The Formation of Complexes between Aza Derivatives of Crown Ethers and Primary Alkylammonium Salts. Part 9.[1] Bicyclic Derivatives of Diaza Crown Ethers

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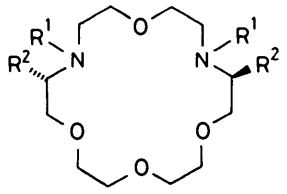
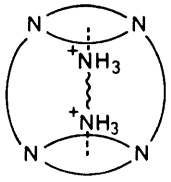
The bridged diaza-15-crown-5 derivatives (**12a—c**) and (**16**) form complexes with alkylammonium cations $R\overset{+}{N}H_3$ in organic solvents. The ^{1}H n.m.r. spectra of the complexes (**12**)·$R\overset{+}{N}H_3$ show that they are mostly of the inclusion type (**3**) but in a few cases a second diastereoisomeric complex, possibly (**4**), is also formed. These bicyclic hosts do not show particularly high selectivity in complexation on the basis of competition between pairs of guest cations.

Aza crown ethers are convenient host molecules for the complexation of alkylammonium cations and in some cases the formation of complexes takes place with very high selectivity.[2] For example, the selective complexation of (*R*)- and (*S*)-forms of chiral primary alkylammonium cations has been achieved in solution [3] using the optically active diaza-18-crown-6 derivatives (**1**) but these compounds were not effective for enantioselective extraction from aqueous solutions of chiral ammonium salts. We have also demonstrated in our earlier work [4] the advantages of using tricyclic crown ether derivatives for guest recognition by the selective formation of inclusion complexes shown diagramatically in (**2**). Before investigating the synthesis of further tricyclic hosts we turned our attention to bicyclic crown ether derivatives to determine whether the inclusion complexes (**3**) could be obtained, and whether it was possible to observe enantioselective complexation by optically active hosts of this type.



(**1**)



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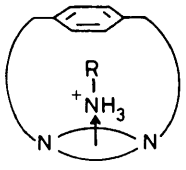

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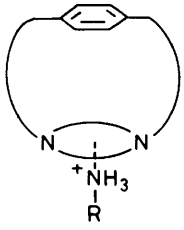
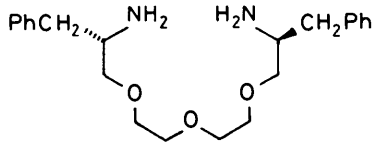


(**4**)



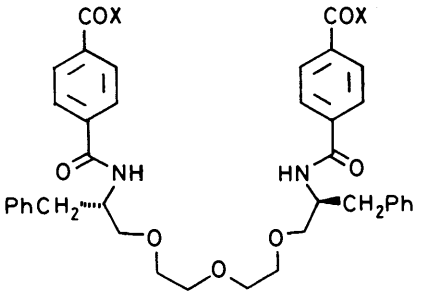
(**5**)

The essential feature of a bicyclic host for alkylammonium cation complexation is that the host molecule should have its binding forces [see arrow in (**3**)] predirected, as a result of synthesis, into the cavity to avoid unproductive or unselective external complexation as in (**4**). This can be achieved, on the basis of our earlier work,[1,5] by using 12- and 15-membered aza crown macrocycles as the binding site of the bicyclic receptor. In this earlier work [3] we had also used optically active diamines, for example (**5**), which were readily obtained from amino alcohols, as the source of chirality. We therefore used the same diamine (**5**) as a chiral bridging unit for the chiral bicyclic systems. In addition, one or more aromatic rings were inserted into the bridges of all bicyclic systems as indicated in (**3**); this provides a simple experimental test for inclusion complexation using ^{1}H n.m.r. spectroscopy,[4] since the group R of a guest cation would lie in the shielding zone of the aromatic system.

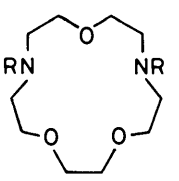
The diamine (**5**) reacted with 4-methoxycarbonylbenzoyl chloride to give the diamide (**6a**) which was readily converted into the dicarboxylic acid (**6b**) and hence the bis-acid chloride (**6c**). The reaction between diaza-15-crown-5 (**7**) and the bis-acid chloride (**6c**), under high dilution conditions, gave an acceptable yield of the bicyclic tetra-amide (**10**) which was reduced with diborane in tetrahydrofuran to give the optically active macrobicyclic tetramine (**11**).

The bicyclic host (**11**) formed a complex with methylammonium thiocyanate but it was not possible to show that larger guest cations, such as benzylammonium thiocyanate could be complexed. The studies were therefore extended to include the bicyclic systems (**12**), derivable by synthesis from the substituted diaza-15-crown-5 (**8**). Space filling (CPK) molecular models indicated that the $-(CH_2)_3-$ linkages in the bridges of (**12**) presented less steric hindrance to complexation of the more bulky alkylammonium cations $R\overset{+}{N}H_3$ than the $-CH_2-Ar-CH_2-$ linkages in the host (**11**).

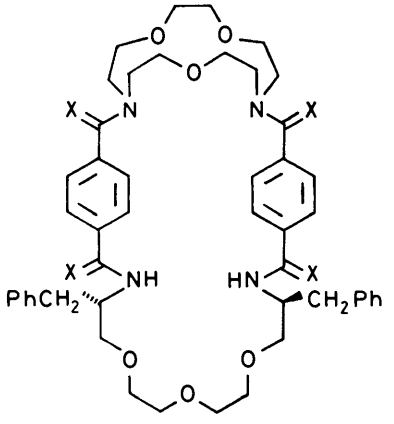
The tetra-amine (**8**), prepared from diaza-15-crown-5 (**7**) by cyanoethylation and reduction, reacted under high dilution conditions with the bis-acid chlorides (**15**) to give moderate yields of the achiral macrobicyclic amides (**12**). A similar reaction between the tetra-amine (**8**) and the bis-acid chloride (**6c**) gave a low yield of the chiral macrobicyclic amide (**16**). The bicyclic hosts (**12a—c**) and (**16**) all contain an alkylated diaza-



(6) a; X = OMe
b; X = OH
c; X = Cl

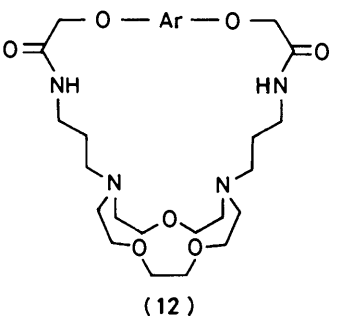


(7) R = H
(8) R = $CH_2CH_2CH_2NH_2$
(9) R = Me

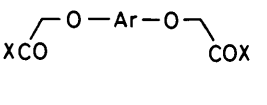


(10) X = O
(11) X = H_2

15-crown-5 system and are potentially suitable hosts for primary alkylammonium cations without further structural modification.

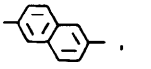


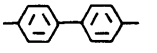
(12)

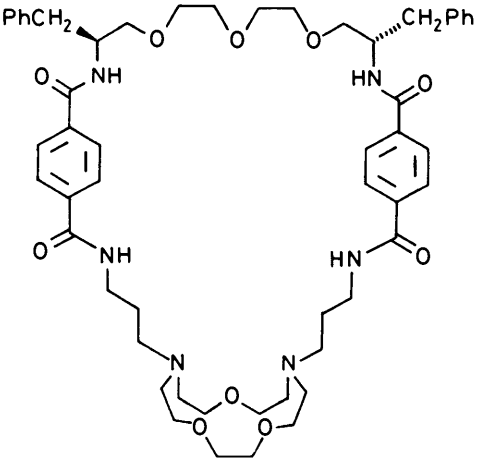


(13) X = OEt
(14) X = OH
(15) X = Cl

in (12) and (13)–(15): a; Ar =  ,

b; Ar =  ,

c; Ar = 



(16)

Results and Discussion

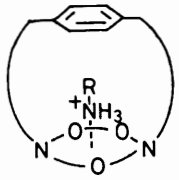
Studies of Complex Formation.—The ^{1}H n.m.r. spectra of a range of complexes between guest primary alkylammonium cations $R\overset{+}{N}H_3$ and 1 molar equivalent of each of the hosts (**12a—c**) are summarised in Table 1. In many cases all or some of the guest signals show significant shifts to high field as compared with the corresponding signals for complexes

Table 1. ^{1}H N.m.r. spectra[a] of guest cations in complexes with hosts (**12a—c**) and (**9**)

	^{1}H N.m.r. of guest $CH(\beta)CH(\alpha)\overset{+}{N}H_3$									
	None		(9)		(12a)		(12b)		(12c)	
Guest Cation/Host	H(α)	H(β)	H(α)	H(β)	H(α)	H(β)	H(α)	H(β)	H(α)	H(β)
$CH_3\overset{+}{N}H_3$	2.54		2.45		2.15		1.39		1.66	
$CH_3CH_2\overset{+}{N}H_3$	3.11	1.37	2.87	1.29	2.87	1.22	2.45	0.98	2.47	0.95
$(CH_3)_2CH\overset{+}{N}H_3$	3.52	1.39	3.32	1.24	3.36	1.25	3.25	1.04	3.03	0.94
$(CH_3)_3\overset{+}{N}H_3$		1.46		1.33		1.35		1.27		1.16
$PhCH_2\overset{+}{N}H_3$	4.10		3.92				3.56		3.48	
$PhCH_3CH\overset{+}{N}H_3$	4.43	1.66	4.27	1.59			4.25	1.54	4.17	1.48
$EtO_2CCH_2\overset{+}{N}H_3$	3.88		3.59				2.99		3.15	
$EtO_2CCH_2NHCOCH_2\overset{+}{N}H_3$	4.10		3.58				3.16		3.06	

[a] Spectra recorded at 20 °C for 1 : 1 Guest : Host ratios and 0.1-M solutions in CD_2Cl_2 using a Bruker WM 250 n.m.r. spectrometer, all guests were used as thiocyanate salts. Chemical shifts are reported in (δ p.p.m.) relative to $SiMe_4$.

of the unbridged diaza-15-crown-5 derivative (**9**). This is consistent with the formation of an inclusion complex (**17**) in which all, or a part, of the group R lies in the shielding zone of the bridging aromatic system.[6] These shifts to high field for the guest protons are presented in graphical form for $H_3\overset{+}{N}$–C(α)*H* and $H_3\overset{+}{N}$–C–C(β)*H* for all of the complexes studied in the Figure, which shows a number of general trends. Induced high field shifts tend to be greater for –C(α)*H* than for –C(β)*H* as might be expected and shifts tend to be greater for the smaller guest cations than for the larger guest cations. In some cases high field shifts are almost absent, although there is kinetic evidence for complexation (see below), and this is particularly



(**17**)

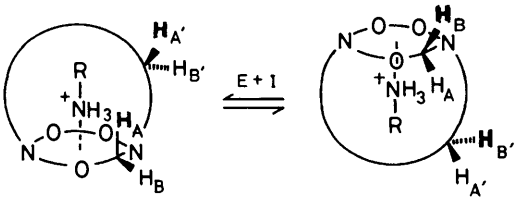
the case for the host (**15a**), which has the smallest cavity of all of the compounds studied, and guests other than the methylammonium cation. Finally, the shifts to high field induced by the two adjacent aromatic rings of the naphthalene unit of (**12b**) are in some cases greater than those induced by the two separate aromatic rings of the biphenyl unit of (**12c**).

The temperature dependence of the ^{1}H n.m.r. spectra of the complexes of alkylammonium cations with crown ethers has been used to examine a number of different rate processes,[1,4,5,7] some of which involve dissociation of the complex and hence the associated free energies of activation. These free energies of activation give information on the relative binding energies of related complexes. The ^{1}H n.m.r. spectra of most of the complexes formed between the hosts (**12a**—**c**) and primary alkylammonium cations show temperature dependence within the temperature range +20 to −100 °C. This temperature dependence and the associated free energies of activation are summarised in Table 2. The various spectroscopic changes listed in Table 2 are all consistent with a process (**18a**) ⇌ (**18b**) which involves dissociation of the complex, conformational inversion of the crown macrocycle with simultaneous rotation of the bridging ring from one face of the

Table 2. Temperature dependence of ^{1}H n.m.r. spectra[a] of complexes of hosts (**12a**—**c**) and free energies of activation ($\Delta G^{\ddagger}$) for associated rate processes

Host	Guest cation	Signal[b]	$\nu_A - \nu_B$/Hz	T_c/K (±10 K)	$\Delta G^{\ddagger}$[c]/kcal mol^{-1} (±0.5 kcal mol^{-1})
(**12a**)	$MeNH_3^+$	$NCH_2CH_AH_BCH_2N$	79	253	12.1
(**12a**)	$MeCH_2NH_3^+$	$NCH_2CH_AH_BCH_2N$[d]	47	223	10.9
(**12a**)	$(Me)_2CHNH_3^+$	$NCH_2CH_AH_BCH_2N$[d]	85	223	10.6
(**12a**)	$(Me)_3CNH_3^+$	$NCH_2CH_AH_BCH_2N$[d]	43	223	10.9
(**12b**)	$MeNH_3^+$	$NCH_2CH_AH_BCH_2N$	59	243	11.8
(**12b**)	$MeCH_2NH_3^+$	$NCH_AH_BCH_2O$	60	228	11.0
(**12b**)	$(Me)_2CHNH_3^+$	$NCH_2CH_AH_BCH_2N$	38	213	10.5
(**12b**)	$(Me)_3CNH_3^+$	$(Me)_3CNH_3^+$[e]	118	223	10.5
(**12b**)	$PhCH_2NH_3^+$	$NCH_AH_BCH_2CH_2N$	66	243	11.7
(**12b**)	$PhCH_2NH_3^+$	$NCH_2CH_AH_BCH_2N$	29	223	11.1
(**12b**)	$PhCHMeNH_3^+$	$ArOCH_2CO$[f]	*ca.* 7	223	*ca.* 11.7
(**12b**)	$EtO_2CCH_2NH_3^+$	$NCH_AH_BCH_2O$	59	233	11.3
(**12b**)	$EtO_2CCH_2NHCOCH_2NH_3^+$	$NCH_2CH_AH_BCH_2N$	30	228	11.3
(**12b**)	$EtO_2CCH_2NHCOCH_2NH_3^+$	$ArOCH_AH_BCO$[g]	13	223	11.0
(**12c**)	$MeNH_3^+$	$NCH_2CH_AH_BCH_2N$	38	228	11.2
(**12c**)	$MeCH_2NH_3^+$	$NCH_2CH_AH_BCH_2N$	42	213	10.4
(**12c**)	$MeCH_2NH_3^+$	$ArOCH_AH_BCO$[g]	31	213	10.4
(**12c**)	$(Me)_2CHNH_3^+$	$NCH_2CH_AH_BCH_2N$	28	213	10.6
(**12c**)	$(Me)_3CNH_3^+$	$NCH_2CH_AH_BCH_2N$	42	208	10.1
(**12c**)	$PhCH_2NH_3^+$	$NCH_2CH_AH_BCH_2N$	42	223	10.9
(**12c**)	$PhCH_2NH_3^+$	$ArOCH_AH_BCO$[g]	25	223	10.9
(**12c**)	$EtO_2CCH_2NH_3^+$	$NCH_AH_BCH_2CH_2N$	150	223	10.4
(**12c**)	$EtO_2CCH_2NHCOCH_2NH_3^+$	$NCH_2CH_AH_BCH_2N$	35	233	11.5
(**12c**)	$EtO_2CCH_2NHCOCH_2NH_3^+$	$NCH_AH_BCH_2CH_2N$	63	243	11.7
(**12c**)	$EtO_2CCH_2NHCOCH_2NH_3^+$	$ArOCH_AH_BCO$[g]	24	223	10.9

[a] Samples prepared as described in footnote *a* of Table 1. [b] Signals from H_A and H_B observable at low temperature coalescing to a broad singlet at T_c. [c] Based upon k_c at T_c, k_c calculated using the approximation for a coalescing pair of mutually coupled signals or a coalescing pair of singlets (ref. 8). [d] Low temperature signals are of unequal intensity probably due to the presence of a second diastereoisomeric complex. [e] Two broad CMe_3 signals observable at low temperatures. [f] Two signals, possibly assignable to the central signals of an AB system, at low temperature. [g] AB system at low temperatures, J_{AB} 14 Hz.



Scheme. Process E + I for a bicyclic host. Individual hydrogen atoms in a CH_2 group in the macrocycle or the bridge are identified by normal and bold type. The subscripts A, B *etc.* refer to molecular environment and hence relate to the chemical shift of the corresponding ^1H n.m.r. signal

macrocycle to the other, followed by recombination of host and guest (Scheme). This is closely related to the process E + I, described in earlier papers[5] of this series for complexes of monocyclic hosts.

The values of $\Delta G^{\ddagger}$ for the process E + I (Scheme) all lie within the range 10—12 kcal mol^{-1} and correlations with the structure of the complex are not obvious. In general these values of $\Delta G^{\ddagger}$ are rather close to those obtained for analogous complexes of the *N,N*-dimethyl-diaza-15-crown-5 (**9**) and the bridge does not have any major effect on the rate of the exchange process E + I.

Since the process (**18a**) $\rightleftharpoons$ (**18b**) is generally slow on the n.m.r. time scale at low temperatures it is possible[5] to check from the n.m.r. spectrum at low temperatures whether the complexes are formed as the expected inclusion diastereoisomer (**3**) or whether a mixture of inclusion (**3**) and addition (**4**) diastereoisomers is formed. For most of the complexes studied there is evidence for the formation of only the complex (**3**) (high field shift of guest protons, single set of guest and host signals at low temperature) but in those cases where the guest cation is too bulky to fit into the host cavity there is some evidence for the formation of two types of complex, presumably (**3**) and (**4**). Thus all the complexes of host (**12c**) appear to be only of the inclusion type (**3**), but the smaller cavity of host (**12b**) appears to result in the formation of both addition (**4**) and inclusion (**3**) species for the complex (**10b**)·$Bu^tNH_3^+$. The host (**12a**) has the smallest cavity of the three hosts (**12**) and the ^1H n.m.r. spectra of the complexes of (**12a**) at low temperatures indicate that only the complex (**12**)·$MeNH_3^+$ is exclusively of the inclusion type (**3**), the other complexes (**12a**)·RNH_3^+ (R = Et, Pr^i, Bu^t) all show evidence for a second type of complex which is probably the addition complex (**4**). From these results it is evident that the diaza-15-crown-5 system[1] can form a *trans,trans* complex if formation of the *cis,cis* complex is prevented by steric interactions. Unfortunately the n.m.r. spectra of mixtures of complexes of types (**3**) and (**4**) are not sufficiently well resolved for the populations of the two types of complex to be estimated.

The selectivity of complexation of a series of guest cations by each host (**12**) has been measured by competition experiments. These were carried out by n.m.r. spectroscopy under conditions of fast guest exchange[3] to avoid the excessive signal broadening that is observed in the n.m.r. spectra of complexes at low temperature. The experiments were conducted on solutions containing 1:1:1 ratios of the host (**12**) and the two competing guest salts; the time averaged signals of the guest salts were noted, and hence the proportions of free and complexed cation determined for each guest species. The results of these competition experiments are summarised in Table 3. The method used may be subject to some systematic error because chemical shifts tend to be sensitive to concentrations of guest and host species but the general trends reported in Table 3 are believed to be reliable. Selectivity in guest complexation by the bicyclic hosts (**12**) is not particularly high presumably because the aza crown macrocycles and the bridges are both rather flexible and also because of the formation of addition complexes (**4**) in some of the less favourable cases. The results summarised in Table 3 indicate, as expected, that selectivity is related to the size of the group R in the guest cation RNH_3^+; in all cases the smallest cation $MeNH_3^+$ is complexed most readily and the largest cation $Bu^tNH_3^+$ least readily.

The optically active host (**16**) forms complexes with the cations $PhCH_2NH_3^+$, and (*R*)- and (*S*)-$PhCHMeNH_3^+$, but the

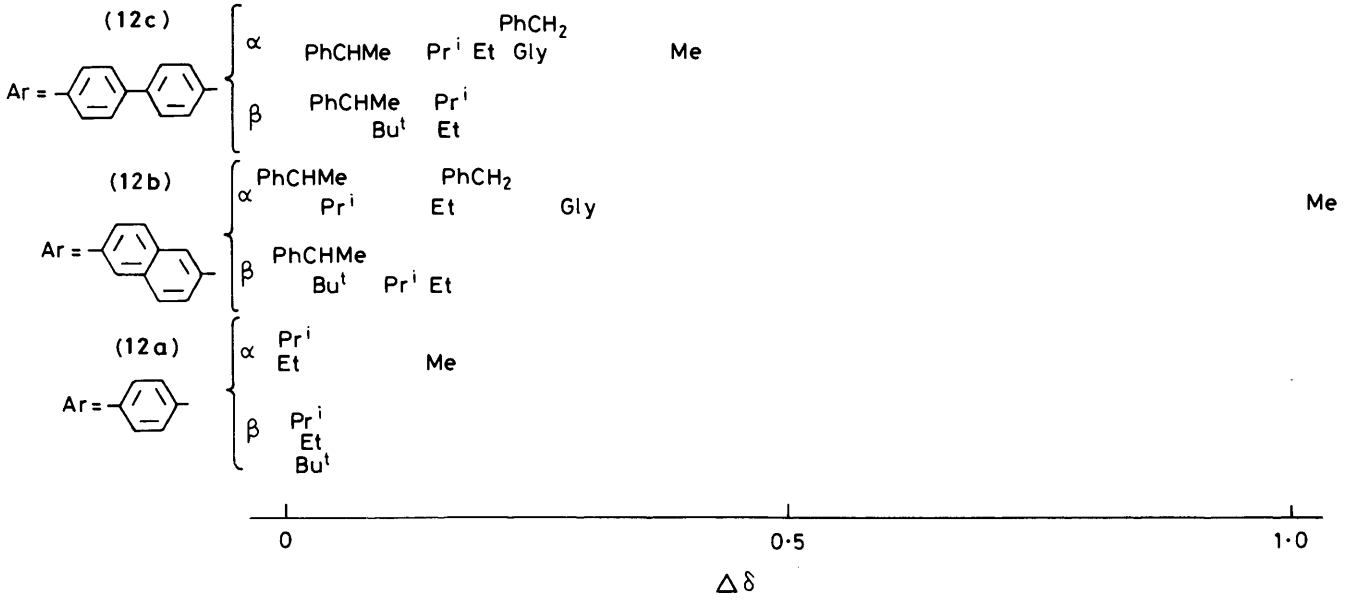


Figure. Induced upfield shifts (Δδ) of C*H*–NH_3^+ and C*H*–C–NH_3^+ protons of guest alkylammonium cations RNH_3^+ in complexes with hosts (**12a**—c). For each host the upper line refers to the α-protons and the lower line to the β-protons, the entries Me, Et, *etc.* refer to the group R in RNH_3^+

Table 3. Competitive complexation[a] of guest cations $R\overset{+}{N}H_3$ by hosts (**12a—c**)

		$R^1\overset{+}{N}H_3:R^2\overset{+}{N}H_3$ in complex for R^2		
Host	R^1	Et	Pr^i	Bu^t
(**12a**)	Me	1:1	5:1	3:1
(**12b**)	Me	2:1	4:1	>8:1
	Et		3:1	>9:1
	Pr^i			4:1
(**12c**)	Me	2:1	7:1	
	Et			
	Pr^i			

[a] Ratios based upon guest chemical shifts in 400 MHz n.m.r. spectra of CD_2Cl_2 solutions of 1:1:1 ratios of (**12**):$R^1\overset{+}{N}H_3\cdot NCS^-$:$R^2\overset{+}{N}H_3\cdot NCS^-$ at 18 °C.

n.m.r. spectra of the complexes are not readily analysed. Selectivity in complexation has therefore been investigated by the extraction of guest salts from aqueous solution using deuteriochloroform solutions of the host (**16**). All three cations are extracted from aqueous solution indicating that complex formation does take place, however the host (**16**) did not show any discrimination (enantiomer recognition) between (*R*)- and (*S*)-$PhCHMe\overset{+}{N}H_3$ and this bridged diaza-15-crown-5 system is clearly not a good approach to an enantioselective host molecule.

The results reported in this paper indicate that the bicyclic systems (**12**) and (**16**) are not suitable for development as selective receptor molecules. This is evidently a result of the rather flexible structures of these bicyclic systems, and the single site for important attractive interactions between the guest and host species which results in limited contact between the two components of the complex. The alternative strategies of using rigid barriers close to the complexing site[3,8] or of using rigid bridges[4,9] in ditopic receptors have proved to be much more successful. The latter approach will be developed in future papers in this series.

Experimental

N.m.r. spectra were run for $CDCl_3$ solutions unless stated otherwise using either a 220 MHz Perkin-Elmer R 34 spectrometer or a 250 MHz WM 250 spectrometer. Spectra for samples at low temperature were recorded using CD_2Cl_2 as the solvent. 400 MHz N.m.r. spectra were run by the SERC service at Sheffield. High resolution mass spectra were measured using an AEI MS 902 spectrometer, spectra using f.a.b. or c.i. were recorded with a VG 7070 spectrometer. Melting points were recorded using a Kofler m.p. apparatus and are uncorrected. T.l.c. was carried out using either silica or alumina on pre-prepared aluminium back plates (Fluka), flash chromatography was carried out using a standard procedure.[10] Solutions of complexes for n.m.r. examination were prepared using the stated molar ratios of the two or three components and are based upon the dilution of standard solutions.

(1S,11S)-1,11-*Dibenzyl*-N,N′-*bis*-(4′-*methoxycarbonylbenzoyl*)-3,6,9-*trioxa*-1,11-*diaminoundecane* (**6a**).—A solution of 4-methoxycarbonylbenzoyl chloride (1.063 g) in tetrahydrofuran was added to a solution of the diamine (**5**)[5] (1.00 g) and triethylamine (0.544 g) in tetrahydrofuran at 0 °C (N_2 atmosphere). The solution was allowed to warm to room temperature and heated under reflux for 24 h. The resulting mixture was filtered (Celite) and the filtrate evaporated to give an oil which was dissolved in ethyl acetate (40 ml), washed with M-HCl (3 × 30 ml) and water (2 × 30 ml), dried, and evaporated to give the *product* (**6**) (1.23 g, 68%) which crystallised as needles, m.p. 140—144 °C, from ethyl acetate–light petroleum (Found: C, 68.9; H, 6.3; N, 4.1. $C_{40}H_{44}N_2O_9$ requires C, 68.9; H, 6.4; N, 4.0%); $\nu_{max.}$(Nujol) 1 720 and 1 650 cm^{-1}; δ AA′BB′ system, δ_A 8.10, δ_B 7.75 (J_{AB} 8 Hz, 2 × 4 ArH), 7.34—7.13 (m, 2 × Ph), 6.78 (d, *J* 9 Hz, 2 × CONH), 4.45 (m, 2 × OCH_2CHN), 3.88 (s, 2 × CO_2CH_3), 3.65—3.70 (m, 4 × CH_2O), 3.49 (m, 2 × OCH_2CH_2N), and 2.90—3.00 (m, 2 × CH_2Ph). The corresponding dicarboxylic acid (**6b**) was obtained from the diester (**6a**) (0.80 g) by heating under reflux for 2 h with potassium hydroxide (0.5 g) in water (10 ml) and methanol (40 ml). The methanol was evaporated off and the residual aqueous solution acidified with M-HCl and extracted with ethyl acetate (5 × 50 ml). The extract was washed with water (2 × 50 ml), dried, and evaporated to give the crude acid (**6b**) as needles (0.73 g, 95%), m.p. 150—170 °C which were used without further purification; $\nu_{max.}$(Nujol) 2 900, 1 705, and 1 640 cm^{-1}; δ(CD_3OD), AA′BB′ system, δ_A 8.03, δ_B 7.77 (J_{AB} 8 Hz, 2 × 4 ArH), 7.1—7.3 (m, 2 × Ph), 4.45 (m, 2 × OCHNH), 3.5—3.7 (m, 2 × OCH_2CH_2O), 3.29 (m, OCH_2CH), and 2.8—3.1 (m, 2 × CH_2Ph).

(3S,13S)-3,13-*Dibenzyl*-2,14,23,32-*tetra*-*aza*-5,8,11,26,29,42-*hexaoxa*[$5^{23.32}$][15,12]*paracyclophane*-1,15,22,33-*tetraone* (**10**).—The dicarboxylic acid (**6b**) (0.55 g) was converted into the corresponding bis-acid chloride (**6c**) (0.55 g, 90%) by heating under reflux for 2.5 h in thionyl chloride (25 ml) containing 3 drops of pyridine. Solutions of the bis-acid chloride (**6c**) (0.55 g) in methylene dichloride (50 ml) and diaza-15-crown-5 (**7**)* (0.168 g) in methylene dichloride (50 ml) were added simultaneously from motor driven syringes (3.0 ml/h) to a stirred solution of triethylamine (0.152 g) in methylene dichloride (2 l). The mixture was stirred at room temperature for 48 h, evaporated to 100 ml, and washed with M-HCl (3 × 50 ml), brine (2 × 50 ml), and water (2 × 100 ml). The solution was dried ($MgSO_4$) and evaporated to give a white foam which was purified by chromatography on alumina [CH_2Cl_2–EtOH (50:1) as eluant] to give the *paracyclophane* (**8**) (0.40 g, 61%) as an oil which slowly crystallised to give plates, m.p. 100 °C (Found: C, 67.3; H, 7.0; N, 7.1. $C_{48}H_{58}N_4O_{10}$ requires C, 67.7; H, 6.9; N, 6.6%); $\nu_{max.}$ 3 300 and 1 640 cm^{-1}; δ AA′BB′ system, δ_A 7.73, δ_B 7.43 (J_{AB} 8 Hz, 2 × 4 ArH), 7.2—7.35 (m, 2 × Ph), 6.87 (m, NH), 4.4—4.6 (m, 2 × NC$H$$CH_2O$), and 2.9—4.0 (m, 2 × CH_2Ph + 12 × OCH_2 + 4 × NCH_2); *m/z* 852 and 850 (M^+).

(3S,13S)-3,13-*Dibenzyl*-2,14,23,32-*tetra*-*aza*-5,8,11,26,29,42-*hexaoxa*[$5^{23.32}$][15,12]*paracyclophane* (**11**).[11]—The tetra-amide (**8**) (0.327 g) was treated with an excess of borane–tetrahydrofuran complex (50 ml, 0.02 mol) at 0 °C (N_2 atmosphere) and heated under reflux for 24 h. The solution was cooled to 0 °C, the excess of reducing agent destroyed by the careful addition of water (5 ml), and the mixture evaporated to dryness. The residual solid was heated under reflux in 6M-HCl (30 ml) for 12 h and the solution cooled and evaporated to dryness. The residue was dissolved in ethanol and the solution passed through IRA-402 (OH^-) ion exchange resin. Evaporation of the eluate gave the *product* (**9**) as a colourless gum (0.12 g, 40%) {Found [for a sample purified using chromatography with CH_2Cl_2–EtOH (60:1)]: C, 66.6; H, 7.6; N, 6.8. $C_{48}H_{66}N_4O_6\cdot CH_2Cl_2$ requires C, 67.0; H, 7.8; N, 6.4%}; δ 7.05—7.4 (m, 18 ArH), 3.25—3.9 (m, 4 × NCH_2Ar, 12 × OCH_2 + 2 × CH_2Ph), 2.9—3.1 (m, 2 × OCH_2CHNH), and 2.6—2.9 (4 × NCH_2).

* Purchased as Kryptofix 21 from Merck-Schuchardt.

1,7-*Bis*(3-*aminopropyl*)-4,10,13-*trioxa*-1,7-*diazacyclopentadecane* (**8**).—A solution of diaza-15-crown-5 (**7**) (1.0 g) was treated with dry acrylonitrile (15.0 g) at 50—60 °C for 36 h (N_2 atmosphere). The product was evaporated under reduced pressure and the residual oil was purified by chromatography on alumina [CH_2Cl_2–EtOH (40:1) as eluant] to give 1,7-biscyanoethyl-4,10,13-trioxa-1,7-diazacyclopentadecane (1.385 g, 93%) as an oil, b.p. 121—125 °C at 0.01 Torr; δ 3.44—3.64 (m, 6 × OCH_2), 2.87 (t, *J* 5.5 Hz, 2 × NCH_2CH_2CN), 2.67—2.82 (m, 4 × NCH_2), and 2.47 (t, *J* 5.5 Hz, 2 × NCH_2CH_2CN); *m/z* 324 (M^+); $\nu_{max.}$ 2 220 cm^{-1}. The dinitrile (1.00 g) was treated with diborane–tetrahydrofuran (1M; 30 ml) at 0 °C and the mixture heated under reflux for 24 h. The solution was cooled to room temperature, the excess of diborane was destroyed by dropwise addition of water (*ca.* 1.0 ml), and the solution was evaporated to give the crystalline borane–tetra-amine adduct. The adduct was heated under reflux for 12 h in 6M-hydrochloric acid (50 ml), the resulting aqueous solution was evaporated and the residual hydrochloride salt converted into the free base using an ion exchange resin (Amberlite IRA-402). The *tetra-amine* (**8**) (1.00 g, 98%) was obtained as an oil which was used without further purification [Found: $(M + 1)^+$, 333.2849. $C_{16}H_{37}N_4O_3$ requires 333.2866]; $\nu_{max.}$ 3 350 cm^{-1}; δ 3.59 (s, OCH_2CH_2O), 3.57 (m, 4 × OCH_2), 2.50—2.70 (m, 6 × NCH_2), 2.43 (t, *J* 5.5 Hz, 2 × NCH_2), 1.85 (br s, 2 × NH_2), and 1.58 (quintet, *J* 5.5 Hz, 2 × $CH_2CH_2CH_2$).

Bisaryloxyacetic Acids (**14a—c**).—The aromatic diol (0.01 mol) was heated under reflux in acetone (40 ml) for 24 h with ethyl bromoacetate (3.4 g, 0.02 mol), and potassium carbonate (13.8 g). The resulting suspension was cooled and filtered and the filtrate evaporated to give the diester (**11**) as a solid which was purified by crystallisation from ethanol. *Diethyl* p-*phenylenedioxydiacetate* (**13a**) (84%) had m.p. 169 °C (Found: C, 59.6; H, 6.3. $C_{14}H_{18}O_6$ requires C, 59.6; H, 6.4%); $\nu_{max.}$ 1 760 cm^{-1}; δ 6.84 (s, 4 × ArH), 4.54 (s, 2 × OCH_2), 4.24 (q, *J* 7 Hz, 2 × OCH_2CH_3), and 1.26 (t, *J* 7 Hz, 2 × OCH_2CH_3). *Diethylnaphthalene*-2,6-*diyldioxydiacetate* (**13b**) (65%) had m.p. 126 °C (Found: C, 65.6; H, 6.6. $C_{18}H_{20}O_6$ requires C, 65.0; H, 6.1%); $\nu_{max.}$ 1 760 cm^{-1}; δ ABC system, δ_A 7.59, δ_B 7.18, δ_C 7.02 (J_{AB} 10 Hz, J_{BC} *ca.* 1.5 Hz, 2 × 3 ArH), 4.66 (s, 2 × OCH_2), 4.24 (q, *J* 7 Hz, 2 × OCH_2CH_3), and 1.23 (t, *J* 7 Hz, 2 × OCH_2CH_3). *Diethyl biphenyl*-4,4′-*diyldioxydiacetate* (**13c**) had m.p. 128 °C (Found: C, 67.4; H, 6.2. $C_{20}H_{22}O_6$ C, 67.0; H, 6.2%); $\nu_{max.}$ 1 760 cm^{-1}; δ AA′BB′ system, δ_A 7.45, δ_B 6.94 (J_{AB} 9 Hz, 2 × 4 ArH), 4.63 (s, 2 × OCH_2), 4.26 (q, *J* 7 Hz, 2 × OCH_2CH_3), and 1.28 (t, *J* 7 Hz, 2 × OCH_2CH_3). The corresponding dicarboxylic acids (**13**) were prepared by refluxing a solution of the diester (6.5 mmol) in ethanol (30 ml) and water (10 ml) containing sodium hydroxide (2 g) for 3 h. The product was precipitated by acidification with 11M-HCl. p-*Phenylenedioxydiacetic acid* (**14a**) sublimed at 250 °C (Found: M^+, 226.0489. $C_{10}H_{10}O_6$ requires *M*, 226.0437); $\nu_{max.}$(Nujol) 2 600—3 100br, 1 740, and 1 710 cm^{-1}; δ[$(CD_3)_2$-SO] 6.83 (s, 4 × ArH), and 4.56 (s, 2 × OCH_2). *Naphthalene*-2,6-*diyldioxydiacetic acid* (**14b**) decomposed at 267 °C (Found: M^+, 276.0612. $C_{14}H_{12}O_6$ requires *M*, 276.0634); $\nu_{max.}$(Nujol), 2 600—3 100br, 1 740, and 1 710 cm^{-1}; δ[$(CD_3)_2SO$], ABC system, δ_A 7.73, δ_B 7.23, δ_C 7.17 (J_{BC} *ca.* 1.5 Hz, J_{AC} 10 Hz, 2 × 3 ArH), and 4.75 (s, 2 × OCH_2). *Biphenyl*-4,4′-*diyldioxydiacetic acid* (**14c**) had m.p. 248 °C (decomp.) (Found: M^+, 302.0807. $C_{16}H_{14}O_4$ requires *M*, 302.0705); $\nu_{max.}$(Nujol) 2 610—3 100br, 1 740, and 1 705 cm^{-1}; δ[$(CD_3)_2SO$], AA′BB′ system, δ_A 7.52, δ_B 6.97 (J_{AB} 8 Hz, 2 × 4 ArH), and 4.68 (s, 2 × OCH_2).

4,8,17,21-*Tetra-aza*-1,11,14,24,32-*pentaoxa*[$5^{8,17}$][24]*paracyclophane*-3,22-*dione* (**12a**).—The dicarboxylic acid (**14a**) was converted into the corresponding bis-acid chloride (**13a**) by heating under reflux with thionyl chloride containing 1 drop of pyridine. Solutions of the amine (**8**) (1.21 g) in dry toluene (70 ml) and the bis-acid chloride (**14a**) (0.96 g) in dry toluene (70 ml) were added simultaneously over 8 h to a stirred solution of triethylamine (12 ml) in toluene (2.5 l). The solution was filtered and the filtrate evaporated. The residual solid was purified by chromatography on alumina [CH_2Cl_2–EtOH (99:1) as eluant] to give the bicyclic diamide (**12a**) (0.92 g, 33%), m.p. 177 °C (Found: C, 59.0; H, 8.0; N, 10.6%; M^+, 522.3075. $C_{26}H_{42}N_4O_7$ requires C, 59.7; H, 8.1; N, 10.7%; *M*, 522.3053); $\nu_{max.}$(Nujol) 3 300 and 1 660 cm^{-1}; δ(CD_2Cl_2) 6.92 (s, 4 × ArH), 4.48 (s, 2 × $ArOCH_2$), 3.56 (s, OCH_2CH_2O), 3.52 (t, *J* 6 Hz, 2 × OCH_2CH_2N), 3.36 (t, *J* 7 Hz, 2 × NCH_2), 3.36 (t, *J* 6 Hz, 2 × OCH_2CH_2N), 2.61 (t, *J* 6 Hz, 2 × NCH_2CH_2O), 2.50 (t, *J* 6 Hz, 2 × NCH_2CH_2O), 2.40 (t, *J* 7 Hz, 2 × NCH_2), and 1.59 (m, 2 × $CH_2CH_2CH_2$).

4,8,17,21-*Tetra-aza*-1,11,14,24,37-*pentaoxa*[$5^{8,17}$][24]-2,6-*naphthalenophane*-3,22-*dione* (**12b**).—The dicarboxylic acid (**14b**) was converted into the corresponding bis-acid chloride (**15b**) by heating under reflux with thionyl chloride containing 1 drop of pyridine. Solutions of the amine (**8**) (0.64 g) in toluene–methylene dichloride (1:1, 80 ml) and the acid chloride (**15b**) (0.61 g) in toluene–methylene dichloride (3:1, 80 ml) were added simultaneously over 10 h to a stirred solution of triethylamine (10 ml) in toluene (2.5 l). The solution was filtered and the filtrate evaporated. The residual solid was chromatographed on alumina [CH_2Cl_2–EtOH (99:1) as eluant] to give the *product* (**12b**) as a white foam (0.19 g, 17%), a sample crystallised from ethanol–light petroleum had m.p. 168 °C (Found: M^+, 572.3234. $C_{30}H_{44}O_7N_4$ requires *M*, 574.3209); $\nu_{max.}$(Nujol) 3 315 and 1 660 cm^{-1}; δ(CD_2Cl_2), ABC system, δ_A 7.71, δ_B 7.19, δ_C 7.12 (J_{AB} 8.5 Hz, J_{BC} 2.5 Hz, 2 × 3 ArH), 4.63 (s, 2 × $ArOCH_2$), 3.50 (s, OCH_2CH_2O), 3.40 (t, *J* 6 Hz, 2 × OCH_2CH_2N), 3.31 (t, *J* 6 Hz, 2 × OCH_2CH_2N), 3.04 (t, *J* 6 Hz, 2 × $NHCH_2$), 2.44 (t, *J* 6 Hz, 2 × NCH_2CH_2O), 2.16 (t, *J* 6 Hz, 2 × NCH_2CH_2O), 2.16 (t, *J* 6 Hz, 2 × NCH_2), and 1.49 (m, 2 × $CH_2CH_2CH_2$).

4,8,17,21-*Tetra-aza*-1,11,14,24,39-*pentaoxa*[$5^{8,17}$][24]-4,4′-*biphenylophane*-3,22-*dione* (**12c**).—The dicarboxylic acid (**14c**) was converted into the corresponding bis-acid chloride (**15c**) by heating under reflux with thionyl chloride containing 1 drop of pyridine. Solutions of the amine (**11**) (1.46 g) in toluene (70 ml) and the bis-acid chloride (**15c**) (1.49 g) in toluene (70 ml) were added simultaneously over 8 h to a stirred solution of triethylamine (12 ml) in toluene (2.5 l). The solution was filtered and the filtrate evaporated. The residual solid was chromatographed on alumina [CH_2Cl_2–EtOH (99:1) as eluant] to give the *product* (**12c**) (0.53 g, 20%) as a solid, decomposing at 240 °C (Found: C, 64.3; H, 7.7; N, 9.3%; M^+, 598.3349. $C_{32}H_{46}N_4O_7$ requires C, 64.2; H, 7.7; N, 9.4%; *M*, 598.3366); $\nu_{max.}$(Nujol) 3 300 and 1 660 cm^{-1}; δ(CD_2Cl_2), AA′BB′ system, δ_A 7.57, δ_B 6.99 (J_{AB} 9 Hz, 2 × 4 ArH), 4.60 (s, 2 × $ArOCH_2$), 3.54 (s, OCH_2CH_2O), 3.50 (t, *J* 6 Hz, 2 × OCH_2CH_2N), 3.30 (t, *J* 6 Hz, 2 × OCH_2CH_2N), 3.00 (t, *J* 6 Hz, 2 × $NHCH_2$), 2.53 (t, *J* 6 Hz, 2 × NCH_2CH_2O), 2.36 (t, 6 Hz, 2 × NCH_2CH_2O), 2.24 (t, *J* 7 Hz, 2 × NCH_2), and 1.54 (quintet, *J* 7 Hz, $CH_2CH_2CH_2$).

(3S,13S)-3,13-*Dibenzyl*-2,14,23,27,36,40-*hexa-aza*-5,8,11,30,33,50-*hexaoxa*[$5^{27,36}$][15,20]*paracyclophane*-1,15,22,41-*tetraone* (**16**).—Solutions of the tetra-amine (**8**) (266 mg) in methylene dichloride and the bis-acid chloride (**6c**) (562 mg) in methylene dichloride (50 ml) were added simultaneously using motor driven syringes (3.0 ml/h) to a stirred solution of triethylamine (162 mg) in methylene dichloride (2 l). The mixture was stirred at room temperature for 48 h, evaporated to

50 ml, and washed with M-HCl (3 × 30 ml), aqueous $NaHCO_3$ (saturated 3 × 30 ml), brine, and water. The solution was dried ($MgSO_4$) and evaporated to give the *product* (**16**) as an oil, purifiable by short-path distillation at >250 °C, 0.05 mmHg (81 mg, 10%) (Found: C, 66.8; H, 7.5; N, 8.3. $C_{54}H_{72}N_6O_{10}$ requires C, 67.2; H, 7.5; N, 8.7%); $\nu_{max.}$ 1 740 and 1 660 cm^{-1}; δ 8.3 (br s, 2 × NH), AA′BB′ system, δ_A 7.85, δ_B 7.76 (J_{AB} 8 Hz, 2 × 4 ArH), 7.1—7.35 (m, 2 × Ph), 4.42 (m, 2 × $NHCHCH_2O$), 3.4—3.7 (m, 12 × OCH_2 + 2 × $CONHCH_2$), 2.95 (d, *J* 7 Hz, 2 × $CHCH_2Ph$), 2.68 (m, 4 × NCH_2), 2.54 (t, *J* 6 Hz, NCH_2CH_2), and 1.71 (quintet, *J* 6 Hz, $NCH_2CH_2CH_2N$).

* The nomenclature of the aza-oxa compounds in this paper is not in accord with IUPAC recommendations for replacement nomenclature. For the correct use of this type of nomenclature, see *J. Chem. Soc., Perkin Trans 1*, 1984, 1707.

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