MACROPOLYCYCLIC COMPOUNDS AS HOST MOLECULES

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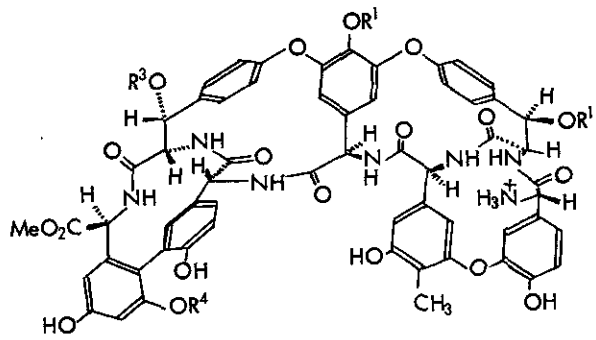
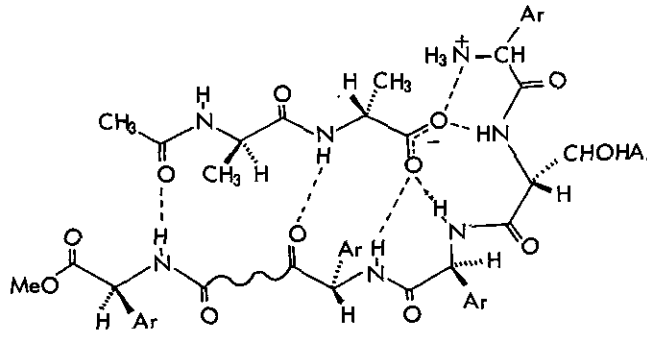
Abstract — The complexation of guest primary alkylammonium salts by mono- and di-aza crown ethers has been studied by NMR spectroscopy and has been shown to be stereoselective in some cases. Macrotricyclic systems derived from diaza-12-crown-4 and diaza-15-crown-5 form inclusion complexes in a highly stereoselective fashion with bis-alkylammonium cations. Chiral aza crown ethers show enantiomer selectivity in complexation which is dependent upon the substituents on the nitrogen atoms. These results have been used for the design of host molecules that catalyse ester cleavage in α-amino acid esters.

The design and synthesis of compounds, other than proteins, that show the high activity and substrate selectivity of enzymes has long presented a challenge to the synthetic organic chemist and it is only recently that substantial progress has been made in meeting this challenge. Thus the study of the natural cyclodextrins as host molecules has been developed by synthetic chemists in a number of highly successful and interesting ways, particularly by their structural modification to give more selective and reactive hosts[1] and by the design and synthesis of optimum substrates.[2] Totally synthetic analogues of cyclodextrins have not yet been developed to the same extent, but substantial progress has been reported in selective complexation by water-soluble cyclophanes and in the synthesis of polycyclic systems with permanent cavities that may be occupied by hydrophobic substrates.[3] These synthetic and semi-synthetic hosts depend for their activity upon favourable hydrophobic interactions that lead to the attachment of guest to host. Such hydrophobic forces play an important role in enzyme-substrate interactions but, in addition, there may also be electrostatic interactions between the two components of a molecular complex. These electrostatic interactions may just involve ion-pairing but the related phenomenon of hydrogen bonding is of extremely wide importance in biological systems. Such interactions are particularly well demonstrated by the binding of D-ala-D-ala derivatives to the macropolycyclic peptide-like antibiotics vancomycin, ristocetin (1), and avoparcin.[4] The formation of selective complexes by these antibiotics is based upon specific hydrogen bonding, as shown diagramatically in (2) for the binding of N-acetyl-D-ala-D-ala to the receptor site of ristocetin (1). Such complexation is very encouraging for the synthetic chemist since it dispels the idea that selective complexation requires a host molecule with the dimensions of a protein; however, the structural complexity of ristocetin rules out its use as a close model for a synthetic analogue of a natural enzyme or receptor.



(1) RISTOCETIN

$R^1 - R^4$ = Sugars



(2)

The discovery[5] that crown ethers form complexes with metal cations, particularly alkali metal cations, and with primary alkylammonium cations provided a relatively simple starting point for the synthetic chemist wishing to examine cation complexation through electrostatic guest-host attraction. The imaginative and successful development of crown ethers by D.J. Cram and his co-workers[6] is a notable achievement in the study of synthetic host molecules, and the recent extension[7] of this synthetic work to spherands (3) and other polycyclic hosts having a rigid pre-organised structure[8] that exactly fits the guest molecule points the way to future work in this area.

The synthesis of cryptands (4) by J.M. Lehn and his co-workers[9] and the demonstration that macropolycyclic host molecules showed greater substrate recognition than macromonocyclic hosts indicated an alternative type of structural modification of crown ether systems and encouraged us to investigate aza crown ethers as hosts for alkylammonium cations. In our initial studies[10] we showed that mono- and di-aza crown ethers formed complexes with guest cations which could be examined by NMR spectroscopy.

Thus, for example, the mono-aza-15-crown-5 derivative (5) forms a complex (6)† in which the guest cation is attached to the face of the host macrocycle with a syn-relationship between the guest cation and the N-methyl substituent. This conclusion was based upon the crystal structure of the benzylammonium thiocyanate complex (6, R = $PhCH_2$, X = NCS) and the shift to high field of the NMe signal in the NMR spectrum of the complex (6), as compared with the free host (5), for complexes with guests cations such as $PhCH_2\overset{+}{N}H_3$, $PhCHMe\overset{+}{N}H_3$, and $Ph_2CH\overset{+}{N}H_3$. At low temperatures the NMR spectrum of the complex showed ABCD systems for the NCH_2CH_2O units consistent with a structure (6) in which face to face exchange of the guest cation is slow on the NMR time scale. Analogous results were obtained for the diaza-15-crown-5 system (7) and subsequently, by the groups of J.F. Stoddart[11] and J. Krane[12], for the diaza-12-crown-4 system (8). In both cases, (7) and (8), these diaza crown ethers formed complexes having only the syn, syn-stereochemistry (9)‡ but, in contrast, it was shown[13] that 18-membered mono- and di-aza crowns (10) and (11) formed mixtures of syn and anti complexes. Thus, at low temperatures where guest-host exchange is slow on the NMR time scale, the NMR spectrum of the complex (11), $PhCH_2\overset{+}{N}H_3$ NCS^- showed signals (host NMe and guest $\overset{+}{N}H_3$) corresponding to a mixture of syn, syn (9), syn, anti (12), and anti, anti (13) complexes.

The reason for the stereoselectivity of complexation by these small crown systems (5), (7), and (8) appears to be the more rigorous stereochemical requirements for complexation as compared with larger crown systems but, in the absence of a detailed investigation by, for example, molecular mechanics calculations, it is difficult to be more precise. Ring systems larger than 18-membered give, in general, poorly defined complexes with alkylammonium salts although we have noted two exceptions.[14] The diaza-24-crown-8 system (14) forms a reasonably well-defined 2:1 complex with benzylammonium thiocyanate for which the syn, syn, anti, anti-stereochemistry shown in (15) may be proposed on the basis of the NMR spectrum of the complex at -90°C. In contrast the fewer binding sites in the 24-membered ring of the 24-crown-6 derivative (16) are only adequate for the formation of a 1:1 complex and the pronounced high field shifts of the $C\underline{H}\overset{+}{N}$ signals of the guest cation are consistent with the formation of a complex having the 'double-nesting' conformation (17).

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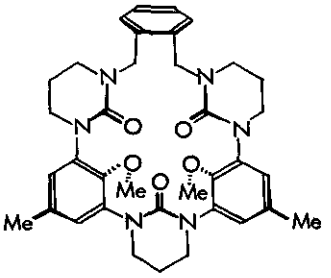
† The complexes between alkylammonium cations and crown ethers are formed by hydrogen bonding between the two components with additional electrostatic interactions between the lone pair electrons on the ring hetero-atoms not involved in hydrogen bonding and the positive charge on the guest cation. These binding forces are maximised by the use of solvents of low dielectric constant such as chloroform and methylene chloride. The low freezing point of CD_2Cl_2 make it a particularly useful solvent for the NMR spectroscopy of complexes in the temperature range -110°C to +35°C and for complexes at higher temperatures we have used $CDCl_3$. In most cases complexation is relatively insensitive to small amounts of water in the solvent and the results quoted in this review refer to complexation in CD_2Cl_2 (99.3%D) as provided by CEA, France. Unless otherwise stated results refer exclusively to ^1H NMR spectra.

‡ In this, and similar formulae, the crown ether system is represented by an ellipse for simplicity. In a number of cases the guest cation is represented by a sphere for similar reasons.



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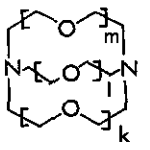

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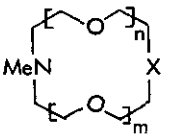
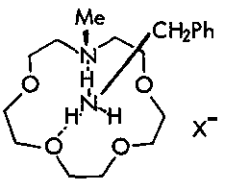


(5) m = 1, n = 2, X = O
(7) m = 1, n = 2, X = NMe
(8) m = n = 1, X = NMe
(10) m = n = 2, X = O
(11) m = n = 2, X = NMe
(14) m = n = 3, X = NMe



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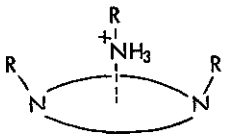
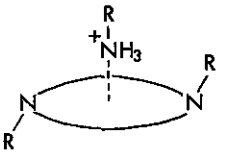


(9)



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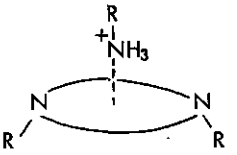

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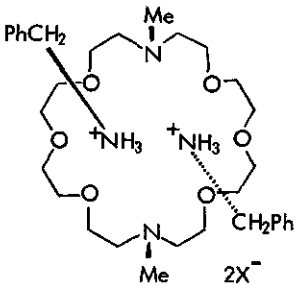

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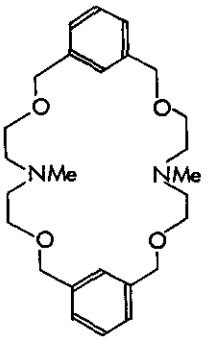

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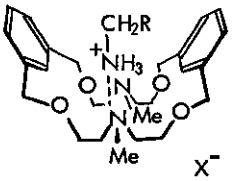
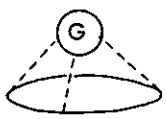


(17)

Monocyclic hosts, such as (5) - (11), show relatively little structural recognition for the guest cation because of the limited extent of guest-host contact in a complex of the addition type (18). It was realised, by analogy with the work on cryptands,[9] that inclusion complexes (19) of polycyclic hosts would have more guest-host contact and hence provide greater opportunity for designing hosts with good guest recognition. The aza crown ethers offer an excellent basis for the synthesis of polycyclic hosts since the attachment of the required bridges at stereochemically labile tertiary amino centres (see 19) avoids the stereochemical problems associated with bridging between stereochemically rigid carbon centres. The syn, syn stereochemistry (9) of complexation by 12- or 15-membered aza crown ethers ensures that if these macrocycles are placed at either end of the cavity (see 19) the complexation is directed inwards, leading to the formation of an inclusion complex of the type shown. Furthermore the introduction of structurally rigid

bridges (X in 19) would produce compounds with cavities of defined dimensions. Provision of this rigidity by the aromatic rings of the bridges $-CH_2ArCH_2-$ leads to potentially simple synthetic routes and the introduction of an experimental probe for inclusion, rather than addition, of a substrate guest cation. Thus an included guest lying within the cavity provided by the polycyclic system (see 20 - 24) also lies within the shielding zones of the aromatic rings when ring currents are induced in the rings during an NMR experiment.



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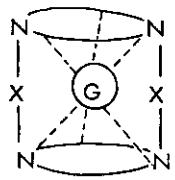

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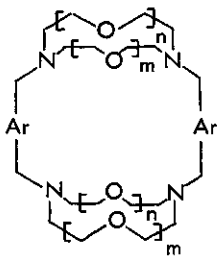
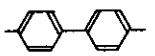
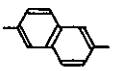
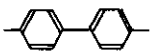


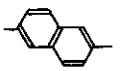
(20) m = n = 1, Ar = 

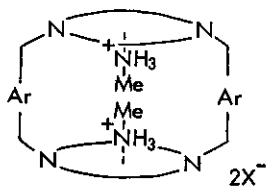
(21) m = n = 1, Ar = 

(22) m = 1, n = 2; Ar = 

(23) m = 1, n = 2, Ar = 

(24) m = 1, n = 2, Ar = 

(33) m = n = 2, Ar = 



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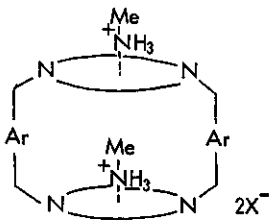
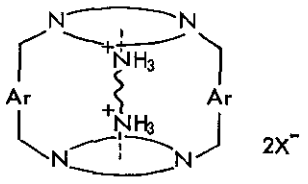


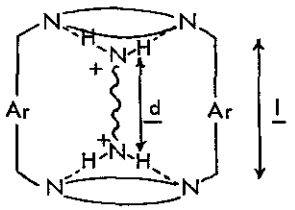
(26)

All of these expectations were realised[15] by the tricyclic host molecules (20)-(24) which were readily prepared by the reaction of diaza-12-crown-4 or diaza-15-crown-5 with the appropriate dibromide, $BrCH_2ArCH_2Br$. The tricycle (20) has the smallest cavity of the series and the NMR spectra of its complexes are typical. Thus, (20) forms a 1:1 complex with methylammonium thiocyanate and the NMR spectrum of the included guest cation shows, as expected, an NMe signal at significantly higher field (δ 1.17) than free methylammonium thiocyanate (δ 2.58). The host (20) also forms a 2:1 complex with methylammonium thiocyanate and it is clear from the NMR spectrum at -70^0C that the two guest methylammonium cations are in different environments since one NMe group (δ 0.33) shows a high field shift and the other (δ 3.04) shows a low field shift relative to the free salt (δ 2.58). In addition the protons of the aromatic rings are observable as an ABCD system at -70^0C and the ^{13}C NMR spectrum of the 2:1 complex is also consistent with two different environments for the guest cations. Whether this complex has the 'inside, inside' structure (25) or the 'inside, outside' structure (26) is not clear, but the larger cavity of (22) undoubtedly forms a 2:1 complex of structure (25) since the NMR spectrum of the guest salt in the complex (22), $2(Me\overset{+}{N}H_3NCS^-)$ shows only a single high field NMe signal (δ 0.44) at low temperatures.

The hosts (20) to (24) are particularly suitable as receptors for bis-ammonium cations $\overset{+}{N}H_3(CH_2)_n\overset{+}{N}H_3$ with which they are expected to form the inclusion complexes (27), provided that the separation of the two guest $\overset{+}{N}H_3$ groups is appropriate for the separation of the two crown rings as predetermined by the rather rigid CH_2-Ar-CH_2 bridge. *In particular space filling CPK molecular models* indicated that the cavity of the host (20) is sufficiently large to accommodate the $\overset{+}{N}H_3(CH_2)_2\overset{+}{N}H_3$ bis-cation and the NMR spectrum of the complex (20), $\overset{+}{N}H_3(CH_2)_2\overset{+}{N}H_3, 2NCS^-$ at 25°C shows the signal from the guest CH_2 groups shifted considerably to high field (δ 1.28) as compared with the spectrum of the free guest salt (δ 3.10) providing excellent evidence for the formation of an inclusion complex (c.f. 27). *At very low temperatures (<-70°C) the guest CH_2 signal* broadens and collapses and appears as two broad multiplets, probably assignable to an AA'BB' system (δ_A 2.14, δ_B 0.94) in which one CH_2 proton shows a remarkable 4 ppm shift to high field as compared with the spectrum of the free guest. The host spectrum shows analogous changes and at very low temperatures the spectrum is consistent with a 'frozen' inclusion complex (27) in which each of the two crown rings adopts a single chiral conformation, for example the [3 3 3 3] *conformation*[12] found for diaza-12-crown-4, and rotation of the benzene rings in the bridges is hindered. This result is typical of the results that have been obtained for a number of complexes (27) in which the host tricycle adopts a single conformation so that there is a unique stereochemistry of complexation.



(27)



$\underline{d} = \underline{l} - 2$ Å

(28)

The small cavity of the host (20) is unable to accept larger bis-cations and the NMR spectrum of a 1:1 mixture of this host with the guest salt $H_3\overset{+}{N}(CH_2)_3\overset{+}{N}H_3$ only shows high field signals for the guest bis-cation at low temperatures (<-50°C). On the other hand the longer cavity of the host (21) can accept much longer bis-cations and on the basis of NMR evidence *similar to that described above it forms* 1:1 inclusion complexes with the salts $\overset{+}{N}H_3(CH_2)_n\overset{+}{N}H_3, 2NCS^-$ for the salts with n=4 to 7, but not with the salts with n=3 and n=8. The NMR spectra of the complexed salts show substantial high field shifts and in the presence of an excess of a guest salt separate signals can be seen for free and complexed guest, provided that the sample temperature is sufficiently low so that guest exchange is slow on the NMR time scale. This also permits the *direct study of competition between different* guest cations. Thus the NMR spectrum of the complex (21), $\overset{+}{N}H_3(CH_2)_5\overset{+}{N}H_3, 2NCS^-$ is unchanged by the addition of the salt $\overset{+}{N}H_3(CH_2)_4\overset{+}{N}H_3, 2NCS^-$ other than by the appearance of signals due to the uncomplexed, shorter bis-cation. This shows very clearly that the longer cation is complexed preferentially and similar experiments can be carried out for a series of guest salts.

In this way it is possible to show that the host (21) selects the bis-cations with n = 5 and n = 6 with almost equal preference. Selectivities for the series of hosts (20) to (24) are summarised in the Table. These selectivities are readily rationalised in terms of complexation of the type shown diagramatically in (28), the relationship between the $\overset{+}{N}$ --- $\overset{+}{N}$ distance in the fully extended conformation of the bis-cation and the C--Ar--C distance in the bridge indicated by the Table is approximately that shown in (28).

TABLE

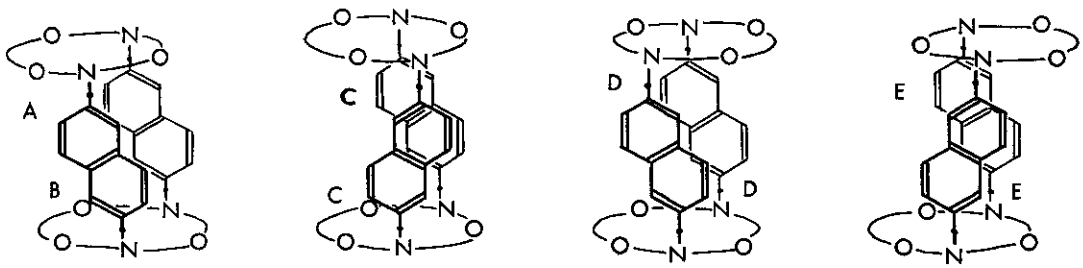
Selectivity of hosts (20) to (24) for guest salts

Host	l[a]	Guest preference[b]	d for preferred guest[a]
20	5.8	2 ≫ 3	3.6
21	10.1	3 ≪ 4 < 5, 6 > 7 ≫ 8	7.9
22	5.8	2 > 3 > 4	3.6
23	7.9	3 ≪ 4 > 5 > 6	6.1
24	10.1	4 < 5 ≪ 6 > 7	8.5

[a] d and l defined in formula (28) in $\overset{0}{A}$

[b] The numbers refer to n in $\overset{+}{N}H_3(CH_2)_n\overset{+}{N}H_3$

The host (23) is of interest because it can adopt four possible conformations (29) to (32) related by either rotation of the bridging naphthalene system or by rotation of the 15-membered crown macrocycles. The complex formed by methylammonium thiocyanate (2:1 guest : host ratio) shows four different high field NMe signals at low temperatures (δ 0.15, 0.38, 0.68, and 0.71) assignable to guest cations in four of the five possible environments indicated by the letters A to E in the formulae (29) to (32). Complexation of a simple $R\overset{+}{N}H_3$ cation by the host (23) is therefore not stereoselective. The host (23) forms a strong 1:1 complex with the bis-cation $\overset{+}{N}H_3(CH_2)_4\overset{+}{N}H_3$ which shows the expected two high field NCH_2 signals at +37°C, corresponding to the guest α-CH_2 and β-CH_2 (δ - 0.37 and 0.94 respectively). At lower temperatures these two signals broaden and each splits into two to give four signals (δ - 0.93, -0.22, 0.50, and 0.89) corresponding to four different CH_2 groups in a complex formed by the host (23) in the conformation (29). Additional signals (δ - 0.49, 0.83) are also detectable from a minor species of higher symmetry. At very low temperatures (-104°C) the four CH_2 signals of the major species are replaced by eight signals (δ - 1.78, -0.85, -0.61, -0.27, -0.06, 0.02, 0.81, and 1.12) corresponding to a complex in which all eight guest protons are in different environments. This is consistent with a complex based upon the conformation (29) in which each of the 15-membered macrocycles adopts a chiral conformation and conformational inversion is slow on the NMR time scale. Thus the complex (23), $\overset{+}{N}H_3(CH_2)_4\overset{+}{N}H_3$, $2NCS^-$ is formed with high stereoselectivity in spite of the numerous conformational possibilities for the host tricycle.

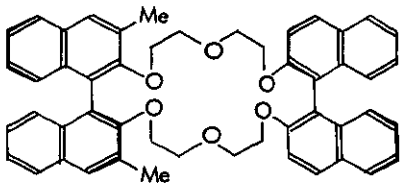


(29) (30) (31) (32)

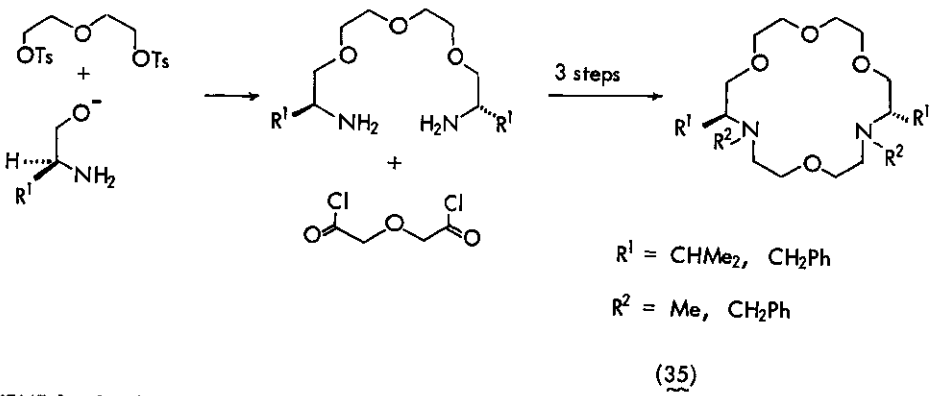
Similar studies of tricyclic host molecules have been reported by J.M. Lehn's group,[16] in this case the tricycles were based upon the diaza-18-crown-6 system and it is probable that simple ammonium cations $R\overset{+}{N}H_3$ can be bound to the outside of the host if they are too large to fit within the cavity. The bis-ammonium cations $\overset{+}{N}H_3(CH_2)_n\overset{+}{N}H_3$ form inclusion complexes with these hosts that are analogous to those formed by the hosts (20) to (24). The crystal structures of the free host (33) and of the complex (33), $\overset{+}{N}H_3(CH_2)_5\overset{+}{N}H_3$ have been reported and compared. The proposed structure (27) for these complexes is fully supported and it is particularly interesting to note that complexation involves significant conformational changes relative to the conformation of the free host in the crystalline state.

The ability of crown ethers to form complexes with alkylammonium cations in a structurally selective manner has led to a number of examples of enantiomer recognition in complexation by chiral crown ethers. The most notable examples are provided by the crown ethers studied by D.J. Cram and co-workers in which the axial chirality of a 2,2'-dihydroxy-1,1'-binaphthyl system is included in the crown macrocycle. In some cases high enantioselectivity has been achieved and the host (34) shows particularly high enantiomer recognition (an EDC value of up to 31 at 0^0C) for salts of phenylglycine methyl ester and analogous salts of other amino acid esters.[17] Chiral aza-crown ethers (35) may be synthesised in a convenient manner[18] from optically active amino alcohols, derivable from amino acids, using the route outlined in Scheme 1. For suitable substituents on the nitrogen atoms (e.g. 35, $R^2 = CH_2Ph$) complexation of guest α-phenylethylammonium cations shows a moderately high enantioselectivity; the host (35), derived from a natural amino acid, showing a preference for complexation of the (R)-configuration of the guest salt. Unfortunately this enantioselectivity is lost in the presence of water which results in the formation of a hydrated complex, probably with the composition (35), H_2O, $PhCHMe\overset{+}{N}H_3$ NCS^-.

The receptor properties of crown ethers provide an excellent opportunity to investigate the synthesis of enzyme analogues with two important limitations: (a) the substrate must generally be cationic and (b) the reaction must be carried out in a solvent of low polarity. These two limitations point clearly to amino acid derivatives as the substrates and a function as an analogue of a protease. Most reported studies have concentrated upon the initial thiolysis step involved in the action of a cysteine protease such as papain. In particular it has been shown that the intra-complex thiolysis (36) → (37) can



(34)



R^1 = $CHMe_2$, CH_2Ph

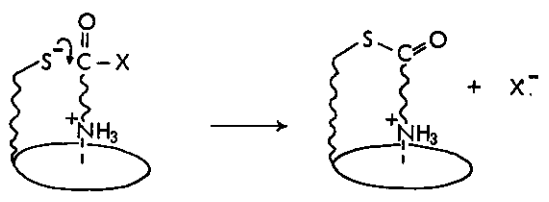
R^2 = Me, CH_2Ph

(35)

SCHEME 1. Synthesis of chiral diaza-18-crown-6 derivatives

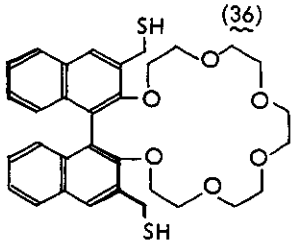
be significantly accelerated relative to an analogous reaction of the uncomplexed substrate. The host molecule required for the thiolysis (36) → (37) is a crown ether system carrying one or more suitably located -SH groups, and if the crown ether is chiral its catalytic function is potentially enantioselective.

In the first reported study of this type involving crown ethers, D.J. Cram and his co-workers[19] showed that substrate amino acid p-nitrophenyl esters [c.f. (36) and (37), X = $OCOC_6H_4NO_2$]

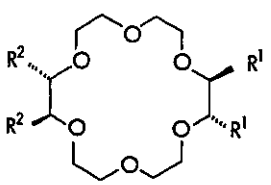


(36)

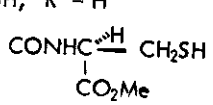
(37)



(38)

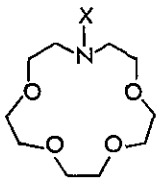


(39) R^1 = CH_2SH, R^2 = H

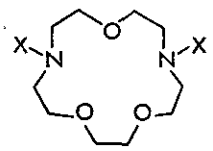
(40) $R^1 = R^2$ = 

underwent a rapid intra-complex transacylation reaction in the presence of the dithiol (38) in solvents such as 20% ethanol-methylene chloride. Under suitable conditions rate enhancements of up to 1170 times were found for the intra-complex reaction as compared with the reaction in the presence of an acyclic analogue of (38). The chiral binaphthyl system (38) also showed substrate enantioselectivity and rates of thiolysis for D- and L- amino acid ester substrates differed by factors of up to 9.2 in the most favourable case (L-Leu and D-Leu). Similar accelerations of up to 2500 times for the intra-complex thiolysis reaction have also been reported[20] for the crown ether derivative (39), derived from tartaric acid. The analogous crown ethers (40), derived from tartaric acid and L-cysteine, catalyse the transacylation reactions of dipeptide p-nitrophenyl esters[21] with rate enhancements of up to 15,000 times and with high enantioselectivity in some cases.

Our own work has concentrated on the derivation of similar catalysts by simple synthetic routes from aza crown ethers. Our initial studies[22] were based upon the derivatives (41) and (42) which have phenolic hydroxyl groups in the side chains. These were shown to undergo an intra-complex acylation reaction in the presence of glycine p-nitrophenyl ester at rates up to 70 times faster than the rates of the general base catalysed ethanolysis reactions in the presence of a similar concentration of the corresponding N-3-phenylpropyl crown ether (Scheme 2).



(41)



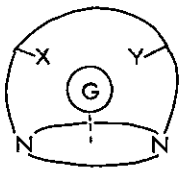
(42)

	10^5 k/s^{-1}	10^5 k/s^{-1}
X = $(CH_2)_3Ph$	3	3
X = $(CH_2)_3$- 	141	198
X = $(CH_2)_3$- 	-	6

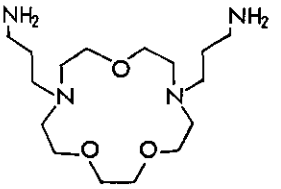
SCHEME 2. First order rate constants for p-nitrophenol release from substrate $\overset{+}{N}H_3CH_2CO_2C_6H_4NO_2$ Br^- (1.625×10^{-4} M) at 25°C in CH_2Cl_2/ EtOH (95:5) in the presence of crown ether derivatives (41) or (42) (3.3×10^{-3} M).

These rather modest rate enhancements have been increased in a more recent study which has as its objective the development of a catalytic system, shown diagramatically in (43), in which the functional groups of the catalyst and the substrate are brought together in the cavity of a bicyclic aza crown ether derivative. As the first part of this study the bis-aminopropyl-diaza crown ether (44) was prepared and acylated with the

symmetrical anhydrides of suitably protected amino acid derivatives. Selective deprotection of the products gave the series of crown ether derivatives (45). The crown ethers with -SH groups or free imidazolyl groups in the side chains were compared with analogous crown ether derivatives lacking these reactive functional groups. The results of this study, using glycine p-nitrophenyl ester as the substrate, are summarised in Scheme 3. It is clear from these results that both reactive groups are reasonably effective in intra-complex cleavage of the substrate ester group. We assume that the thiolysis involves the formation of a thioester intermediate but it is not yet clear whether the reaction with the imidazolyl side chain involves a nucleophilic mechanism, with the formation of an acylimidazole intermediate, or general base catalysis of ethanolysis of the substrate by the solvent ethanol. The bifunctional catalyst with both -SH and imidazolyl

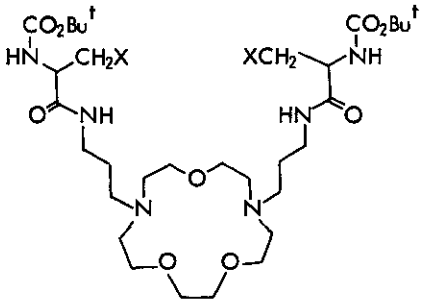


(43)

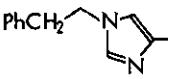
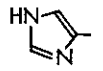


(44)

groups in the side chains gives a thiolysis reaction comparable in rate with that of the bis-thiol, but it is not yet clear whether the imidazolyl group is able to catalyse ethanolysis of the thioester formed by the initial transacylation reaction. The bicyclic bis-thiol (46) is the first system of type (43) that we have examined but initial results suggest that the additional bridge between the two side chains does not exhance the rate of the intra-complex thiolysis reaction.

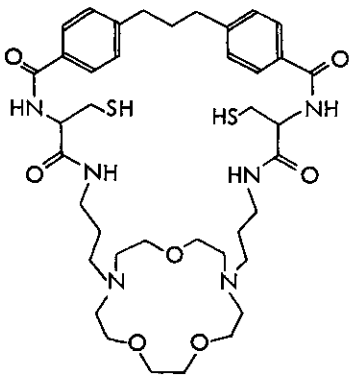


(45)

X	10^5 k/s^{-1}
Me_2CH-	5.9
$PhCH_2S$-	4.0
HS-	2160
HO-	12.7
	9.7
	341
HS- and 	516

SCHEME 3. First order rate constants for p-nitrophenol release from substrate $\overset{+}{N}H_3CH_2CO_2C_6H_4NO_2\ Br^-$ (1.626×10^{-4} M) at 25°C in CH_2Cl_2/EtOH (95:5) in the presence of crown ether derivatives (45) (3.3×10^{-3} M).

We note that the hydroxyl group of a serine side chain is not an efficient catalytic function in our system, it is probable that more strongly basic reaction conditions and more accurate location of the hydroxyl group relative to the ester group of the substrate are necessary to obtain an effective rate enhancement for the intra-complex alcoholysis reaction as compared with base catalysed ethanolysis by the solvent ethanol. Both of these conditions have been satisfied in a very important recent study by D.J. Cram and H.E. Katz.[24]



(46)

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