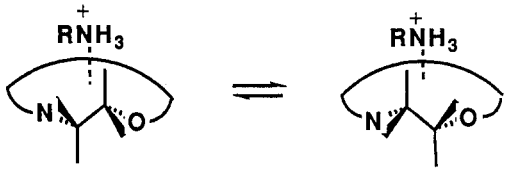
Scheme 1



(a) Exchange of guest (E_G) or host (E_H)



(b) Face to face guest exchange (E + I)



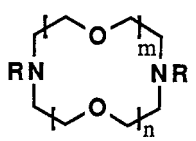
(c) Conformational change within a complex (C)

Rate processes detectable by nmr spectroscopy for complexes of aza crown ether (in this Scheme and in similar diagrams a crown ether is indicated by an ellipse and aza crown ethers are indicated by the inclusion of nitrogen atoms and substituents in the representation).

The first process (Scheme 1a) involves exchange of guest or host molecules between the free and complexed state which is probably in most cases a process that involves dissociation and recombination as indicated. The second process is more complex (Scheme 1b) and it involves dissociation of the complex followed by a conformational change of the free host molecule to enable subsequent binding of the guest species on the opposite face of the host from that originally occupied. Such "face to face" guest exchange generally has a slightly

higher energy barrier than simple guest or host exchange. Under conditions where this process is slow the various $-CH_2CH_2-$ units of crown ether or aza crown ether hosts are observable as ABCD systems which are therefore diagnostic of complexation. The third type of process (Scheme 1c) is the fastest of the three and involves conformational changes within the complex that do not require dissociation, such changes often involve rotation about a CH_2-CH_2 bond from one gauche conformation to another. Under conditions where host or guest exchange is slow on the nmr time scale it is possible to examine competition between a pair of guest molecules for the host binding site and hence obtain a direct measurement of the relative association constants for complexation which may be regarded as the degree of guest recognition.

The various rate processes summarised in Scheme 1 have been discussed in detail. The most important conclusion drawn from this early work was that in some cases complexation is stereoselective, giving a unique complex, and in other cases complexation gives a mixture of diastereoisomeric complexes. In particular diaza-12-crown-4 4a and diaza-15-crown-4 4b hosts form only cis,cis-complexes 5a with a syn relationship between the side chains on the nitrogen atoms and the guest cation, whereas the larger 18-membered ring of the diaza-18-crown-6 system 4c or 4d gives a mixture of the diastereoisomeric complexes 5a, 5b, and 5c. Macrocycles larger than 18-membered, such as diaza-21-crown-7 4e and diaza-24-crown-8 4f, also show no stereoselectivity in complexation.



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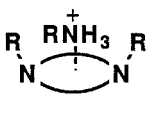
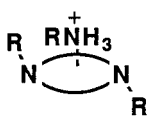
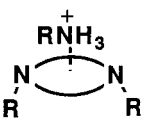
a : m = n = 1
b : m = 1, n = 2
c : m = n = 2
d : m = 1, n = 3
e : m = 2, n = 3
f : m = n = 3



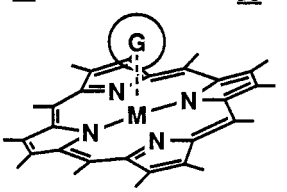
5a



5b



5c



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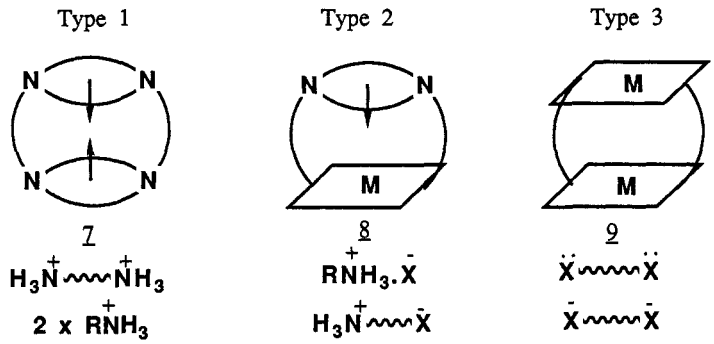
The use of metalloporphyrins as host molecules has been rather little developed except for applications as nmr shift reagents.[9] The Zn II and Co III porphyrins form complexes with a variety of nitrogen containing ligands and in some cases ligand exchange may be slow on the nmr time scale. The nmr spectrum of a guest G bound as a ligand to the central metal atom of a metalloporphyrin, as in 6, shows very large high field shifts in its nmr spectrum as compared with the unbound state due to the large diamagnetic ring current of the aromatic metalloporphyrin system. Thus diagnosis of complexation in solution may be made very readily for metalloporphyrin hosts which have low magnetic moments.

Recently, more complex hosts based upon metalloporphyrins have been described (ref. 10), but there has as yet been no systematic investigation of their complexation properties other than with oxygen and carbon monoxide as models (ref. 11) for haemoglobin and cytochromes.

DITOPIC RECEPTORS

The polymacrocyclic hosts 7 contain two diaza crown ether receptor sites and such ditropic receptors are potential hosts for the species shown below the structure. The hosts will be referred to as ditopic receptors of type 1 and provided that the diaza crown ether systems are 12- or 15-membered the guest cations must be bound to the inner face of the receptor macrocycles by analogy with the stereochemistry of the complexes 5a, as indicated by the arrows in 7. Analogous ditopic receptors may be based upon a combination of diaza crown ether and metalloporphyrin receptor sites 8 and two metalloporphyrin sites 9, these receptors should function as hosts for the guests indicated below the structures. The properties of these three types of ditopic receptor (Scheme 2) will be discussed in the following sections of this article.

Scheme 2

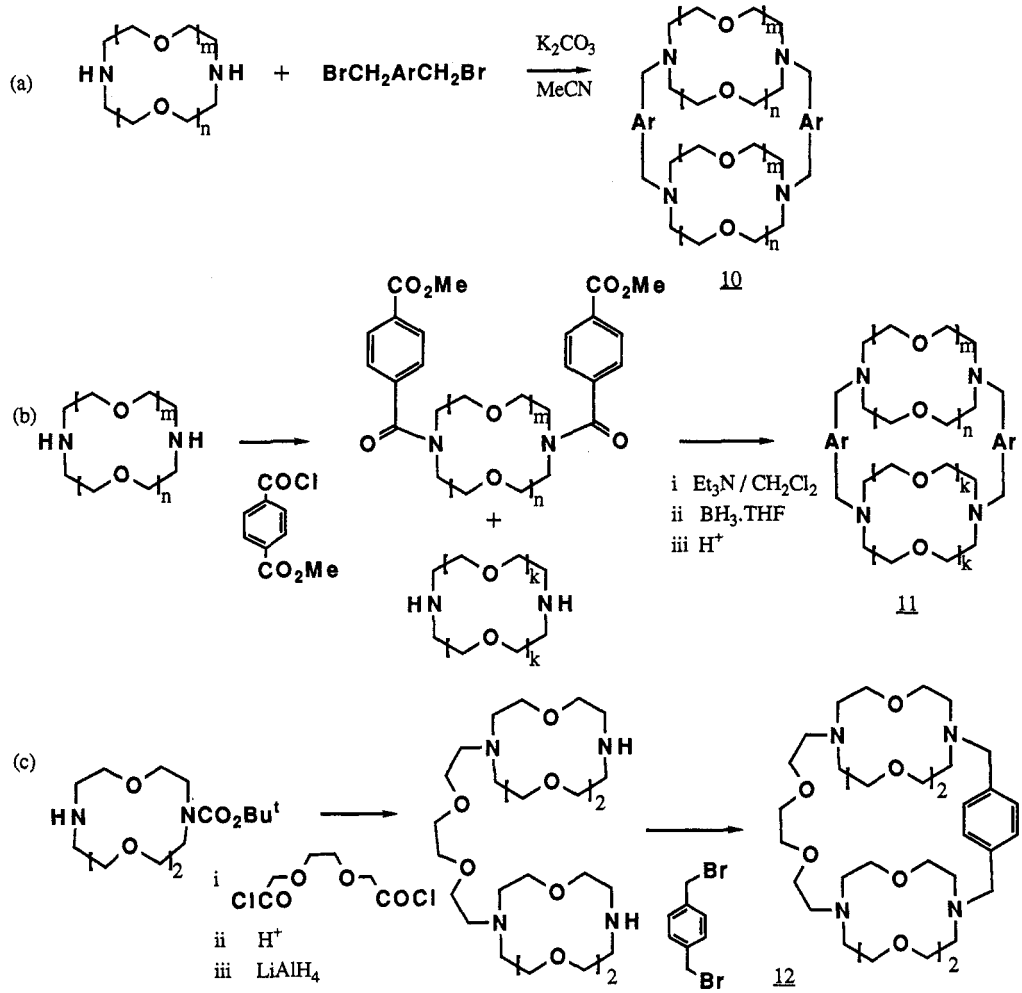


Synthetic ditopic receptors (in this Scheme and similar diagrams elsewhere the rectangle refers to a porphyrin system and M to the central metal atom if present).

DITOPIC RECEPTORS OF TYPE 1

The ditopic receptors 7 were prepared either by a simple one-step procedure (ref. 12) (Scheme 3a) for symmetrical systems 10 or by a multistep syntheses (ref. 13) (Scheme 3a and 3b) for asymmetrical systems 11 and 12.

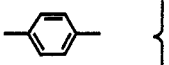
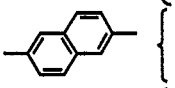
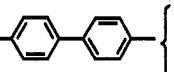
Scheme 3



Synthesis of ditopic receptors of type 1
(for definitions of Ar m, n, and k see Table)

The complexing properties of the hosts 10, 11, and 12 were examined using ^{1}H and ^{13}C nmr spectroscopy, the more important results will be summarised here. The ^{1}H nmr spectrum of a free receptor, for example 10f, shows that the crown ether macrocycles undergo rapid conformational inversion (AA'BB' systems for the NCH_2CH_2O units) but addition of one molar equivalent of the salt $H_3\overset{+}{N}(CH_2)_2\overset{+}{N}H_3 \cdot 2NCS^-$ to a $CDCl_3$ solution of 10f at 25°C causes a dramatic change in the spectrum. In particular the NCH_2CH_2O units give rise to a well defined ABCD system (analysable by using the COSY technique), indicating that molecular motion in the complex is restricted, and the signal due to the $-CH_2CH_2-$ unit of the guest dication is shifted to high field because it lies within the shielding zone of the aromatic rings of the CH_2ArCH_2 bridges. As expected, the geminal coupling constants within the NCH_2CH_2O units are consistent with a gauche arrangement about the C-C bond corresponding to an optimum conformation for complexation. For less than a molar equivalent of either host or guest component the nmr spectrum shows that the processes E_H and E_G (Figure 1a) are slow on the nmr time scale. The selectivity of host 10f for the dications $H_3\overset{+}{N}(CH_2)_x\overset{+}{N}H_3$ is very high and a 1:1:1 mixture of 10f and the dications with x = 2 and 3 shows an nmr spectrum consistent with the formation of the complex $10f.\overset{+}{N}H_3(CH_2)_2\overset{+}{N}H_3$ only. Thus the host 10f can distinguish between guest dications that differ in length by only one $-CH_2-$ group and in general all of the hosts 10a-f and 11a and b show similarly high levels of recognition for guest dications in the series $H_3\overset{+}{N}(CH_2)_2\overset{+}{N}H_3$. The results of an extensive examination of host-guest selectivity for these ditopic systems is summarised in the Table, together with further related results obtained by J.M. Lehn and co-workers (ref. 14).

TABLE. Selectivity of hosts 10 and 11 for complexation of dications $H_3\overset{+}{N}(CH_2)_x\overset{+}{N}H_3$

Host[a]	Ar[a]	m[a]	n[a]	k[a]	Selectivity[b]
10a		1	1		x = 2
10b		1	2	2	x = 2 > 3 > 4
11a		1	2	2	x = 2 > 3 > 4
10c		2	2		x = 2 > 3 ~ 4[c]
11c		1	2	3	x = 2 ~ 3 ~ 4 > 5
10d		1	2		x = 3 > 4 > 5 > 6
11b		1	2		x = 3 < 4 ~ 5 > 6
10e		2	2		x = 4 < 5 > 6 > 7 >8[c]
10b		1	1		x = 4 < 5 ~ 6 > 7 >8
10g		1	2		x = 4 < 5 < 6 > 7
10h		2	2		x = 7 > 8 > 9[c]
10f		1	2		x = 2 > 3
12					x = 2 ~ 3 > 4 ~ 5

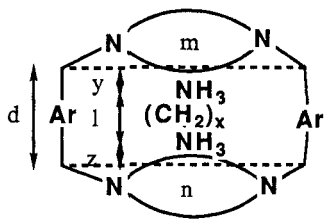
[a] Ar, m, n, and k refer to formula 10 or 11 as indicated in column 1.

[b] The symbols < generally indicates preferential complexation of the dication with the number of (CH_2) groups on the right hand side of the symbol and > has an analogous significance. The symbol ~ indicates approximately equal complexation of the salts indicated on both sides of the symbol.

[c] Result reported by J.M. Lehn and co-workers (ref.14).

The high precision with which the hosts 10 and 11 recognise the dications arises from a number of characteristics of the host molecules. Thus the bridges contain a rigid $-CH_2ArCH_2-$ group with a characteristic fixed distance d between the two $-CH_2-$ carbon atoms and for small crown ether rings the separation of the two bridges (as estimated from CPK models) is only sufficient to enclose an extended $-(CH_2)_n-$ chain in the guest dication, consequently the distance ℓ between the two $\overset{+}{N}$ centres in the guest dication is also accurately defined. The selectivity summarised in the Table can be rationalised in terms of the model 13 for the complex in which m and n indicate the size of the receptor macrocycles. This model shows that the distance d for optimum complexation should equal the sum of ℓ and the two shorter distances y and z which represent the closeness of approach of the guest $\overset{+}{N}$ centres to the aza crown ether macrocycles. From calculated values of d and ℓ and the results in the Table the best values of y and z for macrocycles of different sizes

can be calculated, these are shown at the side of the model 13 and, not surprisingly, the results show that the larger rings are penetrated more deeply by the guest $-\overset{+}{N}H_3$ groups than the smaller rings as shown in 14a-c. Thus the high selectivity shown by the rigid ditopic receptors 10 and 11 can be readily explained by the model 13.



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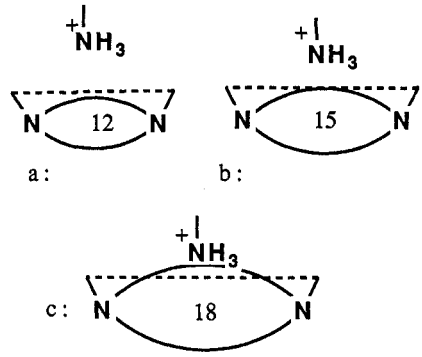
$d = l + y + z$

m/n	y/z
12	1.0 A
15	0.8 A
18	0.4 A



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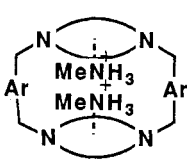
The less rigid ditopic receptors 11c and 12 show a rather different type of guest selectivity. Thus the 24-membered diaza crown macrocycle in 11c can adopt conformations which enable this host to form complexes equally readily with the guest salts $H_3\overset{+}{N}(CH_2)_x\overset{+}{N}H_3$, x = 2 - 4 but complexation falls off rapidly when the guest dication is too long (x = 5,6) to fit into even the most extended conformation of the host cavity. The host 12 has a rigid link and a flexible link between the two aza crown ether receptor sites. This host forms complexes equally readily with the dications $H_3\overset{+}{N}(CH_2)_x\overset{+}{N}H_3$, x = 2 and 3 which are bound more strongly than the longer pair of dications having x = 4 and 5. These results can be explained in the terms of a lower energy conformation of the host which has a shorter cavity appropriate for the shorter pair of dications and a higher energy conformation of the host which has a longer cavity which fits the longer pair of dications. It is possible that the shorter conformation has a gauche arrangement about the central OCH_2-CH_2O bond and the longer conformation has an anti arrangement about this bond.

Ditopic hosts of the type 10 which have 12- or 15-membered diaza crown ether receptor sites also form 2:1 complexes of the inclusion type 15 with methylammonium cations and, in general, the 2:1 complexes are formed in preference to the 1:1 complexes 16. This may indicate that the first cation to enter the cavity opens it up so that the second cation is more readily received, but attempts to model this allosteric effect have not been successful.



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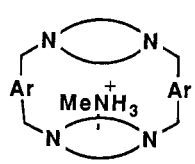

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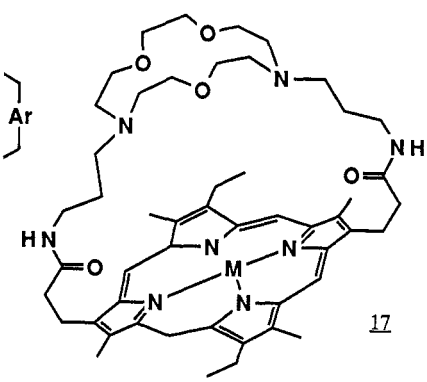

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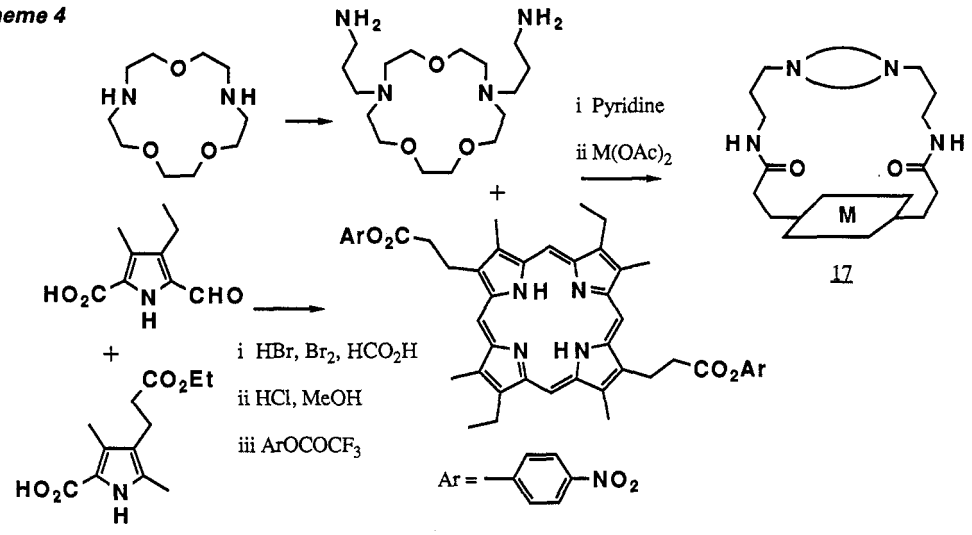
DITOPIC RECEPTORS OF TYPE 2

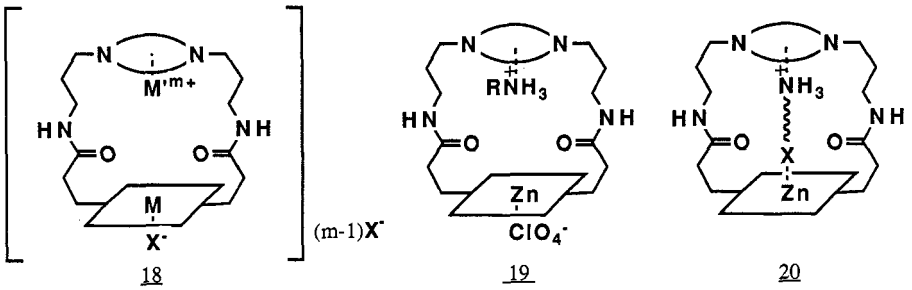
Only one compound of this type, the crown capped porphyrin 17, has been prepared by the synthetic route outlined in Scheme 4 (ref. 15). The ditopic receptor 17, M = Zn has a characteristic fluorescence spectrum in EtOH which is partly quenched in the presence of paramagnetic metal salts $M'X_n$. This is assumed to be a consequence of formation of the complex 18, which is believed to involve both anionic and cationic components of the guest salt. The association constants K_a for formation of the complexes 18 M = Zn and Cu, calculated from the dependence of fluorescence quenching upon the concentration of host 17 and the guest salt, show only minor dependence upon the metal M and the two receptor sites in 17 appear to behave independently of one another. With primary alkyl ammonium salts

Scheme 4



Synthesis of crown capped porphyrin 17

$R\overset{+}{N}H_3 \cdot Cl\overset{-}{O}_4$ as the guest species the host 17, M = Z_n appears to form the complexes 19 with a corresponding change in the absorption spectrum of the zinc porphyrin system. Calculated values of K_a for complexation of a range of guest salts show virtually no dependence upon guest structure, and in particular there is no evidence for cooperative binding of a functionalised alkyl ammonium cation through the formation of a complex of the type 20. This may be a consequence of the choice of the counter ion ClO_4^- and possibly also the rather flexible $-(CH_2)_2CONH(CH_2)_3-$ bridges which link the two receptor sites.

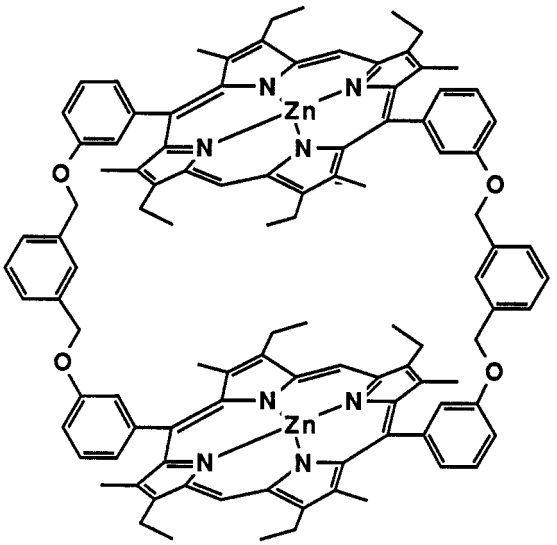


18 19 20

DITOPIC RECEPTORS OF TYPE 3

One host molecule of this type, the face-to-face porphyrin 21, has been synthesised and examined. The relatively rigid bridge that links the two diaryl porphyrin units of 21 is analogous to the bridges in the ditopic receptors 10 and 11 and similar host-guest selectivity might be expected, particularly in view of the well defined structure of the porphyrin system.

The separation of the two zinc atoms in 21 in the conformation shown is ~12.2 Å, which is a suitable separation for the formation of 4,4'-dipyridyl inclusion complex 22. The addition of one molar equivalent of 4,4'-dipyridyl to a $CDCl_3$ solution of host 21 results in a considerable change in the ^1H nmr spectrum of both components. In particular the guest signals are shifted to high field (α-H, Δδ -7.18 ppm; β-H, Δδ - 2.94 ppm) as compared with free 4,4'-dipyridyl, this is a consequence of the ring current of the two porphyrin systems and the large induced shifts as, compared with those reported (ref. 16) for the guest in the pyridine complex of zinc tetraphenylporphyrin 23 (α-H, Δδ -5.87 ppm; β-H, Δδ -1.76 ppm), are consistent with the formation of the inclusion complex 22. For a 2:1 ratio of guest to host in $CDCl_3$ at -40°C the ^1H nmr spectrum shows separate signals for free and complexed host indicating slow exchange, the coalescence temperature for these signals is ca. 0°C indicating a rather higher barrier to guest exchange than in the complex 23. In addition there is no indication that the presence of an excess of the guest leads to the formation of a 2:1 (G:H) complex as found for a rather more flexible face-to-face porphyrin system (ref. 17).



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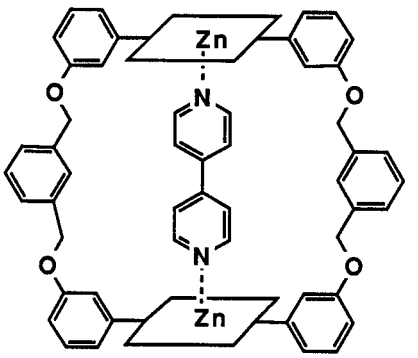

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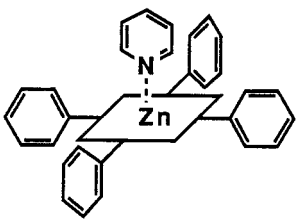

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