Macrocyclic and Macropolycyclic Compounds based upon 1,3-Disubstituted Propane Units

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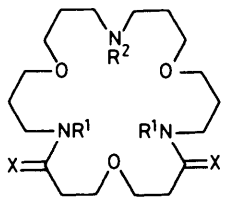
Synthetic routes to the macrocyclic polyamine derivatives (**1**) and (**3**) are described, together with an investigation of the complexing properties of the triamines (**1d**) and (**3d**) with primary alkylammonium cations. Macrotricyclic and macrotetracyclic compounds may be obtained from the macrocycle (**1**) by a stepwise procedure whereas macrocycle (**3b**) can be converted into a macrotricyclic derivative in a one step alkylation procedure. The alkylation of the tetrahydropyrimidone (**18**) with αα'-dibromo-*m*-xylene gives the calix[4] arene analogue (**19**) which adopts the 'cone' (**21a**) and '1,3-alternate' (**21b**) conformations. The macrocyclic hexa-amine (**23**) may be synthesized by a simple alkylation procedure whereas the octa-amine (**27**) required a systematic stepwise synthesis. The hexa-amine salt (**23**)·6 HBr shows selectivity in forming inclusion complexes with the dicarboxylate anions $^{-}O_2C(CH_2)_nCO_2^{-}$

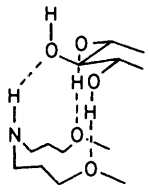
A variety of macrocyclic and macropolycyclic compounds has been examined in the search for synthetic host molecules. Crown ethers and analogues,[1] based upon 1,2-disubstituted ethane units, have proved to be suitable hosts for a range of cationic species and a few neutral molecules[2] and the rigid, predictably structured spherands[3] have been used, more recently, as hosts for cations. Other guest species, particularly liphophilic neutral molecules, may be complexed by water-soluble cyclophanes.[4] Macrocyclic hosts based upon 1,3-disubstituted propane units have been used more rarely, but protonated macrocyclic polyamines of this type have been shown[5,6] to complex anions and polyanions and these units have also been used in the design of ligands for metal cations. The ability of such macrocycles to complex alkylammonium cations has not been reported and, because of the wide range of structural variation that can be introduced by simple synthetic procedures, we report in this paper the results of an investigation of some aspects of both cation and anion complexation by hosts of this type.

The target macrocycles initially selected for this study were the mixed oxygen and nitrogen based macrocycles (**1**) because, on the basis of CPK molecular models, it appeared that the spacing between the hetero-atoms might lead to host molecules with an ability to form complexes with cations and also, through the hydrogen bonding shown diagramatically in (**2**), with guest mono-saccharides, such as glucose. The related macrocycle (**3**) was also prepared to allow a comparison between the complexing properties of (**1**) and an analogous system having a much closer resemblance to the corresponding triaza crown ether system (**4**).[7] The latter has been shown to be an excellent host for alkylammonium cations. We chose to synthesize the hosts (**1**) and (**3**) by reduction of the macrocyclic diamides (**1a**) and (**3a**) and the required diamine and bis-acid chloride were obtained in each case by conventional routes which are described briefly below.

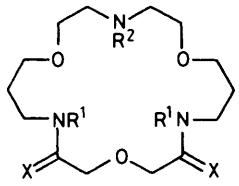
The reaction of 3-aminopropanol with β-propiolactone in acetonitrile gave, in a solvent dependent reaction,[8] a high yield (85%) of the product of *N*-alkylation, the amino acid (**5a**), and a low yield of the product of *N*-acylation, the amide (**6**). The amino acid (**5a**) was converted into the *N*-tosyl derivative (**5b**) which was reduced with lithium aluminium hydride to give a rather low yield (47%) of the diol (**7**). A rather more satisfactory route to the diol (**7**) involved a sequence of *N*-toluene-*p*-sulphonylation, hydrolysis, and reduction from the dinitrile



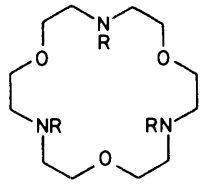
(**1**)



(**2**)



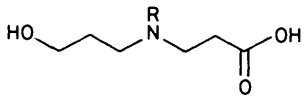
(**3**)



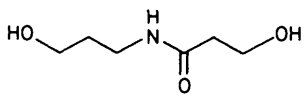
(**4**)

in (**1**) and (**3**): **a**; X = O, R^1 = H, R^2 = $SO_2C_6H_4Me$
b; X = H_2, R^1 = H, R^2 = $SO_2C_6H_4Me$
c; X = H_2, R^1 = R^2 = H
d; X = H_2, R^1 = R^2 = Me

(**8a**). This sequence was superior to the alternative sequence of hydrolysis followed by *N*-toluene-*p*-sulphonylation and reduction because of the high tendency of β-amino acid derivatives to undergo base catalysed elimination. The synthesis of the chain extended diamine (**9a**) from the diol (**7**) involved cyanoethylation and reduction with aluminium hydride, prepared[9] *in situ* from lithium aluminium hydride and sulphuric acid. The use of basic reagents, such as lithium aluminium hydride, for this reduction gave a complex mixture of products presumably resulting from base catalysed elimination[10] from the β-alkoxy nitrile system or one of its reduction products. The bis-acid chloride (**10**) was readily prepared from the known dinitrile (**11**). Base catalysed reaction of the diamine (**9a**) with the bis-acid chloride (**10**),

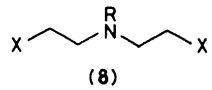


(5)

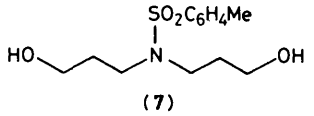


(6)

a; R = H
b; R = $MeC_6H_4SO_2$



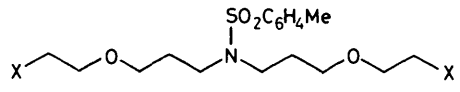
(8)



(7)

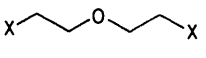
a; R = H, X = CN
b; R = $SO_2C_6H_4Me$, X = CN
c; R = $SO_2C_6H_4Me$, X = CO_2H

to give the macrocyclic diamide (**1a**), was best carried out under conditions of high dilution in toluene, using synchronised motor-driven syringes to deliver the reagents simultaneously. Failure to use this technique to avoid an excess of base in the reaction mixture resulted in considerably reduced yields of the required macrocycle (**1a**).

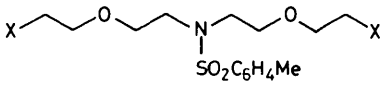


(9)

a; X = CH_2NH_2
b; X = CN



(10) X = COCl
(11) X = CN



(12)

a; X = CH_2NH_2
b; X = CN

Reduction of the macrocyclic diamide (**1a**) with lithium aluminium hydride proved unsatisfactory due to base catalysed elimination from the β-alkoxy amide units in the macrocycle; this difficulty could readily be avoided by using the diborane–tetrahydrofuran complex as the reducing agent. The resulting *N*-tosyl macrocycle (**1b**) could be deprotected by reduction with lithium aluminium hydride in refluxing tetrahydrofuran to give the macrocyclic tri-amine (**1c**).

The related macrocyclic diamide (**3a**) was prepared by a similar high dilution cyclisation reaction involving diglycollyl chloride and the diamine (**12b**); the latter was obtained from *N*-tosyldiethanolamine by a sequence of cyanoethylation and reduction. Reduction of the diamide (**3a**) with lithium aluminium hydride in refluxing tetrahydrofuran gave the triamine (**3c**) and reduction with diborane gave the *N*-tosyl derivative (**3b**) of the triamine (**3c**). Both macrocyclic triamines (**1c**) and (**3c**) were converted into the corresponding *N*,*N*′,*N*″-trimethyl derivative by the Eschweiler-Clarke procedure.

Synthesis of the macrocyclic diamide (**1a**) was achieved in only a moderate yield (27%) by addition of the two reactants, (**9a**) and (**10**), simultaneously to cold toluene. This method did not employ the pre-dilution technique, described by Vögtle and others,[11] because this requires the use of refluxing solvents. The diamide (**1a**) is prone to elimination, and even when refluxing dichloromethane (b.p. 40 °C) was used in an apparatus with a pre-dilution stage the yield of the macrocycle (**1a**) from the reactants, (**9a**) and (**10**), was sharply reduced. The analogous macrocycle (**3a**), which does not have the same tendency to undergo elimination, was made in a satisfactory yield (45%) using a pre-dilution stage and refluxing dichloromethane as the solvent.

The methylated macrocycles (**1d**) and (**3d**) were examined for their ability to form complexes with primary alkylammonium cations using methods that have been fully described in our work on aza crown ethers.[11] The ^1H n.m.r. spectra of both macrocycles were independent of temperature over the range +25 °C to −90 °C and the n.m.r. spectra of solutions of (**1d**) containing 1 and 2 molar equivalents of benzylammonium thiocyanate or (*S*)-phenethylammonium thiocyanate also showed no temperature dependence within this temperature range apart from slight line broadening. On the basis of our previous studies[12] this indicates that the triamine (**1d**) does not form a strongly bound complex with guest alkylammonium cations. The macrocycle (**3d**) resembles a triaza crown ether more closely and did show evidence for complexation of alkylammonium cations. Thus the ^1H n.m.r. spectrum of a 1:1 mixture of host (**3d**) and guest benzylammonium thiocyanate shows pronounced temperature dependence for the $-CH_2-$ groups in the macrocycle. At low temperatures the $-CH_2-$ triplets or multiplets broaden and separate into two broad signals corresponding[12,13] to a slow rate for the face-to-face exchange (E + I) of the guest cation shown diagramatically in the Figure. From coalescence temperatures and low temperature

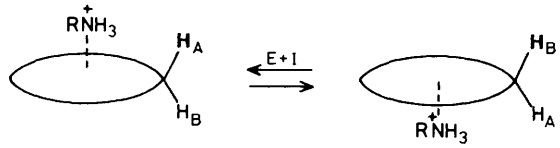


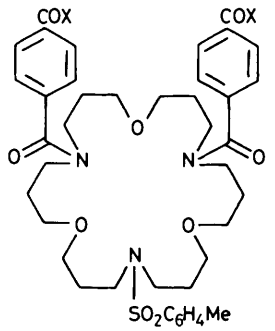
Figure. Face-to-face guest exchange in a complex of an alkylammonium cation. The oval represents a macrocycle and the individual protons of a $-CH_2-$ group of the macrocycle are identified by normal and bold type, the subscrips A and B indicate the differing molecular environments of the two protons

signal separation[14] the free energy barrier for the process (E + I) is a little lower ($\Delta G^{\ddagger}$ *ca.* 10.5 kcal mol^{-1}) than that found for the analogous complexes of aza, diaza, and triaza crown ethers.[7,12,13] Similar effects were observable in the ^1H n.m.r. spectrum of a 1:1 mixture of host (**3d**) and guest (*S*)-phenethylammonium thiocyanate, with additional complexity at low temperatures due to the chirality of the guest cation.[11] We conclude from this brief examination that the 1,3-disubstituted propane unit does not provide a satisfactory basis for alkylammonium cation complexation in contrast with the highly satisfactory results[1] obtained from macrocycles based upon the 1,2-disubstituted ethane unit.

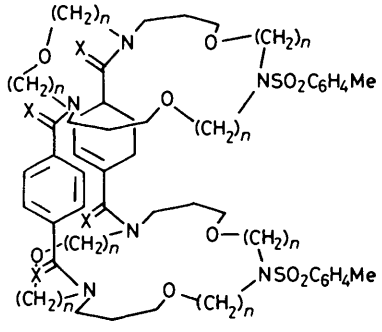
The possibility that either of the macrocycles (**1c**) or (**3c**) might form a complex with glucose was also investigated [see formula (2)]. Solutions of D-glucose in D_2O were extracted with deuteriochloroform containing 1,2, and 5 molar equivalents of (**1c**) and (**3c**) but the ^1H n.m.r. spectrum of the organic layer showed no evidence for the presence of glucose and no macrocycle was discovered in the aqueous layer. No evidence for complexation was seen in the ^1H n.m.r. spectrum of a 1:1 mixture of D-glucose and the tris-hydrochloride of (**1c**) in D_2O either, since the chemical shifts of both components were

identical with these of the pure compounds in D_2O. It appears that ligands, such as (**1c**), do not have sufficient structural rigidity (pre-organisation[3,15]) to provide adequate binding energy through hydrogen bonding interactions of the type shown in (**2**), to overcome intramolecular hydrogen bonding in both molecules and the favourable solvation of D-glucose in aqueous solution. The solution to this problem may lie in the development of a rigid polycyclic receptor with good pre-organisation of ligand sites.

We have shown in our work on aza crown ethers that macropolycyclic hosts may have the ability to show a high level of guest recognition[16,17] and it was of interest to prepare polycyclic derivatives of the triaza macrocycles (**1c**) and (**3c**). In particular, the conversion of the *N*-tosyl macrocycle (**1b**) into a tricyclic receptor molecular and the conversion of the macrocyclic triamine into a tetracyclic receptor have been investigated. Reaction of macrocycle (**1b**) with α,α′-dibromo-*p*-xylene gave a single major product in moderate yield but mass spectrometry showed that this was a bicyclic product formed by bridging two of the nitrogen atoms of the macrocycle rather than the required tricyclic product. A more systematic stepwise route to tricyclic systems was therefore investigated. The reaction of macrocycle (**1b**) with 4-methoxycarbonylbenzoyl chloride gave the diester (**13a**) in good yield. Hydrolysis of the



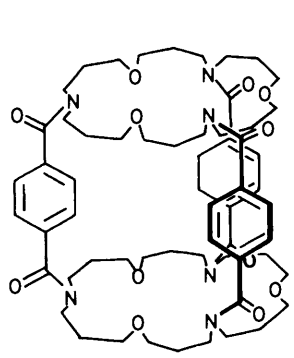
(**13**)
a; X = OMe
b; X = OH
c; X = Cl



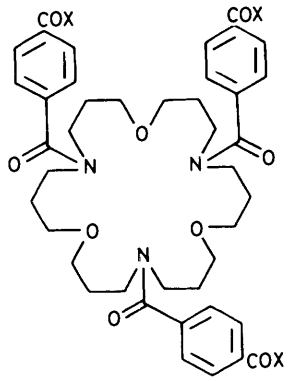
(**14**) *n* = 3, X = O
(**15**) *n* = 2, X = H_2

diester (**13a**) with methanolic potassium hydroxide gave the diacid (**13b**) which was converted into the corresponding bis-acid chloride (**13c**) with thionyl chloride in dichloromethane. Acylation of the macrocyclic diamine (**1b**) with the acid chloride (**13c**), under high-dilution conditions in dichloromethane, gave a moderate yield (30%) of the macrotricyclic amide (**14**). Unfortunately, structure (**14**) could not be further elaborated because repeated attempts to reduce the amide linkages and remove the tosyl protecting group failed. In contrast, the macrocyclic diamine (**3b**) reacted with α,α′-dibromo-*p*-xylene to give the macrotricyclic amine (**15**) in moderate yield (30%); evidently the $N(CH_2)_2O(CH_2)_2N$ system is too short for bridging by a *p*-xylylene unit and this prevents the formation of a bicyclic system. Analogous methods have proved suitable for the preparation of tricyclic compounds from diaza-15-crown-5 and diaza-12-crown-4 systems.

Finally the macrotetracycle (**16**) was prepared in moderate yield (28%) by the reaction of the tris-acid chloride (**17c**) with the macrocyclic triamine (**1c**) under high dilution conditions. Unfortunately, once again, attempted reduction of the tetracyclic hexa-amide with diborane or lithium aluminium hydride failed to give a pure sample of the corresponding tetracyclic hexa-amine.

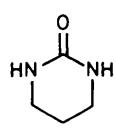


(**16**)

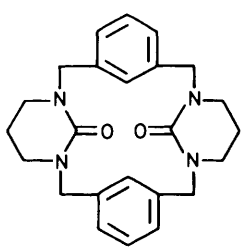


(**17**)
a; X = OMe
b; X = OH
c; X = Cl

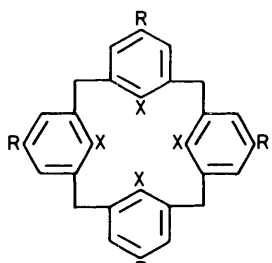
Since the 1,3-disubstituted propane system is also found in the tetrahydropyrimidone sub-units (**18**) of some spherand systems[3,18] we also report a brief investigation of the possibility of generating calixarene analogues based, in part, upon this same sub-unit. The reaction of the dianion from (**18**), generated by reaction with sodium hydride in dimethyl sulphoxide, with α,α′-dibromo-*m*-xylene gave a mixture of products from which the macrocycle (**19**) could be isolated in low yield (7%) [M^+, 404.2218 from mass spectrometry, compound (**18**) requires M^+, 404.2212]. The product (**19**) is an analogue of the calix[4]



(**18**)



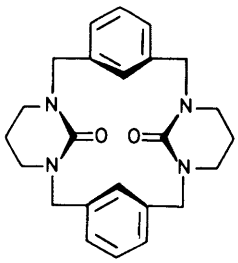
(**19**)



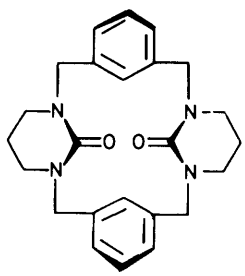
(**20**)

arenes (**20**) which have been extensively studied by Gutsche and others [19,20] and it was of interest to compare the conformational behaviour of the tetrahydropyrimidone analogue (**19**) with that of the calix[4] arene systems. The benzyl methylene protons of (**19**) gave an AB system (δ_A 5.67, δ_B 3.17, J_{AB} 16 Hz) in the ^{1}H n.m.r. spectrum at −40 °C corresponding to a major conformation with further low intensity signals (δ_A 5.74, δ_B 3.62, J_{AB} 16 Hz) in the same region assignable to a minor conformation. The minor and major signals coalesce at 0 °C and finally at +70 °C the major A and B proton signals coalesce. The multiplets from the $-(CH_2)_3-$ groups of the tetrahydropyrimidone ring show analogues temperature dependence within this temperature range. Four conformations of the calix[4]arene system have been recognised [20] and the n.m.r. spectra are consistent with two of them, the 'cone' (**21a**) and '1,3-alternate' (**21b**) conformations, which have appropriate symmetry for the observation of a single AB system from the benzyl CH_2 group. The other two, the 'partial cone' and '1,2-alternate' conformations,[20] would each give two AB systems of equal intensity because of their lower symmetry.

It is of interest that in conformations (**21a**) and (**21b**) the interactions between the C=O dipoles may be greater than in the other calixarene conformations, it has been suggested that in non-polar solvents the cone conformation of some calix[4]-



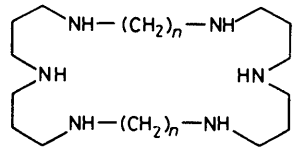
(21a) Cone



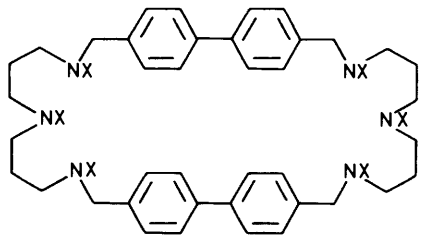
(21b) 1,3-Alternate

arenes (**20**; X = OH) may be stabilised by intramolecular hydrogen bonding [20] but this obviously does not apply to (**21a**). However calix[4]arenes (**20**; X = OMe) also adopt the cone conformation and this provides a closer analogy for the stability of the conformation (**21a**). Whether (**21a**) or (**21b**) is the major conformation is certainly not clear from the n.m.r. spectra but, by analogy with calix[4]arenes, the cone conformation (**21a**) seems more likely to by the major conformaton.*

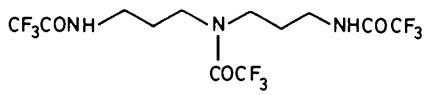
The 1,3-disubstituted propane system has also been used as a sub-unit in protonated polyamines which act as hosts for anionic species,[5,6] our study of this sub-unit was therefore extended to some simple cyclophane system which might also act as anion receptors. Hosseini and Lehn [6] have shown that the protonated hexa-amines (**22**) function as selective receptors for the dicarboxylate anions, $^-O_2C(CH_2)_nCO_2^-$. In particular the macrocycle (**22a**) preferentially complexes the succinate and glutarate dianions, whereas the longer cavity of (**22**) selects the pimelate and suberate dianions but also form a strong complex with the malonate dianion. It was of interest to determine whether this selectivity involves inclusion of the guest anion in the cavity of the macrocycle; this is consistent with the reported



(**22**)
a; n = 7
b; n = 10



(**23**) X = H
(**25**) X = $COCF_3$

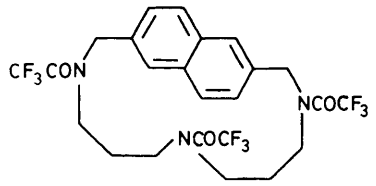


(**24**)

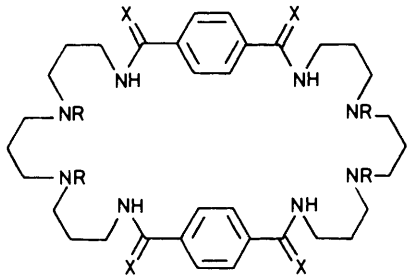
selectivity but we decided to test for the formation of inclusion complexes by using methods similar to those that have proved successful for detecting inclusion complexes of dications.[16,17] The biphenylophane (**23**) was readily synthesized by the base-catalysed reaction [21] of tris(trifluoroacetyl)-1,7-diamine-4-aza-heptane (**24**) with 1,4-bis(bromomethyl)biphenyl. The fully protected macrocycle (**25**) was obtained in low yield (4.9%) but it could be deprotected very readily to give the hexa-amine (**23**), isolated as the hexa-hydrobromide salt. This method for making macrocycles is, as expected, not generally applicable, and the corresponding reaction between the tris-amide (**24**) and 2,6-bis(bromomethyl)naphthalene gave only the cyclophane (**26**) in moderate yield (26%). This difficulty can only be overcome by a stepwise synthesis and this is illustrated by the synthesis of the macrocyclic octa-amine (**27**). The tetra-amine derivative (**28b**), prepared from *N,N*-bis(tosyl)-1,3-diaminopropane by a sequence of cyanoethylation and reduction, reacted with 4-methoxycarbonylbenzoyl chloride to give the diester (**29a**). Hydrolysis of (**29a**), conversion into a bis-acid chloride, and reaction with the tetra-amine derivative (**28b**) under conditions of high dilution gave a moderate yield of the macrocyclic tetra-amide (**30**). Reduction and deprotection with lithium aluminium hydride in refluxing tetrahydrofuran gave the octa-amine (**27**), which was isolated as the octahydrobromide salt.

The formation of inclusion complexes (**31**) of dianions by the host macrocycle (**23**)·6 HCl should result in induced shifts to high field of the $-(CH_2)_n-$ signals in the ^{1}H n.m.r. spectrum of the guest since it lies in the shielding zones [22] of the bridging aromatic rings. Such high field shifts were observed for 1:1 ratios of guest and host and they are summarised in Table 1. The magnitudes of the shifts are similar for both 10^{-3}M and 10^{-2}M solutions of both components and we assume from this result that association constants are large so that the induced chemical shifts correspond to virtually complete complexation of the dianion. Values for induced chemical shift are maximum for

* The observed free energy of activation ($\Delta G^{\ddagger}$ *ca.* 15 kcal mol^{-1}) for the inversion process is comparable with that found [20] for the calix[4] arenes, and although its origin is not clear from studies of space filling (CPK) molecular models it is presumably associated to some extent with the passage of the carbonyl group through the internal calixarene cavity.

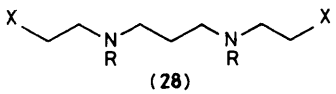


(26)



(27) X = H_2, R = H

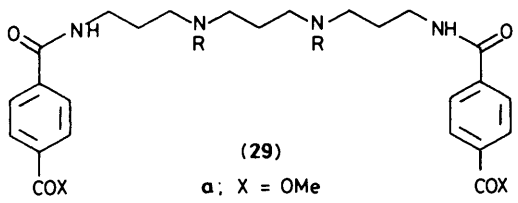
(30) X = O, R = $MeC_6H_4SO_2$



(28)

a; X = CN b; X = CH_2NH_2

In (28) and (29) R = $MeC_6H_4SO_2$



(29)

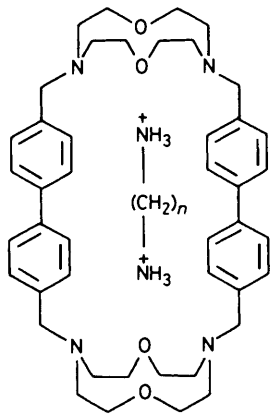
a; X = OMe

b; X = OH

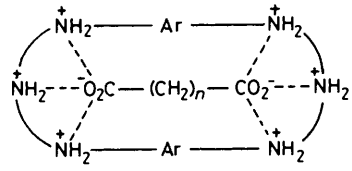
c; X = Cl

n = 4, 5, and 6 corresponding to optimum inclusion of these three guest dianions. The fall in value for $n < 4$ and $n > 6$ presumably results from the competing formation of complexes of types other than the inclusion complex (**31**) for the shorter dianions (n = 1, 2, and 3) but may also result from low values for association constants for the longer dianions, which tend to precipitate as the free dicarboxylic acids at concentrations greater than 10^{-3}M. We note that the induced high field shifts are considerably smaller (Δδ *ca.* 0.5 p.p.m.) than the shifts observed[16,17] for guest dications in the complexes (**32**) (Δδ 1—2 p.p.m.). This is consistent with a more open structure for the monocyclic hosts, as compared with the tricyclic hosts, in which the $-CH_2-$ groups of the guest are at a greater distance from the biphenyl bridges.

Although the octa-aza macrocycles (**27**), as their octahydrobromide salts, have greater charge than the protonated hexaaza macrocycles (**23**) they are less satisfactory as host molecules in that the induced high field shifts of the $-CH_2-$ protons of guest dianions are small and tend to increase for shorter chain lengths without showing any maximum (Table 2). Thus there is no clear evidence for selective inclusion in this series. This may



(32)



(31)

Table 1. Induced high field chemical shifts (Δδ) for ^{1}H n.m.r. signals of dicarboxylate anions $^-O_2C(CH_2)_nCO_2^-$ complexed by host macrocycle (**23**)·6 HBr

Guest Dianion n	$-\Delta\delta^{a,b}$ α	β	γ, δ,[c] ε[c]
1	0.10 (0.10)		
2	0.20 (0.24)		
3	0.31 (0.30)	0.32 (0.29)	
4	0.42 (0.45)	0.44 (0.48)	
5	0.44 (0.50)	0.49 (0.54)	0.48 (0.52)
6	0.43	0.47	0.47
7	0.31	0.37	0.39
8	0.21	0.27	0.30
9	0.13	0.20	0.25

[a] Values refer to chemical shifts for ^-O_2C-C(α)H_2-C(β)H_2-*etc.* for a solution of $NaO_2C(CH_2)_nCO_2Na$ (10^{-3}M) and host (**23**)·6 HBr (10^{-3}M) in D_2O–CD_3CN (4:1) at 25 °C. [b] Values in parentheses refer to a solution of 10^{-2}M in both components. For $n \geqslant 6$ the free dicarboxylic acid crystallises out from the solution. [c] The signals for C(δ)H_2 and C(ε)H_2 overlap with the signal for C(γ)H_2.

Table 2. Induced high field chemical shifts (Δδ) for ^{1}H n.m.r. signals of dicarboxylate anions $^-O_2C(CH_2)_nCO_2^-$ complexed by host macrocycle (**27**)·8 HBr

Guest Dianion n	$-\Delta\delta^{a}$		γ, δ[b], ε[b]
1	<0.1[c]		
2	0.12		
3	0.07	0.11	
4	0.09	0.09	
5	0.06	0.07	0.07
6	0.03	0.06	0.05
7	0.03	0.05	0.04
8	−0.01	0.03	0.04

[a] As for footnote to Table 1. [b] The signals for C(δ)H_2 and C(ε)H_2 overlap with the signal for C(γ)H_2. [c] Signal overlaps with host signal.

result from the greater length of the bridging tetra-amine unit in (**27**) as compared with the tri-amine unit in (**23**) so that the aromatic rings are further away from the $-(CH_2)_n-$ chain of the guest dianion. Furthermore both macrocycles, (**23**) and (**27**), are polycations in which repulsion between positive charges will tend to favour the extended conformation of the protonated polyamine unit (all torsion angles 180°) and a non-ideal conformation for carboxylate complexation. Additional structure to locate the positively charged $-\overset{+}{N}H_2-$ centres in an appropriate complimentary relationship to the negatively charged oxygen atoms of each carboxylate group is required for more selective inclusion of dicarboxylate anions. This strategy has proved highly successful in selective cation complexation[3,15] but it has not yet been generally applied for the synthesis of prestructed hosts for anion complexation although there are examples involving selective complexation of simple anions.[23]

Experimental

7-Hydroxy-4-azaheptanoic Acid (**5a**).—3-Aminopropan-1-ol (7.5 g) in acetonitrile (10 ml) was added dropwise over 15 min to a well stirred solution of β-propiolactone (7.6 g) in acetonitrile (100 ml); the mixture was stirred for 1 h, cooled to 0 °C, and kept for a further 2 h. The precipitated solid was removed by filtration and crystallised from ethanol to give the *product* (**5a**) (10.0 g, 66%), m.p. 132 °C (Found: C, 49.1; H, 8.8; N, 9.7. $C_6H_{13}NO_3$ requires C, 49.0; H, 8.9; N, 9.5%); $\nu_{max.}$(KBr) 3 000—3 600br, 3 160, and 1 575 cm^{-1}; δ(D_2O) 3.70 (t, *J* 6 Hz, OCH_2CH_2), 3.18 (t, *J* 6 Hz, NCH_2CH_2), 3.15 (t, *J* 6 Hz, NCH_2CH_2), 2.52 (t, *J* 6 Hz, CH_2CH_2CO), and 1.90 (m, $CH_2CH_2CH_2$).

N-*Tosyl*-*7-hydroxy*-*4-azaheptanoic Acid* (**5b**).—Toluene-*p*-sulphonyl chloride (1.9 g) was added in portions over 10 min to a solution of the amino acid (**5a**) (1.47 g) in water (10 ml) containing sodium carbonate (1.06 g) at 70 °C. The mixture was maintained at 70 °C for a further 2 h, cooled, acidified (6M HCl), and washed with dichloromethane (3 × 25 ml). The combined washings were dried ($MgSO_4$) and evaporated to give the *product* (**5b**) (2.15 g, 71%) which was purified by crystallisation from ethyl acetate–light petroleum to give a sample, m.p. 93—94 °C (Found: C, 51.3; H, 6.4; N, 4.7. $C_{13}H_{19}NO_5S$ requires C, 51.8; H, 6.4; N, 4.65%); $\nu_{max.}$(KBr) 3 430, 1 710, and 1 595 cm^{-1}; δ($CDCl_3$) AA′BB′ system, δ_A 7.70, δ_B 7.32 ($J_{AB} = J_{A'B'}$ 8 Hz, 4 ArH), 5.60 (br s, OH), 3.68 (t, *J* 6 Hz, OCH_2CH_2), 3.40 (t, *J* 6 Hz, NCH_2CH_2), 3.22 (t, *J* 6 Hz, NCH_2CH_2), 2.61 (t, *J* 6 Hz, CH_2CH_2CO), 2.40 (s, Ar*Me*), and 1.76 (quintet, *J* 6 Hz, $CH_2CH_2CH_2$).

N-*Tosyl*-3,3′-*iminobispropionitrile* (**8b**).—Toluene-*p*-sulphonyl chloride (9.53 g) was added in portions over 30 min to a stirred solution of 3,3′-iminobispropionitrile[24] (6.15 g) in pyridine (20 ml) at 10 °C. The mixture was stirred at room temperature for 4 h and poured into stirred hydrochloric acid (200 ml, 2M). The precipitated solid was removed by filtration, washed with hydrochloric acid (2M), and dried to give the *product* (**8b**) (12.34 g, 89%). Recrystallisation from ethyl acetate–light petroleum gave colourless needles, m.p. 103 °C (Found: C, 56.4; H, 5.5; N, 14.9. $C_{13}H_{15}N_3O_2S$ requires C, 56.3; H, 5.45; N, 15.2%); $\nu_{max.}$($CHCl_3$) 2 240 and 1 595 cm^{-1}; δ($CDCl_3$) AA′BB′ system, δ_A 7.70, δ_B 7.32 ($J_{AB} = J_{A'B'}$ 8 Hz, 4 ArH), 3.45 (t, *J* 6 Hz, 2 × NCH_2CH_2), 2.72 (t, *J* 6 Hz, 2 × CH_2CH_2CN), and 2.42 (s, Ar*Me*).

N-*Tosyl*-3,3′-*iminobispropionic Acid* (**8c**).—The dinitrile (**8b**) (40.3 g) in hydrochloric acid (400 ml, 11.4M) was heated under reflux for 2 h. The reaction mixture was cooled and the crystalline precipitate removed by filtration. The crystals were washed with water, dried, and recrystallised from ethyl acetate to give the *product* (**8c**) (43.5 g, 95%) as colourless needles, m.p. 169—170 °C (Found: C, 49.8; H, 5.5; N, 4.6. $C_{13}H_{17}NO_6S$ requires C, 49.5; H, 5.4; N, 4.4%); $\nu_{max.}$(KBr) 3 600—2 800br, 1 705, 1 595 cm^{-1}; δ(CD_3OD) AA′BB′ system, δ_A 7.70, δ_B 7.32 ($J_{AB} = J_{A'B'}$ 8 Hz, 4 ArH), 3.40 (t, 2 × NCH_2CH_2), 2.59 (t, *J* 6 Hz, 2 × CH_2CH_2CO), and 2.42 (s, Ar*Me*).

N-*Tosyl*-3,3′-*iminobispropan*-1-*ol* (**7**).—A solution of the diacid (**8c**) (40 g) in tetrahydrofuran (THF) (200 ml) was added dropwise over 30 min to a solution of sodium borohydride (11.34 g) in THF (400 ml) containing boron trifluoride–diethyl ether (50.4 ml). The mixture was stirred for 2 h at room temperature, the excess of diborane was destroyed by the addition of water, and aqueous sodium hydroxide (150 ml; 3M) added. The reaction mixture was heated at 35 °C for 30 min, cooled, and saturated with sodium chloride. The organic layer was separated, washed with aqueous sodium chloride (2 × 150 ml), and evaporated to dryness. The residue was dissolved in dichloromethane and the solution dried ($MgSO_4$) and evaporated to give the *product* (**7**) as a viscous oil (33 g, 91%), which was used without further purification; $\nu_{max.}$($CHCl_3$) 3 500br, and 1 595 cm^{-1}; δ($CDCl_3$) AA′BB′ system, δ_A 7.70, δ_B 7.32 ($J_{AB} = J_{A'B'}$ 8 Hz), 3.67 (t, *J* 6 Hz, 2 × OCH_2CH_2), 3.30 (br s, removed by D_2O shake, 2 × OH), 3.22 (t, *J* 6 Hz, 2 × NCH_2CH_2), 2.41 (s, Ar*Me*), and 1.76 (m, 2 × $CH_2CH_2CH_2$). [Found: $(M - C_2H_5O)^+$, 242.0851. $C_{11}H_{16}NO_3S$ requires 242.0871].

N-*Tosyl*-3,3′-*iminobis*-1-(2-*cyanoethoxy*)*propane* (**9b**).—Sodium hydride (0.07 g) was added to a solution of the diol (**7**) (14.95 g) in THF (200 ml) and the mixture was stirred at room temperature for 10 min. Acrylonitrile (7.0 ml) was added dropwise over 30 min and the mixture stirred for a further 4 h. Hydrochloric acid (2.0 ml, 6M) was added and the mixture filtered through basic alumina (grade H). The filtrate was evaporated to dryness to give the product (**9b**) (19.5 g, 95%) as an oil (Found: M^+, 393.1705. $C_{19}H_{27}N_3O_4S$ requires M^+, 393.1722); $\nu_{max.}$ 2 240 and 1 595 cm^{-1}; δ($CDCl_3$) AA′BB′ system, δ_A 7.70, δ_B 7.30 ($J_{AB} = J_{A'B'}$ 8 Hz, 4 ArH), 3.58 (t, *J* 6 Hz, 2 × OCH_2CH_2), 3.48 (t, *J* 6 Hz, 2 × OCH_2CH_2), 3.17 (t, *J* 6 Hz, 2 × NCH_2CH_2), 2.55 (t, *J* 6 Hz, 2 × CH_2CH_2CN), 2.40 (s, ArMe), and 1.79 (m, 2 × $CH_2CH_2CH_2$).

N-*Tosyl*-3,3′-*iminobis*-1-(3-*aminopropoxy*)*propane* (**9a**).—A solution of the cyano ether (**9b**) (23.3 g) in THF (500 ml) was added dropwise to a well stirred solution of aluminium hydride prepared from lithium aluminium hydride (10.0 g) and sulphuric acid (12.96 g) in THF (500 ml) at 0 °C. The mixture was stirred at room temperature for 3 h, the excess of hydride was destroyed by the dropwise addition of water, and the mixture was filtered. The alumina residues were washed with THF and the combined filtrate and washings evaporated to dryness to give the diamine (**9a**) (14.9 g, 63%) as an oil which was used without further purification; $\nu_{max.}$($CHCl_2$) 3 370 and 1 598 cm^{-1}; δ($CDCl_3$) AA′BB′ system δ_A 7.65, δ_B 7.27 ($J_{AB} = J_{A'B'}$, 8 Hz, 4 ArH), 3.42 (t, *J* 7 Hz, 2 × OCH_2CH_2), 3.37 (t, *J* 6 Hz, 2 × OCH_2CH_2), 3.15 (t, *J* 6 Hz, 2 × NCH_2CH_2), 2.72 (t, *J* 6 Hz, 2 × $CH_2CH_2NH_2$), 2.37 (s, Ar*Me*), 1.75 (m, 2 × $CH_2CH_2CH_2$), 1.65 (m, 2 × $CH_2CH_2CH_2$), and 1.56 (br s, removed by D_2O shake, 2 × NH_2).

3,3′-*Oxybispropionic Acid Dichloride* (**10**).—3,3′-Oxybispropionitrile[25] (**11**) (40 g) in hydrochloric acid (500 ml; 6M) was heated under reflux for 2 h. The mixture was cooled and evaporated to dryness and the residual gum extracted with THF (2 × 150 ml). The extract was evaporated to dryness and dissolved in ethyl acetate (250 ml) and the resulting solution was dried ($MgSO_4$) and evaporated to give the crude diacid as a

gum which was heated under reflux for 3 h with thionyl chloride. Excess of thionyl chloride was removed by evaporation and the residual oil distilled to give the bis-acid chloride (**10**) (34.2 g, 67%) as an oil, b.p. 85—88 °C at 1.0 Torr; $\nu_{max.}$ 1 795 cm^{-1}; δ($CDCl_3$) 3.75 (t, *J* 6 Hz, 2 × OCH_2) and 3.10 (t, *J* 6 Hz, 2 × $OCH_2CH_2CO_2H$).

21-*Tosyl*-1,9,17-*trioxa*-5,13,21-*triazacyclotetracosane*-6,12-*dione* (**1a**).—A solution of the diamine (**9a**) (6.95 g) and triethylamine (3.7 g) in dichloromethane (70 ml) and a solution of the bis-acid chloride (**10**) (3.43 g) in toluene (70 ml) were added simultaneously, using synchronised motor-driven syringes, to vigorously stirred toluene (3 l) at room temperature at a rate of 5 ml per h. The reaction mixture was stirred for a further 24 h, decanted from precipitated polymeric material, and evaporated to dryness. The residual brown oil was dissolved in dichloromethane, washed with hydrochloric acid (2M) and water, dried ($MgSO_4$), and evaporated to dryness. The residual oil was chromatographed on alumina and eluted with dichloromethane–ethanol (98:2) to give the *macrocycle* (**1a**) (2.46 g, 27%) as a crystalline solid, m.p. 92 °C (Found: C, 56.7; H, 7.5; N, 8.2%; M^+, 527.2655. $C_{25}H_{41}N_3O_7S$ requires C, 56.9; H, 7.8; N, 8.0%; M^+, 527.2605); $\nu_{max.}$($CHCl_3$) 3 380 and 1 665 cm^{-1}; δ($CDCl_3$) AA′BB′ system, δ_A 7.70, δ_B 7.32 ($J_{AB} = J_{A'B'}$, 8 Hz, 4 ArH), 6.63 (br s, 2 × NH), 3.70 (t, *J* 6 Hz, 2 × OCH_2CH_2), 3.47 (t, *J* 6 Hz, 4 × OCH_2CH_2), 3.35 (t, *J* 6 Hz, 2 × NCH_2CH_2), 3.20 (t, *J* 6 Hz, 2 × NCH_2CH_2), 2.42 (t, *J* 6 Hz, 2 × CH_2CH_2CO), 2.42 (s, Ar*Me*), 1.85 (m, 2 × $CH_2CH_2CH_2$), and 1.76 (m, 2 × $CH_2CH_2CH_2$).

5-*Tosyl*-1,9,17-*trioxa*-5,13,21-*triazacyclotetracosane* (**1b**).—A solution of the macrocyclic diamide (**1a**) (0.59 g) in THF (10 ml) was added dropwise to a stirred solution of borane–THF complex (11.2 ml, 1M) and the mixture heated under reflux for 2 h. The reaction mixture was cooled, excess of borane destroyed by dropwise addition of water, and the solvent was evaporated to give a residual gum which was heated under reflux with hydrochloric acid (10 ml; 6M) for 2 h. The solvent was evaporated and the residual white solid was dissolved in ethanol and passed repeatedly down a column of Amberlite-140 ion exchange resin (OH form) until the eluant was alkaline. The eluant was evaporated to dryness to give the *product* (**1b**) (0.53 g, 96%) as a colourless oil (Found: M^+, 499.3066. $C_{25}H_{45}N_3O_5S$ requires M^+, 499.3080); $\nu_{max.}$($CHCl_3$) 3 300 and 1 596 cm^{-1}; δ($CDCl_3$) AA′BB′ system, δ_A 7.68, δ_B 7.28 ($J_{AB} = J_{A'B'}$ 8 Hz, 4 ArH), 3.45 (t, *J* 6 Hz, 2 × OCH_2CH_2), 3.40 (t, *J* 6 Hz, 2 × OCH_2CH_2), 3.38 (t, *J* 6 Hz, 2 × OCH_2CH_2), 3.15 (t, *J* 6 Hz, 2 × NCH_2CH_2), 2.65 (m, 4 × NCH_2CH_2), 2.40 (s, Ar*Me*), and 1.68 (m, 6 × $CH_2CH_2CH_2$ + 2 × NH).

1,9,17-*Trioxa*-5,13,21-*triazacyclotetracosane* (**1c**).—The diamine (**1b**) (2.0 g) in THF (20 ml) was added dropwise to a stirred solution of lithium aluminium hydride (3.0 g) in THF (100 ml). The mixture was heated under reflux (N_2 atmosphere) for 36 h, cooled in ice to < 10 °C, and water added dropwise to destroy the excess of hydride. The mixture was filtered, the residual alumina washed with THF, and the combined filtrate and washings evaporated to dryness to give a residual oil which was dissolved in dichloromethane and filtered through Celite. The filtrate was evaporated to give the crude triamine (**1c**) as an oil which was dissolved in hydrochloric acid (10 ml; 5M) and the solution washed with dichloromethane and evaporated to give the solid *tris-hydrochloride salt*. The salt was recrystallised from ethanol–ether to give hygroscopic crystals, m.p. 250 °C (0.84 g, 46%) (Found: C, 45.2; H, 9.7; N, 8.3. $C_{18}H_{42}N_3O_3Cl_3 \cdot H_2O$ requires C, 45.7; H, 9.4; N, 8.9%).

5,13,21-*Trimethyl*-1,9,17-*trioxa*-5,13,21-*triazacyclotetracosane* (**1d**).—The macrocyclic triamine (**1c**) (0.57 g) was heated under reflux with formaldehyde (2 ml; 40% aqueous solution) and formic acid (2 ml) for 24 h. The solution was cooled, hydrochloric acid (10 drops, 10M) was added, and the mixture stirred for 10 min. Potassium hydroxide solution (20 ml; 10% aqueous solution) was added and the mixture extracted with dichloromethane (3 × 25 ml). The extracts were dried (Na_2CO_3) and evaporated and the residual oil purified by chromatography on alumina (CH_2Cl_2 and CH_2Cl_2–EtOH 98.2 as eluants) to give the *methylated macrocycle* (**1d**) (0.27 g, 42%) as an oil (Found: M^+, 387.3452); δ($CDCl_3$) 3.46 (t, *J* 6 Hz, 6 × CH_2O), 2.43 (t, *J* 6 Hz, 6 × CH_2N), 2.18 (s, 3 × NMe), and 1.72 (m, 6 × $CH_2CH_2CH_2$).

N-*Tosyl* -2,2′-*iminobis*-1-(3-*aminopropoxy*)*ethane* (**12a**).—The reaction of *N*-tosyldiethanolamine (25.9 g) with acrylonitrile (11.7 g) gave the cyano ether (**12b**) (34.7 g, 95%) as a colourless oil which was used without further purification; $\nu_{max.}$($CHCl_3$) 2 240 cm^{-1}; δ($CDCl_3$) AA′BB′ system, δ_A 7.70, δ_B 7.30 ($J_{AB} = J_{A'B'}$ 8 Hz, 4 ArH), 3.65 (t, *J* 6 Hz, 2 × OCH_2), 3.60 (t, *J* 6 Hz, 2 × OCH_2), 3.40 (t, *J* 6 Hz, 2 × NCH_2), 2.53 (t, *J* 6 Hz, 2 × CH_2CN), and 2.40 (s, ArMe). A solution of the cyano ether (**12b**) (18.25 g) in THF (500 ml) was added to a well stirred solution of aluminium hydride [prepared from lithium aluminium hydride (10.0 g) and sulphuric acid (12.96 g)] in THF (500 ml) Work-up in the usual manner gave the diamine (**12a**) (11.6 g, 62%) as an oil which was used for the synthesis of macrocycle (**3a**) without further purification; δ($CDCl_3$) AA′BB′ system, δ_A 7.72, δ_B 7.28 ($J_{AB} = J_{A'B'}$ 8 Hz, 4 ArH), 3.55 (t, *J* 6 Hz, 2 × OCH_2), 3.45 (t, *J* 6 Hz, 2 × OCH_2), 3.36 (t, *J* 6 Hz, 2 × NCH_2), 2.75 (t, *J* 6 Hz, 2 × NCH_2), 2.38 (s, Ar*Me*), 1.70 (s, 2 × NH_2), and 1.60 (m, 2 × $CH_2CH_2CH_2$).

18-*Tosyl*-1,8,15-*trioxa*-5,11,18-*triazacycloicosane*-6,10-*dione* (**3a**).—Solutions of diglycollic acid dichloride (8.83 g) in dichloromethane and the diamine (**12a**) (19.25 g) and triethylamine (10.35 g) in dichloromethane were each made up to 70 ml with dichloromethane. The solutions were added simultaneously at 5 ml per hour using synchronised motor driven syringes, to well stirred dichloromethane (2.5 l) heated under reflux, using a high dilution apparatus with a pre-dilution stage.* The mixture was stirred at room temperature for 24 h, the solvent evaporated off, and the residual solid dissolved in dichloromethane, washed (2M HCl, water), dried, and evaporated to give the crude macrocycle. The product was purified by chromatography on alumina (CH_2Cl_2–EtOH 98:2) and recrystallisation from benzene–cyclohexane to give the macrocyclic diamide (**3a**) (10.89 g, 45%) as colourless needles, m.p. 134—135 °C (Found: C, 53.7; H, 7.2; N, 8.8. M^+, 471.2004. $C_{21}H_{33}N_3O_7S$ requires C, 53.5; H, 7.05; N, 8.9%; M^+, 471.2039); $\nu_{max.}$ 3 400, and 1 670 cm^{-1}; δ($CDCl_3$) AA′BB′ system, δ_A 7.70, δ_B 7.32 ($J_{AB} = J_{A'B'}$ 8 Hz, 4 ArH), 7.13 (br 2 × NH), 4.00 (s, 2 × OCH_2CO), 3.61 (t, *J* 6 Hz, 2 × OCH_2), 3.53 (t, *J* 6 Hz, 2 × OCH_2), 3.40 (m, 4 × NCH_2), 2.42 (s, Ar*Me*), and 1.77 (m, 2 × $CH_2CH_2CH_2$).

18-*Tosyl*-1,8,15-*trioxa*-5,11,18-*triazacycloicosane* (**3b**).—The macrocyclic diamide (**3a**) (0.5 g) was reduced using the borane–THF complex (5.3 ml; 1M solution in THF) heated under reflux for 2 h. The product was isolated in the usual manner to give the *macrocyclic diamine* (**3a**) (0.44 g, 94%) as an oil (Found: M^+, 433.2444. $C_{21}H_{37}N_3O_5S$ requires M^+, 443.2454); $\nu_{max.}$ 3 500—3 100br cm^{-1}; δ($CDCl_3$) AA′BB′ system, δ_A 7.72, δ_B 7.31 ($J_{AB} = J_{A'B'}$ 8 Hz), 3.55 (m, 4 × OCH_2), 3.49 (t, *J* 6 Hz, 2 × OCH_2), 3.37 (t, *J* 6 Hz, 2 × NCH_2), 2.75 (t, *J* 6 Hz, 2 × NCH_2), 2.06 (t, *J* 6 Hz, 2 × NCH_2), 2.42 (s, Ar*Me*), 2.1 (br s, 2 × NH), and 1.74 (m, 2 × $CH_2CH_2CH_2$).

* The apparatus was constructed as described by F. Vögtle in ref. 11.

1,8,15-*Trioxa*-5,11,18-*triazacycloicosane* (**3c**).—The macrocyclic diamide (**3a**) (0.5 g) was reduced with lithium aluminium hydride (0.4 g) in refluxing THF (50 ml) for 36 h. The product was isolated in the usual way to give the *macrocyclic triamine* (**3c**) (0.141 g, 55%) as an oil; δ($CDCl_3$), 3.55 (m, 6 × OCH_2), 2.77 (m, 6 × OCH_2), 1.76 (m, 2 × $CH_2CH_2CH_2$), and 1.4 (s, 3 × NH). Treatment of the triamine (0.305 g) with formic acid (1 ml) and formaldehyde (1 ml; 40% aqueous solution) and heating under reflux for 24 h gave 5,11,18-*trimethyl*-1,8,15-*trioxa*-5,11,18-*triazacycloicosane* (**3d**) (0.199 g, 57%) as an oil (Found: M^+, 311.2835. $C_{17}H_{37}N_3O_3$ requires M^+, 311.2808); δ($CDCl_3$) 3.54 (m, 6 × OCH_2), 2.66 (t, *J* 6 Hz, 2 × NCH_2), 2.57 (t, *J* 6 Hz, 2 × NCH_2), 2.50 (t, *J* 6 Hz, 2 × NCH_2), 2.32 (s, NMe), 2.23 (s, 2 × NMe), and 1.72 (m, 2 × $CH_2CH_2CH_2$).

5,13-*Bis*(4′-*methoxycarbonylbenzoyl*)-21-*tosyl*-1,9,17-*trioxa*-5,13,21-*triazacyclotetracosane* (**13a**).—4-Methoxycarbonylbenzoyl chloride (0.64 g) in THF (10 ml) was added dropwise to a solution of the macrocyclic triamine derivative (**1b**) (0.8 g) and triethylamine (0.36 g) in THF over a period of 30 min and the mixture stirred for a further 2 h. The mixture was filtered and the filtrate evaporated to give a yellow gum which was purified by chromatography on alumina (CH_2Cl_2–EtOH, 98:2 as eluant) to give the required *diamide* (**13a**) as a foam (1.10 g, 84%) (Found: M^+, 823.3705. $C_{43}H_{57}N_3O_{11}S$ requires M^+, 823.3714); $\nu_{max.}$ 1 720 and 1 620 cm^{-1} δ($CDCl_3$) 8.05 (d, *J* 8 Hz, 4 ArH), 7.65 (d, *J* 8 Hz, 2 ArH), 7.40 (d, *J* 8 Hz, 4 ArH), 7.28 (d, *J* 8 Hz, 2 ArH), 3.90 (s, 2 × OMe), 2.9—3.7 (br m, 6 × OCH_2 + 6 × NCH_2), 2.37 (s, Ar*Me*), and 1.5—2.1 (br m, 6 × $CH_2CH_2CH_2$). The corresponding dicarboxylic acid (**13b**) was obtained by hydrolysis of the diester (**13a**) (0.50 g) with potassium hydroxide (0.15 g) in refluxing methanol (25 ml) for 30 min. The solution was evaporated to dryness and the residue dissolved in water (10 ml), acidified (6M HCl), and extracted with dichloromethane. The extracts were dried ($MgSO_4$) and evaporated to give the dicarboxylic acid (**13b**) (0.48 g, 100%) as a foam [Found: $M + H^+$, 796.32 (f.a.b.m.s.). $C_{41}H_{54}N_3O_{11}S$ requires 796.3479] $\nu_{max.}$($CHCl_3$) 1 705 and 1 620 cm^{-1}; δ($CDCl_3$) 10.4 (br s, disappears on D_2O shake, 2 × CO_2H), 8.05 (br m, 4 ArH), 7.65 (br m, 2 ArH), 7.42 (br m, 4 ArH), 7.28 (br m, 2 ArH), 2.90—4.0 (br m, 6 × OCH_2 + 6 × NCH_2), 2.35 (s, ArMe), and 1.4—2.2 (br m, 3 × $CH_2CH_2CH_2$).

N,N′-*Bis-tosyl Macrotricyclic Tetra-amide* (**14**).—The dicarboxylic acid (**13b**) (0.203 g) was heated under reflux in thionyl chloride (15 ml) for 4 h. The solution was evaporated to dryness and the residual crude bis-acid chloride (**13c**) (0.22 g) used without further purification; $\nu_{max.}$ 1 777, 1 740, and 1 627 cm^{-1}. Solutions of the bis-acid chloride (**13c**) (0.294 g) in dichloromethane (40 ml) and the macrocyclic diamine (**1b**) (0.165 g) and triethylamine (0.2 g) in dichloromethane (40 ml) were added simultaneously, using synchronised motor-driven syringes, over a period of 6 h to well stirred toluene (1.5 l). The mixture was stirred overnight and then evaporated to dryness. The residual gum was dissolved in dichloromethane (20 ml) and the solution washed (2M HCl, H_2O), dried (Na_2SO_4), and evaporated to dryness. The *product* (**14**) (0.13 g, 30%) was obtained as a foam after chromatography on alumina (CH_2Cl_2–EtOH 98:2 as eluant); $\nu_{max.}$ 1 620 cm^{-1}; δ 7.70 (br m, 4 ArH), 7.36 (m, 12 ArH), 2.9—3.9 (br m, 12 × OCH_2 + 12 × NCH_2), 2.38 (s, 2 × Ar*Me*), and 1.4—2.2 (br m, 12 × $CH_2CH_2CH_2$). The mass spectrum showed peaks up to *m/z* 1 103 [M − $MeC_6H_4SO_2$]$^+$ but no molecular ion at *m/z* 1 258.

Macrotricyclic Amine (**15**).—Solutions of the macrocyclic diamine (**3b**) (0.986 g) and α,α′-dibromo-*p*-xylene (0.587 g) in acetonitrile (100 ml) were added simultaneously over a period of 2 h to a well stirred suspension of potassium carbonate (5 g) in acetonitrile (300 ml) at 80 °C. The mixture was stirred at 80 °C for 24 h, cooled, and evaporated to dryness. The residual gum was extracted with dichloromethane, and the extract washed with water, dried (K_2CO_3), and evaporated. The residue was purified by chromatography on alumina (CH_2Cl_2–EtOH 98:2 as eluant) to give the *product* (**15**) (0.33 g, 27%) as a colourless gum (Found: M^+ 1 090.5793. $C_{58}H_{86}N_6S_2O_{10}$ requires M^+, 1 090.5846); δ($CDCl_3$) AA′BB′ system, δ_A 7.67, δ_B 7.23 (J_{AB} = $J_{A'B'}$ 8 Hz, 4 ArH), 7.23 (s, 8 ArH), 3.55 (t, *J* 6 Hz, 4 × OCH_2), 3.50 (s, 4 × ArCH_2), 3.47 (t, *J* 6 Hz, 4 × OCH_2), 3.38 (t, *J* 6 Hz, 4 × CH_2N), 3.30 (m, 4 × CH_2N), 2.55 (t, *J* 6 Hz, 4 × CH_2N), 2.50 (t, *J* 6 Hz, 4 × CH_2N), 2.37 (s, 2 × Ar*Me*), and 1.70 (m, 4 × $CH_2CH_2CH_2$).

5,13,21-*Tris*(4-*carboxybenzoyl*)-1,9,17-*trioxa*-5,13,21-*triazacyclotetracosane* (**17b**).—The triamine (**1c**) (0.37 g) in THF (50 ml) reacted with 4-methoxycarbonylbenzoyl chloride (0.64 g) to give the *triester* (**17a**) (0.77 g, 87%), as a foam after purification of the crude product by chromatography on alumina (CH_2Cl_2–EtOH 98:2 as eluant) (Found: M^+, 831.3950. $C_{45}H_{57}N_3O_{12}$ requires *M*, 831.3942); $\nu_{max.}$ 1 720 and 1 625 cm^{-1}; δ($CDCl_3$) AA′BB′ system, δ_A 8.08, δ_B 7.43 (J_{AB} = $J_{A'B'}$ 8 Hz, 3 × C_6H_4), 3.90 (s, 3 × CO_2Me), 3.00—3.75 (m, 6 × OCH_2 + 6 × NCH_2), and 1.4—2.1 (m, 6 × $CH_2CH_2CH_2$). Hydrolysis of the triester (**17a**) (0.27 g) with potassium hydroxide (0.1 g) in methanol (15 ml) gave the tricarboxylic acid (**17b**) (1.4 g, 100%) as a foam (Found: $[M + H]^+$, 790.3486. $C_{42}H_{52}N_3O_{12}$ requires 790.3493); $\nu_{max.}$ 1 710 and 1 600 cm^{-1}; δ(CD_3OD), 8.13 (br m, 6 ArH), 7.50 (br m, 6 ArH), 2.9—3.8 (br m, 6 × OCH_2 + 6 × NCH_2), and 1.4—2.2 (br m, 6 × $CH_2CH_2CH_2$).

Macrotetracyclic Tetra-amide (**16**).—The tris-acid chloride (**17c**) was prepared from the tricarboxylic acid (**17b**) (0.869 g) by reaction with thionyl chloride (20 ml) in dichloromethane (10 ml). The reaction mixture was heated under reflux for 4 h and evaporated to dryness to give the tris-acid chloride (**17c**) (0.98 g) which was used without further purification; $\nu_{max.}$ 1 760, 1 740, and 1 635 cm^{-1}. Solutions of the tris-acid chloride (**17c**) (0.40 g) in dichloromethane (40 ml) and the macrocyclic triamine (**1c**) (0.162 g) and triethylamine (0.2 g) in dichloromethane (40 ml) were added simultaneously using synchronised motor driven syringes to well stirred dichloromethane (1 l). The crude reaction product was purified by chromatography on alumina (CH_2Cl_2–EtOH 99:1 as eluant) to give the *macrotetracycle* (**16**) (0.141 g, 28%) as a crystalline solid, m.p. 272—273 °C after recrystallisation from benzene–cyclohexane (Found: C, 65.95; H, 7.8; N, 7.5. $C_{60}H_{84}N_6O_{12}$ requires C, 66.6; H, 7.8; N, 7.8%); $\nu_{max.}$ 1 620 cm^{-1}; δ($CDCl_3$) 7.00—7.70 (br m, 12 ArH), 2.9—4.5 (br m, 12 × OCH_2 + 12 × NCH_2), and 1.0—2.4 (br m, 12 × $CH_2CH_2CH_2$).

2,6;15,19-*Biscarbonyl*-2,6,15,19-*tetra-aza*[7.7]*metacyclophane* (**19**).—Tetrahydro-2-pyrimidone (**18**) (2.00 g) and sodium hydride (1.06 g) were stirred in dimethyl sulphoxide (DMSO) (100 ml) for 4 h. A solution of α,α′-dibromo-*m*-xylene (5.28 g) in DMSO (100 ml) was added dropwise over 1 h and the mixture stirred overnight. Water (0.5 ml) was added and the mixture concentrated to a volume of 15 ml; chloroform (50 ml) was added and precipitated solids removed by filtration through Celite. The filtrate was concentrated to a volume of 15 ml and left overnight, the product which crystallised from the solution was recrystallised from benzene–cyclohexane to give the *calixarene analogue* (**19**) (0.28 g 7%) as colourless crystals, m.p. 230 °C (Found: M^+, 404.2218. $C_{24}H_{28}N_4O_2$ requires M^+, 404.2212), $\nu_{max.}$($CHCl_3$) 1 625 cm^{-1}; δ($CDCl_3$) 7.0—7.3 (m, 8 ArH), 5.66 (br d, *J* 15.5 Hz, 4 × CH_AH_B), 3.60 (br d, 15.5 Hz, 4 × CH_AH_B), 3.19 (m, 4 × NCH_2CH_2), and 1.83 (m, 2 ×

$CH_2CH_2CH_2$); δ ($CDCl_3$, −37 °C) ABC_2 system, δ_A 7.30, δ_B 7.22, δ_C 7.12 (J_{AC} 8 Hz, 2 × 4 ArH), AB system, δ_A 5.67, δ_B 3.71 (J_{AB} 16 Hz, 4 × $ArCH_AH_B$), 3.32 (dt, *J* 12, 7 Hz, 4 × $NCHHCH_2$), 3.21 (dt, *J* 12, 4 Hz, 4 × $NCHHCH_2$), and 1.89 (m, 2 × $CH_2CH_2CH_2$); in addition a minor species was associated with a further AB system, δ_A 5.74, δ_B 3.62 (J_{AB} 16 Hz, 4 × $ArCH_AH_B$).

N,N′,N″-*Tris*(*trifluoroacetyl*)-1,5,9-*triazanonane* (**24**).—Trifluoroacetic anhydride (12.0 g) was added dropwise over 1 h to a stirred solution of 1,7-diamino-4-azaheptane (2.5 g) and triethylamine (5.78 g) in dichloromethane (50 ml) at 10 °C. The mixture was stirred for 30 min, washed with hydrochloric acid (2 × 50 ml, 2M) and water (50 ml), and dried. Evaporation of the solution gave a colourless oil which crystallised. Crystallisation from benzene–cyclohexane gave the *triamide* (**24**) (3.98 g, 85%), m.p. 76 °C (Found: C, 34.4; H, 3.4; N, 9.9. $C_{12}H_{14}N_3O_3F_9$ requires C, 34.4; H, 3.4; N, 10.0%); $\nu_{max.}$(Nujol) 3 320 and 1 700 cm^{-1}; δ[$CDCl_3$–$(CD_3)_2SO$] 8.75 (br s, NH), 8.4 (br s, NH), 3.46 (t, *J* 6 Hz, 2 × NCH_2CH_2), 3.25 (t, *J* 6 Hz, 2 × NCH_2CH_2), and 1.85 (m, 2 × $CH_2CH_2CH_2$).

2,6,10,25,29,33-*Hexakis*(*trifluoroacetyl*)-2,6,10,25,29,33-*hexa-aza*[11.11](4,4′)*biphenylophane* (**25**).—Sodium hydride (0.29 g) was added to a solution of the triamide (**24**) (1.59 g) in dimethylformamide (DMF) (500 ml) and the mixture stirred for 2 h. A solution of 4,4′-bis(bromomethyl)biphenyl (1.69 g) in DMF (200 ml) was added to the resulting solution over a period of 6 h. The mixture was evaporated to dryness and the residual gum dissolved in dichloromethane. The solution was washed with water, dried, and evaporated. The residue was purified by flash column chromatography (silica, ethyl acetate–dichloromethane, 5:95) to give the *cyclophane* (**25**) as a colourless solid (145 mg, 4.9%) (Found: M^+, 1 194.3394. $C_{52}H_{48}F_{18}N_6O_6$ requires *M*, 1 194.3348); $\nu_{max.}$ 1 690 cm^{-1}.

2,6,10-*Tris*(*trifluoroacetyl*)-2,6,10-*triaza*[11](2,6)*naphthalenophane* (**26**) was prepared in a similar manner from the triamide (**24**) (1.59 g) and 2,6-bis(bromomethyl)naphthalene (1.57 g). The *product* (**26**) (0.75 g, 26%) crystallised from benzene–cyclohexane, m.p. 194—196 °C (Found: C, 50.5; H, 3.9; N, 7.1%; M^+, 571.1469. $C_{24}H_{22}N_3O_3F_9$ requires C, 50.45; H, 3.9; N, 7.35%; *M*, 571.1516); $\nu_{max.}$($CHBr_3$) 1 690 cm^{-1}.

2,6,10,25,29,33-*Hexa-aza*[11.11](4,4′)*biphenylophane* (**23**).—The hexa-amide (**25**) (0.50 g) was heated under reflux for 3 h with a methanolic solution of benzyl trimethylammonium hydroxide (3 ml; 40% solution). The mixture was cooled, diluted with dichloromethane (5 ml), and washed with water. The organic layer was dried and evaporated to give the macrocyclic hexa-amine (**23**) (0.25 g, 96%) as a pale yellow gum; δ 7.3—7.6 (m, 16 ArH), 3.73 (s, 4 × $ArCH_2N$), 2.70 (t, *J* 6 Hz, 4 × NCH_2), 2.67 (t, *J* 6 Hz, 4 × NCH_2), *ca.* 1.85 (br s, 6 × NH), and 1.67 (m, 4 × $CH_2CH_2CH_2$). The product was characterised as the *hexahydrobromide* (**23**; 6 HBr) which crystallised from ethanol–water as a colourless solid, m.p. 300 °C (0.30 g, 68%) (Found: C, 42.6; H, 6.0; N, 7.05. $C_{40}H_{60}N_6Br_6{\cdot}2H_2O$ requires C, 42.1; H, 5.7; N, 7.4%); $\nu_{max.}$(Nujol) 3 400, 1 610, and 1 560 cm^{-1}; δ(D_2O) AA′BB′ system, δ_A 7.82, δ_B 7.60 ($J_{AB'}J_{A'B'}$ 8 Hz, 16 ArH); 4.25 (s, 4 × $\overset{+}{N}CH_2Ar$), 3.06 (m, 8 × $\overset{+}{N}CH_2$), and 2.04 (m, 4 × $CH_2CH_2CH_2$).

N,N′-*Bis*(*tosyl*)-1,3-*diaminopropane*.—The bistoluene-*p*-sulphonamide (66%) was prepared by reaction of the 1,3-diaminopropane with tosyl chloride in pyridine. The product had m.p. 117—118 °C (from ethyl acetate) (Found: C, 53.4; H, 6.0; N, 7.3. $C_{17}H_{22}N_2O_4S_2$ requires C, 53.4; H, 5.8; N, 7.3%).

N,N′-*Bis*(*tosyl*)-NN′-*bis*(2-*cyanoethyl*)-1,3-*diaminopropane* (**28a**).—Sodium hydride (0.1 g) was added to a stirred solution of the bis(tosyl)-1,3-diaminopropane (25 g) in THF (200 ml). After 10 min, acrylonitrile (10.4 g) was added dropwise over 1 h and the mixture stirred overnight. The mixture was diluted with dichloromethane (100 ml) to redissolve precipitated solid and filtered through basic alumina (grade H). The filtrate was evaporated and the residual solid crystallised from benzene–cyclohexane to give the dinitrile (**28a**) (29.4 g, 92%) as white needles, m.p. 112 °C (Found: C, 56.5; H, 5.9; N, 11.4. $C_{23}H_{28}N_4O_4S_2$ requires C, 56.6; H, 5.8; N, 11.5%); $\nu_{max.}$ 2 235 cm^{-1}; δAA′BB′ system, δ_A 7.32, δ_B 7.67 ($J_{AB} = J_{A'B'}$ 8 Hz, 8 ArH), 3.30 (t, *J* 6 Hz, 2 × NCH_2), 3.18 (t, *J* 6 Hz, 2 × NCH_2), 2.69 (t, *J* 6 Hz, 2 × CH_2CN), 2.40 (s, 2 × ArMe), and 1.95 (m, $CH_2CH_2CH_2$).

4,8-*Bis*(*tosyl*)-1,11-*diamino*-4,8-*diazaundecane* (**28b**).—A solution of the dinitrile (**28a**) (1.16 g) in THF (50 ml) was added to a solution of borane–THF complex (50 ml, 0.05 mol BH_3–THF) and the mixture was heated under reflux (N_2 atmosphere) for 2 h. The mixture was cooled, water was added dropwise to destroy the excess of reagent, and the solution was evaporated to dryness. The residual solid was heated under reflux for 2 h with hydrochloric acid (50 ml; 10M), the solution was evaporated to dryness, the residue made alkaline (5M aqueous NaOH), and the product extracted into dichloromethane. The organic extract was extracted with hydrochloric acid (2M), the acidic layer was made basic (5M NaOH), and the product was again extracted into dichloromethane. The extract was dried and evaporated to give the product (**28b**) (0.98 g, 83%) as a yellow oil which was used without further purification; δ, AA′BB′ system, δ_A 7.69, δ_B 7.32 ($J_{AB'}J_{A'B'}$ 8 Hz, 8 ArH), 3.17 (t, *J* 6 Hz, 2 × NCH_2), 3.13 (t, *J* 6 Hz, 2 × NCH_2), 2.72 (t, *J* 6 Hz, 2 × NCH_2), 2.40 (s, 2 × Ar*Me*), 1.85 (m, $CH_2CH_2CH_2$), 1.65 (m, 2 × $CH_2CH_2CH_2$), and 1.62 (s, 2 × NH_2).

N,N′-*Bis*(p-*methoxycarbonylbenzoyl*)-4,8-*bis*(*tosyl*)-1,11-*diamino*-4,8-*diazaundecane* (**29a**).—*p*-Methoxycarbonylbenzoyl chloride (4.00 g) in THF (20 ml) was added dropwise over 30 min to a solution of the diamine (**28b**) (4.91 g) and triethylamine (2.4 g) in THF (50 ml). The mixture was stirred for 3 h, evaporated to dryness, and the residual solid extracted with dichloromethane. The extract was washed with hydrochloric acid (2M) and water, dried, and evaporated to dryness to give the crude product which was purified by flash column chromatography (silica, ethyl acetate–dichloromethane, 2:3) to give the *bis-amide* (**29a**) (6.13 g, 75%) as a colourless foam (Found: C, 59.9; H, 5.85; N, 6.6. $C_{41}H_{48}N_4O_{10}S_2$ requires C, 60.0; H, 5.9; N, 6.8%); $\nu_{max.}$($CHBr_3$) 3 430, 1 720, 1 600, and 1 530 cm^{-1}; δ 8.06 (d, *J* 8 Hz, 4 ArH), 7.92 (d, *J* 8 Hz, 4 ArH), 7.66 (d, *J* 8 Hz, 4 ArH), 7.56 (br, 2 × NH), 7.32 (d, *J* 8 Hz, 4 ArH), 3.94 (s, 2 × OMe), 3.60 (m, 2 × NCH_2), 3.20 (m, 4 × NCH_2), 2.42 (s, 2 × Ar*Me*), and 1.90 (m, 3 × $CH_2CH_2CH_2$). The above diester (4.00 g) was hydrolysed by heating under reflux with sodium hydroxide (1.0 g) in methanol–water (4:1). Work-up for acidic material gave the *diacid* (**29b**) (4.03 g, 100%) contaminated with THF [Found: C, 59.3; H, 5.7; N, 6.5. $C_{39}H_{44}N_4O_{10}S_2{\cdot}0.5(C_4H_8O)$ requires C, 59.4; H, 5.8; N, 6.8%]; $\nu_{max.}$(Nujol) 1 720, 1 700, and 1 640 cm^{-1}; δ 8.04 (d, *J* 8 Hz, 4 ArH), 7.92 (d, *J* 8 Hz, 4 ArH), 7.66 (d, *J* 8 Hz, 4 ArH), 7.58 (br, 2 × NH), 7.30 (d, *J* 8 Hz, 4 ArH), 3.60 (m, α-CH_2 of THF), 3.20 (m, 4 × NCH_2), 2.42 (s, 2 × ArMe), 1.90 (m, 3 × $CH_2CH_2CH_2$), and 1.80 (m, β-CH_2 of THF).

1,5,22,36-*Tetraoxo*-6,10,27,31-*tetrakis*(*tosyl*)-2,6,10,14,23,27,31,35-*octa-aza*[15,15]*paracyclophane* (**30**).—The diacid (**29b**) (3 g) was heated under reflux for 2 h with thionyl chloride (30 ml). Evaporation of the excess of reagent gave the

bis-acid chloride (**29c**) (3.10 g, 100%) as a foam which was used without further purification; $\nu_{max.}$ 1 770 and 1 660 cm^{-1}. Solutions of the bis-acid chloride (**29c**) (2.86 g) in dichloromethane (50 ml) and the diamine (**28b**) (1.80 g) in dichloromethane (50 ml) containing methylamine (1.00 g) were each added at a rate of 5 ml/h * to vigorously stirred dichloromethane (2 l). After the addition was completed the mixture was stirred for a further 12 h, concentrated to 50 ml by evaporation of solvent, washed (2M HCl, water), dried, and evaporated to dryness. The residue was purified by chromatography (alumina, dichloromethane–methanol, 98:2) to give the *macrocycle* (**30**) (1.20 g, 26%) as a pale yellow solid (Found: C, 59.0; H, 6.1; N, 8.5. $C_{62}H_{76}N_8O_{12}S_4$ requires C, 59.4; H, 6.1; N, 8.95%); $\nu_{max.}$(Nujol) 3 300, 1 625, and 1 585 cm^{-1}; δ(CF_3CO_2H) 8.30 (br, 4 × NH) 8.03 (s, 8 ArH), 7.73 (d, *J* 8 Hz, 8 ArH), 7.42 (d, *J* 8 Hz, 8 ArH), 3.80 (br m, 4 × NCH_2), 3.37 (br m, 8 × NCH_2), 2.45 (s, 4 × Ar*Me*), and 2.13 (br m, 6 × $CH_2CH_2CH_2$).

2,6,10,14,23,27,31,35-*Octa-aza*[15.15]*paracyclophane* (**27**).—The macrocyclic amide (**30**) (0.5 g) was added to a solution of lithium aluminium hydride (2.0 g) in THF (150 ml) and the mixture heated with stirring for 48 h. The reaction mixture was cooled to 0 °C and the excess of hydride destroyed by dropwise addition of water; the mixture was filtered and the combined filtrate and THF washings of the precipitated alumina were evaporated to dryness. The residual gum was dissolved in hydrobromic acid (5 ml, 48%) and the solution washed with dichloromethane (2 × 20 ml) and evaporated to dryness. The residual solid crystallised from aqueous ethanol to give the *product* (**27**; 8 HBr) (0.102 g, 21%) as its octahydrobromide salt, m.p. 250 °C (Found: C, 32.6; H, 5.9; N, 8.7. $C_{34}H_{68}Br_8N_8{\cdot}H_2O$ requires C, 32.7; H, 5.6; N, 9.0%); δ(D_2O) 7.63 (s, 8 ArH), 4.36 (s, H_2O 4 × $ArCH_2$), 3.16 (m, 12 × NCH_2), and 2.15 (m, 6 × $CH_2CH_2CH_2$).

* Addition was achieved using a pair of synchronised motor driven syringes, this procedure gave much better yields than non-synchronised slow addition from dropping funnels.

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