The Formation of Complexes between Aza Derivatives of Crown Ethers and Primary Alkylammonium Salts. Part 7.[1] Chiral Derivatives of Aza Crown Ethers

Derek J. Chadwick, Ian A. Cliffe, and Ian O. Sutherland *
Department of Organic Chemistry, The Robert Robinson Laboratories, University of Liverpool, P.O. Box 147, Liverpool L69 3BX
Roger F. Newton
Glaxo Group Research Ltd., Ware, Herts SG12 0DJ

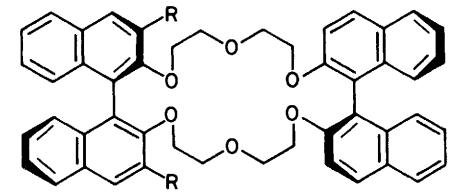
A number of optically active derivatives of diaza-15-crown-5 and diaza-18-crown-6 have been synthesised using amino acids as the source of chirality. The diaza-18-crown-6 derivatives (**21**) show enantioselectivity in the complexation of 1-phenylethylammonium thiocyanate in methylene chloride as determined by ^{1}H n.m.r. spectroscopy. The degree of enantioselectivity depends upon the substituents on the nitrogen atoms of the macrocycle and although the *N,N*-dibenzyl derivatives (**21**) show moderately high enantioselectivity, the *N,N*-dimethyl derivatives (**20**) do not. In the presence of water the hosts (**21**) apparently form hydrated complexes with guest alkylammonium cations with very little enantioselectivity.

Crown ether derivatives have been extensively developed to provide enhanced structural recognition of substrate alkylammonium cations and in particular a number of investigations of enantioselectivity in complexation of chiral alkylammonium salts by chiral crown ethers have been reported. In general the crown ethers used in these studies have been based upon derivatives of 2,2′-dihydroxy-1,1′-binaphthyl[2] or derivatives of suitable optically active natural products[3] such as tartaric acid and carbohydrate derivatives. Examples of successful enantioselectivity have been described, particularly by Cram and co-workers who have reported that hosts of the general type (**1**) show high enantiomer recognition factors for the salts of chiral amino acid esters, for example methyl phenylglycinate hexafluorophosphonate. This enantioselectivity has been applied[4] for the enantioselective transport of guest salts through a chloroform 'membrane' and attachment of the chiral host to polystyrene[5] gave an excellent support for the chromatographic optical resolution of amino acid perchlorates.

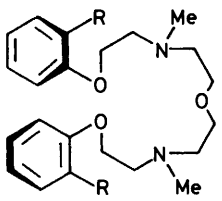
The recognition that aza crown ethers[1,6,7] and their polycyclic derivatives[8] could form strongly bound and well defined complexes with primary alkylammonium salts led us to investigate[9] the chiral aza-crown systems (**2**), analogous to the chiral crown ethers (**1**). However, the aza crown ethers (**2**) gave relatively poor enantiomer recognition with guest phenylethylammonium thiocyanate and the study has not been extended. It appeared possible that better results might be obtained with either the aza crown ethers (**3**), in which the group R* attached to the ring nitrogen atom contains a chiral centre, or the aza crown ethers (**4**), in which the macrocycle includes a chiral $NCHRCH_2O$ unit derivable from an amino acid. The synthesis and properties of aza crown ethers of both types are described in this paper, in all cases amino acids are used as the source of chirality.

A number of aza crown ether analogues in which the chirality is derived from an α-amino acid have been reported[10–12] by other workers, but the macrocycle is only fully reduced in one case (**5**)[10] and in the others (**6**) and (**7**) the nitrogen atoms are part of an amide group.[11,12] Amino acids have also been incorporated into the side chains of the chiral crown ethers (**8**) derived from L-(+)-tartaric acid.[13]

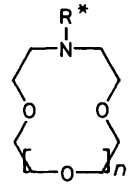
Our initial approach to the synthesis of chiral aza crown ether derivatives was based upon the acylation of monoaza-15-crown-5 (**9**) and diaza-15-crown-6 (**10**) with a suitably protected and activated α-amino acid derivative. A number of procedures suitable for peptide synthesis[14] proved to be unsuitable for



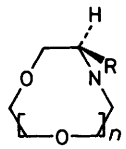
(1) R = H, Me, Pr^i



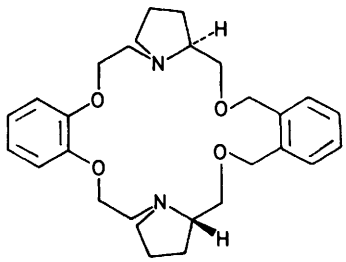
(2) R = H, Pr



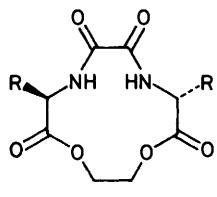
(3)



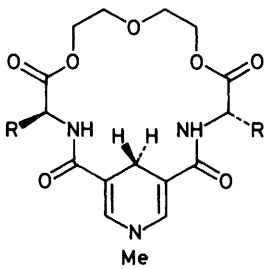
(4)



(5)

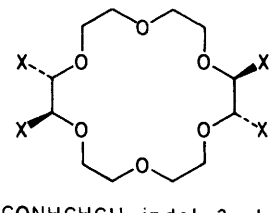


(6)



R Me, Pr^i, $PhCH_2$

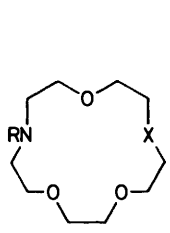
(7)



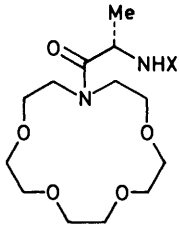
X = L-CONHCHCH$_2$ indol-3-yl
CO$_2$Me
or L-CONHCHCH$_2$SH
CO$_2$Me

(8)

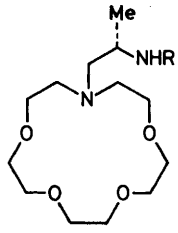
acylating the relatively unreactive secondary amino groups of the aza crown ethers but eventually it was found that the mixed anhydride of diphenylphosphinic acid [15] and an alkoxycarbonyl L-alanine reacted with the monoaza crown ether (**9**) to give good yields of the corresponding amide (**11**). Reduction of the products (**11a** and **b**) with lithium aluminium hydride gave the corresponding diamine (**12a**) or alternatively deprotection of the t-butyloxycarbonyl derivative (**11c**) with hydrochloric acid followed by reduction of the resulting amine (**11d**) gave the diamine (**12b**), characterised as its *N*-acetyl derivative (**12c**).



(**9**) X=O, R=H
(**10**) X=NH, R=H
(**23**) X=NMe, R=Me

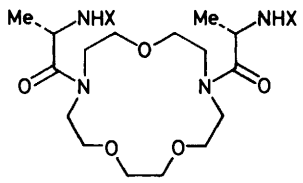


(**11**)
a X=CO_2CH_2Ph
b X=CO_2Et
c X=CO_2Bu^t
d X=H

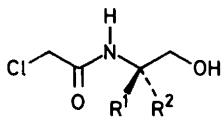


(**12**)
a R=Me
b R=H
c R=Ac

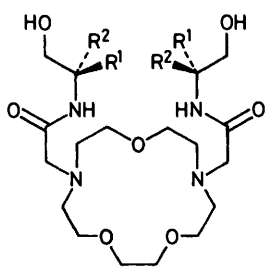
The diaza 15-crown-5 (**10**) was most conveniently acylated to give the diamine (**13a**) by reaction with the symmetrical anhydride of t-butyloxycarbonyl-L-alanine,[14,16] reaction with the asymmetrical diphenylphosphinic anhydride was less satisfactory in this case. The diamide (**13a**) was deprotected (methanolic hydrogen chloride) but difficulty was encountered during attempted reduction of this product (**13b**) to the corresponding tetra-amine with either diborane or lithium aluminium hydride. An alternative approach for the introduction of chiral side chains into the diaza crown ether (**10**) was therefore investigated.



(**13**)
a, X=CO_2Bu^t
b, X=H



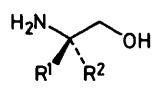
(**14**)



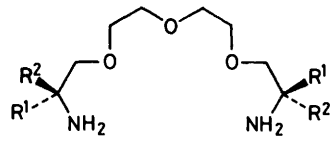
(**15**)
(**14**) and (**15**): **a**, R^1=Ph, R^2=H;
b, R^1=H, R^2=CH_2Ph; **c**, R^1=H, R^2=Me

The *N*-chloroacetamido alcohols (**14**) were prepared by the reaction of the corresponding amino alcohol with chloroacetyl chloride. The diaza crown ether (**10**) was alkylated with each of these *N*-chloroacetamido alcohols to give the derivatives (**15**) which were investigated as hosts for chiral guest alkylammonium cations.

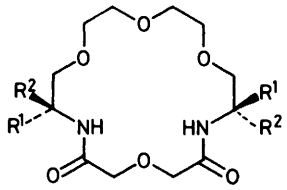
Finally, optically active 2-aminoethanol derivatives (**16**), readily available from the corresponding α-amino acids, were used for the synthesis of optically active diaza 18-crown-6 derivatives.[17] The sodium alkoxides derived from the amino alcohols (**16a**—**c**) reacted with the bis-toluene-*p*-sulphonate of diethylene glycol to give the diamines (**17a**—**c**) in satisfactory yields. The diamines (**17a**—**c**) each reacted with diglycollyl chloride to give moderate yields of the corresponding cyclic amides (**18a**—**c**) which were reduced with lithium aluminium hydride to give the optically active diaza 18-crown-6 derivatives (**19a**—**c**). These crown ethers were either methylated (Eschweiler-Clark) to give the corresponding *N*-methyl derivatives (**20a**—**c**) or benzylated (benzyl bromide) to give the *N*-benzyl derivatives (**21a**—**c**).



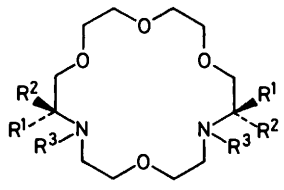
(**16**)



(**17**)



(**18**)



(**19**) R^3=H
(**20**) R^3=Me
(**21**) R^3=CH_2Ph
(**22**) R^1=R^2=H, R^3=Me

(**16**)—(**21**): **a**, R^1=Ph, R^2=H;
b, R^1=H, R^2=CH_2Ph; **c**, R^1=H, R^2=Pr^i

Formation of Complexes by Chiral Aza Crown Ether Derivatives.—In earlier work, we[6,7,18] and others[19] have shown that the complexes formed between aza crown ethers and primary alkylammonium salts may be studied by n.m.r. spectroscopy. In particular, we have shown that mono- and diaza 15-crown-5 derivatives form complexes in which the side chains on the nitrogen atoms are *cis*-related [6] to the guest cation whereas complex formation by most aza 18-crown-6 derivatives is not stereoselective in this sense.[6,7]

The complexes of the chiral aza 15-crown-5 derivatives (**12**) and (**15**) were, therefore, expected to have a *cis*-relationship between the side chains containing the centres of chirality and the guest cation with the possibility that side chain-guest interactions might lead to enantioselectivity. In accord with expectation the mono-aza crown ether derivative (**12c**) formed a complex with benzylammonium thiocyanate in which the host C–Me signals in the ^1H n.m.r. spectrum of the complex were shifted to higher field relative to the analogous signal in the n.m.r. spectrum of the free host. Furthermore, the n.m.r. spectrum of the complex showed temperature dependence analogous to that shown by other aza crown ether complexes but, unfortunately, the changes in the spectrum were not

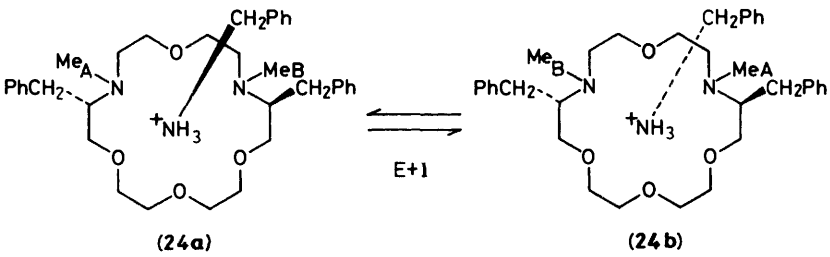
sufficiently well defined to carry out the same type of detailed study that we have reported[6] for the *N*-methyl derivative of mono-aza 15-crown-5 (**9**).

The complexes of the diaza 15-crown-5 derivatives (**15**) gave rather more definitive ^{1}H n.m.r. spectra. In particular, the spectra of the complexes of all three hosts (**15a**—**c**) with benzylammonium thiocyanate were distinct from those of the uncomplexed species. For example, the NCH_2CO protons of the complexed hosts gave well defined AB systems as compared with the singlet signals* observable for the same NCH_2CO groups in the spectra of the free hosts. At low temperatures the signals of the n.m.r. spectra of the complexes broadened and the NCH_2CH_2O multiplet moved to higher field as the temperature was lowered and eventually split to give two broad signals. This we associate with slow face-to-face exchange of the guest molecule with $\Delta G^{\ddagger}$ 11.5—12.0 kcal mol^{-1} (Table 1) for the exchange process, calculated on the basis of coalescence data.[20] No changes were observed in the n.m.r. spectra which could be attributed to the presence of more than one species of complex in the solution and, by analogy with our earlier studies, we believe that the complex has *cis,cis*-stereochemistry as found for other complexes of diaza 15-crown-5 (**23**).

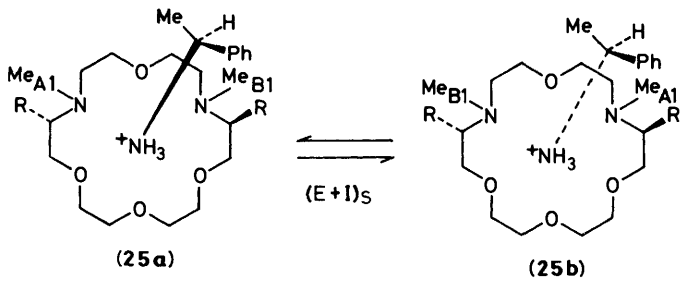
The three hosts (**15a**—**c**) all form complexes with both (*R*)- and (*S*)-1-phenylethylammonium thiocyanate and in each case the differences between the n.m.r. spectra of the complex with the (*R*)- and (*S*)-guest were consistent with the formation of a pair of diastereoisomeric complexes. The n.m.r. spectra are temperature dependent and, although the spectrum of the complex of host (**15b**) shows only line broadening at low temperatures, the N–CH_2CH_2–O signals of the complexes of (**15a**) and (**15c**) separate into two broad signals at low temperatures corresponding to a slow rate for the process (E + I). The energy barriers derived for this process from the coalescence data are similar, within the limits of experimental error (±0.3 kcal mol^{-1}), for both the (*R*)- and the (*S*)-guest and there is therefore no evidence for differing dynamic stability of the two diastereoisomeric complexes. The spectrum of the complex (**15b**), (*R*)-$PhCHMeNH_3NCS^-$ is quite distinct from that of the complex (**15b**), (*S*)-$PhCHMeNH_3NCS^-$ but the spectrum of a solution of host (**15b**) containing two molar equivalents of (*R,S*)-phenylethylammonium thiocyanate is different from that of either of the diastereoisomeric 1:1 complexes and consistent with the formation of a rapidly equilibrating mixture of the two complexes. It is not possible to comment on the composition of this mixture but there is clearly no strong enantiomer selectivity in the formation of 1:1 complexes.

The ^{1}H n.m.r. spectra of the complexes of host (**15a**) with one equivalent of (*R*)- or (*R,S*)-2-hydroxy-1-phenylethylammonium thiocyanate show temperature dependence that is similar to that shown by the spectra of the analogous complexes of (*R*)- and (*R,S*)-1-phenylethylammonium thiocyanate. The derived free energies of activation for the process (E + I) are of the same order for both types of guest and they do not indicate that there is any important stabilising hydrogen-bonding interaction between the functionalised side chains of host (**15a**) and the 2-hydroxy group of the phenyl(hydroxy)ethylammonium salt (see Table 1 for details).

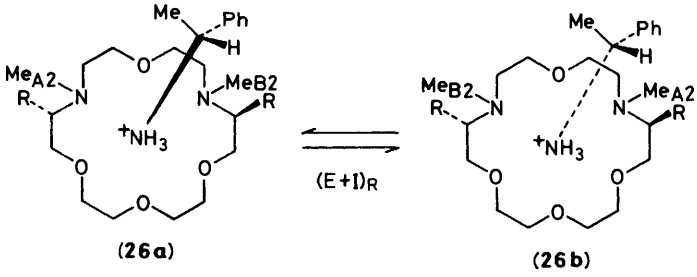
The ^{1}H n.m.r. spectra of the complexes of the diaza 18-crown-6 derivatives (**20a**—**c**) with either benzylammonium thiocyanate or (*R*)- and (*S*)-1-phenylethylammonium thiocyanate in CD_2Cl_2 showed upfield shifts of the host N–Me signals as compared with the spectra of the uncomplexed macrocycles (Table 2). As the temperature was lowered the host NMe signals broadened and separated into two broad singlets which became sharper and the OCH_2 and NCH_2 signals from the host showed complex temperature dependence which could not be interpreted. In contrast, the guest $^+NH_3$ signal remained as a single broad singlet with no indication of more than a single species of complex, in contrast with the complexes[7] of the unsubstituted diaza-18-crown-6 derivative (**22**). The significant upfield shift of one of the two NMe groups of the hosts (**20a**—**c**) in the complex as compared with the free host requires that this NMe group lies in the shielding zone of the phenyl substituent in the guest cation. The complex is therefore formed with some stereoselectivity and it must be of either the *cis,cis*- or *cis,trans*-type. The temperature dependence of the host NMe signals is also shown by the complex of the host (**20b**) with the achiral guest benzylammonium cation, in this case the two different signals can be associated with a complex (**24**) in which the guest cation is attached to a face of the chiral host. The face to face exchange of the guest cation (**24a**)⇌(**24b**) (E + I) results in



(**24a**) (**24b**)



(**25a**) (**25b**)



(**26a**) (**26b**)

* The NCH_2CO protons are diastereotopic in both the free and complexed host, but both protons accidentally have the same chemical shift in the free host.

Table 1. Temperature dependence of ^{1}H n.m.r. spectra (220 MHz) of complexes of diaza-crown ether derivatives (**15a—c**) in CD_2Cl_2

Host	Guest cation[a]	Ratio G:H	Signal	Spectral change[b,c]	T_c (±5°C)	$\Delta G^{\ddagger}$[d] (∓0.3 kcal mol^{-1})	Process
(15a)	$PhCH_2\overset{+}{N}H_3$	1:1	NCH_2CH_2O	A + B ⟶ AB	−32	11.5	(E + I)
(15a)	(*S*)-$PhCHMe\overset{+}{N}H_3$	1:1	NCH_2CH_2O	A + B ⟶ AB	−35	11.5	(E + I)
(15a)	(*R*)-$PhCHMe\overset{+}{N}H_3$	1:1	NCH_2CH_2O	A + B ⟶ AB	−35	11.6	(E + I)
(15a)	(*R*)-$PhCH(CH_2OH)\overset{+}{N}H_3$	1:1	NCH_2CH_2O	A + B ⟶ AB	−45	11.3	(E + I)
(15a)	(*R,S*)-$PhCH(CH_2OH)\overset{+}{N}H_3$	1:1	NCH_2CH_2O	A + B ⟶ AB	−40	11.5	(E + I)
(15b)	$PhCH_2\overset{+}{N}H_3$	1:1	NCH_2CH_2O	A + B ⟶ AB	−35	11.5	(E + I)
(15b)	(*R*)-$PhCHMe\overset{+}{N}H_3$	2:1	CH*Me*[e]	$Me_1 + Me_2 \longrightarrow Me_{12}$	−38	11.3	E
(15b)	(*S*)-$PhCHMe\overset{+}{N}H_3$	2:1	CH*Me*[e]	$Me_1 + Me_2 \longrightarrow Me_{12}$	−22	11.9	E
(15c)	$PhCH_2\overset{+}{N}H_3$	1:1	NCH_2CH_2O	A + B ⟶ AB	−22	12.0	(E + I)
(15c)	(*R*)-$PhCHMe\overset{+}{N}H_3$	1:1	NCH_2CH_2O	A + B ⟶ AB	−40	11.1	(E + I)
(15c)	(*S*)-$PhCHMe\overset{+}{N}H_3$	1:1	NCH_2CH_2O	A + B ⟶ AB	−42	11.0	(E + I)

[a] All guests used as thiocyanate salts. [b] A and B refer to the two broad signals for the NCH_AH_B group observable at low temperatures, AB refers to the coalesced signal observable at high temperatures. [c] Me_1 and Me_2 refer to the separate CH*Me* signals observable for free and complexed guest at low temperatures, Me_{12} refers to the coalesced signals observable at high temperatures. [d] Calculated using approximate formulae based upon coalescence data (ref. 20) for a coalescing AB system (NCH_2) or a coalescing pair of singlet signals (CHMe). [e] Changes in NCH_2CH_2O signals are too poorly defined to examine the process (E + I).

Table 2. ^{1}H N.m.r. spectra (220 MHz) of complexes of diaza-18-crown-6 derivatives (**20a—c**) in CD_2Cl_2

Host	Guest cation[a]	Ratio G:H	Temp. (°C)	Host spectrum[b] NMe	Guest spectrum[b] CH	Me	$\overset{+}{N}H_3$
(20)[c]	None		25	2.21			
(20a)	(*R*)-$PhCHMe\overset{+}{N}H_3$	1:1	25	2.03	4.39	1.61	
			−70	2.27, 1.15	4.43	1.58	8.48
(20a)	(*S*)-$PhCHMe\overset{+}{N}H_3$	1:1	25	2.19	4.33	1.61	
			−70	2.20, 1.90	4.39	1.63	8.32
(20a)	(*R,S*)-$PhCHMe\overset{+}{N}H_3$	1:1	25	2.11	4.38	1.60	
			−70	2.25, 1.18 (R)	4.45	1.61	8.50 (R)
				1.93 (S)			8.40 (S)
(20a)	(*R,S*)-$PhCHMe\overset{+}{N}H_3$	2:1	25	2.09	4.35	1.60	
			−70	2.25, 1.18 (R)		1.60	8.50 (R)
				1.94 (S)			8.40 (S)
(20b)[c]	None		25	2.39			7.70 (F)
(20b)	$PhCH_2\overset{+}{N}H_3$	1:1	25	1.99 (br)			
			−50	2.09, 1.28			8.31
(20b)	$H_3\overset{+}{O}$	1:1	25	2.67			
			−90	2.79, 2.41			7.50
(20b)	(*R*)-$PhCHMe\overset{+}{N}H_3$	1:1	25	2.15	4.28	1.56	
			−70	2.02, 1.74	4.23	1.52	8.04
(20b)	(*S*)-$PhCHMe\overset{+}{N}H_3$	1:1	25	1.93	4.30	1.48	
			−70	2.07, 1.08	4.35	1.34	8.31
(20b)	(*R,S*)-$PhCHMe\overset{+}{N}H_3$	1:1	25	1.98	4.25	1.49	
			−70	1.99 (R), 1.72 (R)	4.23 (R)	1.50 (R)	8.01 (R)
				2.04 (S), 1.05 (S)	4.34 (S)	1.31 (S)	8.31 (S)
(20b)	(*R,S*)-$PhCHMe\overset{+}{N}H_3$	2:1	25	2.02	4.30	1.56	
			−70	2.02 (R), 1.75 (R)	4.21 (R)	1.55 (R)	8.01 (R)
				2.07 (R), 1.07 (R)	4.34 (S)	1.34 (S)	8.31 (S)
							7.91 (F)
(20c)[c]	None		25	2.32			
(20c)	(*R*)-$PhCHMe\overset{+}{N}H_3$	1:1	25	2.35	4.31	1.56	
			−70	2.21, 1.64	4.38	1.54	8.08
(20c)	(*S*)-$PhCHMe\overset{+}{N}H_3$	1:1	25	2.07	4.31	1.53	
			−70	2.20, 1.12	4.32	1.45	8.21
(20c)	(*R,S*)-$PhCHMe\overset{+}{N}H_3$	1:1	25	2.17	4.31	1.55	
			−70	2.21, 1.65 (R)	4.35	1.55 (R)	8.04 (R)
				1.12 (S)		1.47 (S)	8.21 (S)
(20c)	(*R,S*)-$PhCHMe\overset{+}{N}H_3$	2:1	25	2.16	4.33	1.59	
			−70	2.20, 1.63 (R)	4.30	1.47	8.08 (R)
				1.12 (S)			8.20 (S)
							9.79 (F)

[a] All guests used as thiocyanate salts. [b] Chemical shifts (δ) in p.p.m. relative to $SiMe_4$. The assignments (*R*) and (*S*) for complexes of racemic guests refer to the complex with the (*R*)-guest and (*S*)-guest respectively. The assignment (F) for a 2:1 G:H ratio refers to the uncomplexed guest. [c] Spectrum in $CDCl_3$.

Table 3. Temperature dependence of ^1H n.m.r. spectra (220 MHz) of complexes of diaza-18-crown-6 derivatives (**20a**—**c**) in CD_2Cl_2

Host	Guest cation	Ratio G:H	Signal	Spectral change[a]	T_c (+5 °C)	$\Delta G^{\ddagger}$[b] (±0.3 kcal mol^{-1})	Process
(**20a**)	(*S*)-PhCHMeNH$_3^+$	1:1	NMe	$Me_{A1} + Me_{B1} \longrightarrow Me_{AB1}$	−28	12.1	$(E + I)_S$
(**20a**)	(*R*)-PhCHMeNH$_3^+$	1:1	NMe	$Me_{A2} + Me_{B2} \longrightarrow Me_{AB2}$	−10	12.2	$(E + I)_R$
(**20b**)	PhCH$_2$NH$_3^+$	1:1	NMe	$Me_A + Me_B \longrightarrow Me_{AB}$	−2	12.8	(E + I)
(**20b**)	Me$_3$CNH$_3^+$	1:1	NMe	$Me_A + Me_B \longrightarrow Me_{AB}$	−31	11.8	(E + I)
(**20b**)	H$_3$O$^+$	1:1	NMe	$Me_A + Me_B \longrightarrow Me_{AB}$	−40	11.2	(E + I)
(**20b**)	(*S*)-PhCHMeNH$_3^+$	1:1	NMe	$Me_{A1} + Me_{B1} \longrightarrow Me_{AB1}$	0	12.6	$(E + I)_S$
(**20b**)	(*R*)-PhCHMeNH$_3^+$	1:1	NMe	$Me_{A2} + Me_{B2} \longrightarrow Me_{AB2}$	−30	12.1	$(E + I)_R$
(**20c**)	(*S*)-PhCHMeNH$_3^+$	1:1	NMe	$Me_{A1} + Me_{B1} \longrightarrow Me_{AB1}$	−28	11.4	$(E + I)_S$
(**20c**)	(*R*)-PhCHMeNH$_3^+$	1:1	NMe	$Me_{A2} + Me_{B2} \longrightarrow Me_{AB2}$	−38	11.3	$(E + I)_R$

[a] Details of chemical shift are given in Table 2. The descriptions Me_A, Me_1, *etc.* are defined in formulae (**24**)—(**26**), the descriptions Me_{AB}, Me_{AB1}, *etc.* refer to coalesced pairs of signals. [b] Calculated using the formula for a coalescing pair of singlet signals (ref. 20).

an exchange of environment for the diastereotopic methyl groups Me_A and Me_B.* For a single enantiomer [(*R*) or (*S*)] of the chiral guest phenylethylammonium thiocyanate the situation is similar although it involves the two diastereoisomeric complexes (**25**) [(*S,S*)-host, (*S*)-guest] and (**26**) [(*S,S*)-host, (*R*)-guest] for the hosts (**20b**) and(**20c**) and an analogous pair of diasteroisomeric complexes (*R,R*)-host, (*R*)-guest and (*R,R*)-host, (*S*)-guest] for the host (**20a**). From the coalescence of the NMe signals it is therefore possible to determine independently the free-energy barriers for face-to-face exchange of the guest cation of either the (*R*)- or (*S*)-configuration [processes $(E + I)_R$ and $(E + I)_S$ respectively]. The details of spectroscopic changes and derived free-energy barriers for complexes of the hosts (**20a**—**c**) with achiral and chiral guests are summarised in Table 3. In general, there is little difference between the dynamic stability of complexes of (*R*)- and (*S*)-phenylethylammonium cations in spite of the very considerable differences in the n.m.r. spectra of the diastereoisomeric complexes (Table 2). This suggests limited non-bonded interactions between guest and host and this view is confirmed by the relatively small differences in the magnitudes of the free-energy barriers for face-to-face exchange of guests of differing steric demand (see data for guest PhCH$_2$NH$_3^+$, PhCHMeNH$_3^+$, and Bu^{t}NH$_3^+$ cations in Table 3 and range of $\Delta G^{\ddagger}$ between 11.3 and 12.8 kcal mol^{-1}).

The diaza crown ether derivative (**20b**) forms a complex with the hydronium cation, as reported for other crown ethers.[21] The n.m.r. spectrum of this complex showed the expected lowfield shifts for the NMe groups (Table 2) and similar temperature dependence to that of the complexes with alkylammonium cations. The derived energy barrier for the process (E + I) (Table 3) is rather lower than that found for the complexes with alkylammonium cations.

At low temperatures (−70 °C, Table 2) the ^1H n.m.r. spectra of the complexes of the hosts (**20a**—**c**) with one equivalent of (*R,S*)-phenylethylammonium thiocyanate showed separate signals corresponding to a 1:1 mixture of the two diastereoisomeric complexes. At higher temperatures the processes $(E + I)_R$ and $(E + I)_S$ are both fast and so is the exchange of guest cations of opposite configuration that results in interconversion of the diastereoisomeric complexes. The spectrum of the host is therefore a time-averaged spectrum of the two diastereoisomers, although the spectra of the (*R*)- and (*S*)-guest cations remain distinct as expected.[9]

For each of the hosts (**20a**—**c**) in the presence of an excess of the (*R,S*) guest cation an equilibrium is set up between the two diastereoisomeric complexes.[9] At low temperatures the ^1H n.m.r. spectra in each case showed signals corresponding to the $^+NH_3$ groups of the complexes of the (*R*)-salt and the (*S*)-salt, together with a signal assignable to the uncomplexed guest (Table 2). In principle, the enantioselectivity of complexation could be determined by integration of the two $^+NH_3$ signals from the diastereoisomeric complexes but in practice the signals were too broad for accurate integration. Qualitative examination of the signal intensities indicated that enantioselectivity for a guest phenylethylammonium cation is very low for all three hosts. This is confirmed by the host signals, which resemble those from the 1:1 mixture of the two diastereoisomeric complexes, formed by a 1:1 mixture of host macrocycle and (*R,S*)-phenylethylammonium thiocyanate, over the temperature range +30 to −90 °C.

The ^1H n.m.r. spectra of the complexes of the *N,N'*-dibenzyl diaza 18-crown-6 derivatives (**21a**—**c**) with guest primary alkyl ammonium salts showed line broadening at low temperatures but no tendency for the signal separation associated with a slow rate for processes such as E + I. This behaviour suggests that the complexes formed by these hosts are more weakly bound and an examination of space-filling molecular models shows that the faces of the free macrocycles are sterically crowded. Nevertheless it was possible to examine the spectra for evidence of enantioselectivity in the complexation of guest (*R*)- and (*S*)-phenylethylammonium thiocyanate using a single phase method. Thus the n.m.r. spectrum of the host (**21c**) complexed with one molar equivalent of (*R*)-phenylethylammonium thiocyanate (Figure 1a) in deuteriomethylene chloride at 0 or −20 °C was very different from the spectrum of the diastereoisomeric complex formed with one molar equivalent of the (*S*)-guest under the same conditions (Figure 1b and Table 4). In particular the various host NC*H* signals and the guest C*H* signal showed significant changes in chemical shift as the sample temperature was lowered (Table 4) which were different for the two diastereoisomers. The spectrum of a 1:1 mixture of the host (**21c**) and (*R,S*)-phenylethylammonium thiocyanate showed guest signals corresponding to the formation of the two diastereoisomeric complexes but, as expected, the host signals for the two complexes were time-averaged as a result of rapid guest-host exchange.[9]

However, the spectrum of the host (**21c**) in the presence of *two* molar equivalents of the (*R,S*)-guest salt was virtually identical

* The descriptions Me_A and Me_B in (**24a**) and (**24b**), and similar descriptions in the formulae, are arbitrary since it is not possible to make assigments on the basis of the chemical shifts.

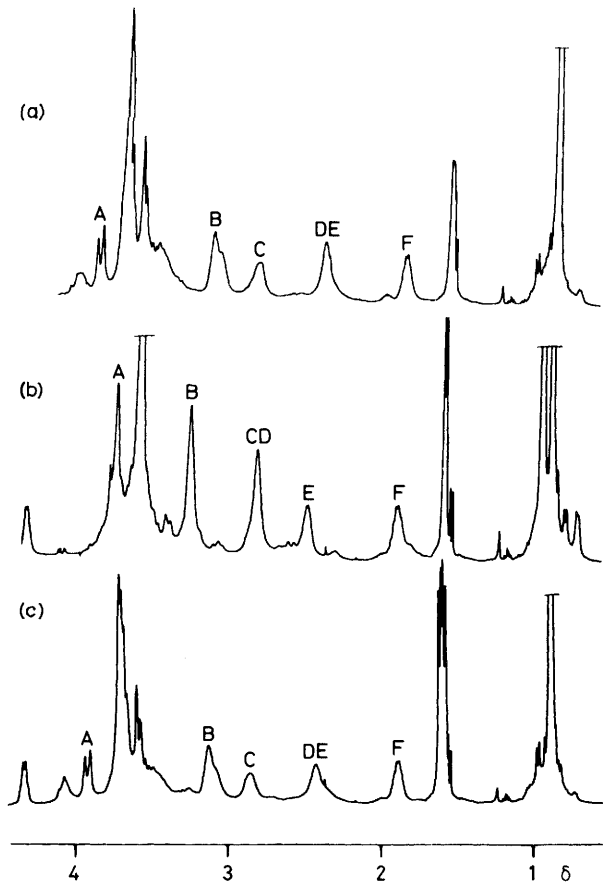


Figure 1. ^{1}H N.m.r. spectrum (400 MHz) of diaza-18-crown-6 derivative (**21c**) with 1-phenylethylammonium thiocyanate in CD_2Cl_2 at −20 °C. (a) (*R*)-guest and (b) (*S*)-guest, 1:1 G:H ratio and (c) (*R,S*)-guest 2:1 G:H ratio. Host signals are labelled A—F in accord with Table 4

(Figure 1c) with that of the host (**21c**) complexed with the (*R*)-guest salt both at 0 °C and at −20 °C. This result indicates that the host (**21c**), derived from (*S*)-valine, selectively forms a complex with the (*R*)- rather than the (*S*)-guest.

In principle, a quantitative measure of enantiomer selectivity should be derivable from the chemical shifts of the host signals [equation (1)] or of the guest signals [equation (2)]. Thus the

$$[(R)G, (SS)H]/[(S)G, (SS)H] = (\delta_S{}^H - \delta_{2RS}{}^H)/(\delta_{2RS}{}^H - \delta_R{}^H) \quad (1)$$

$$[(R)G, (SS)H]/[(S)G, (SS)H] = (\delta_{2RS}{}^{SG} - \delta_F{}^G)(\delta_S{}^{SG} - \delta_F{}^G)/(\delta_R{}^{RG} - \delta_F{}^G)(\delta_{2RS}{}^{RG} - \delta_F{}^G) \quad (2)$$

relative concentrations (of the two diastereoisomeric complexes formed by the (*R*)- and (*S*)-guests [(R)G and (S)G] with the (*S,S*)-host (**21c**) [(SS)H] are given by equations (1) and (2) where $\delta_S{}^H$, $\delta_R{}^H$, and $\delta_{2RS}{}^H$ are the chemical shifts of a selected host signal in the presence of one equivalent of (*S*)-guest, one equivalent of (*R*)-guest, and two equivalents of (*R,S*)-guest respectively. $\delta_S{}^{SG}$ and $\delta_{2RS}{}^{SG}$ Are the chemical shifts of a selected (*S*)-guest signal in solutions containing the host and one equivalent of (*S*)-guest and two equivalents of (*R,S*)-guest respectively, $\delta_R{}^{RG}$ and $\delta_{2RS}{}^{RG}$ have the same significance for the (*R*)-guest signals, and $\delta_F{}^G$ is the corresponding chemical shift for the uncomplexed guest cation.

The application of equations (1) and (2) gave enantioselectivities for complexation of the (*R*)-guest as compared with the (*S*)-guest by host (**21c**) of 3.5:1 at 0 °C and 10:1 at −20 °C (based upon H_D, Table 4). These values are subject to rather large experimental variation because of the difficulty of obtaining accurate chemical shifts for rather broad n.m.r. lines, but they support the conclusions based upon qualitative comparison of spectra (Figure 1). The host (**21b**), derived from (*S*)-phenylalanine, showed similar enantioselectivity for the (*R*)-guest, although the magnitudes of the enantioselectivity (*ca.* 3:1 at 25 °C and 1.4—3.5:1 at 0 °C based on 220 MHz spectra) were rather lower than found for host (**21a**) (for details of 400 MHz spectra, see Figure 2 and Table 5).

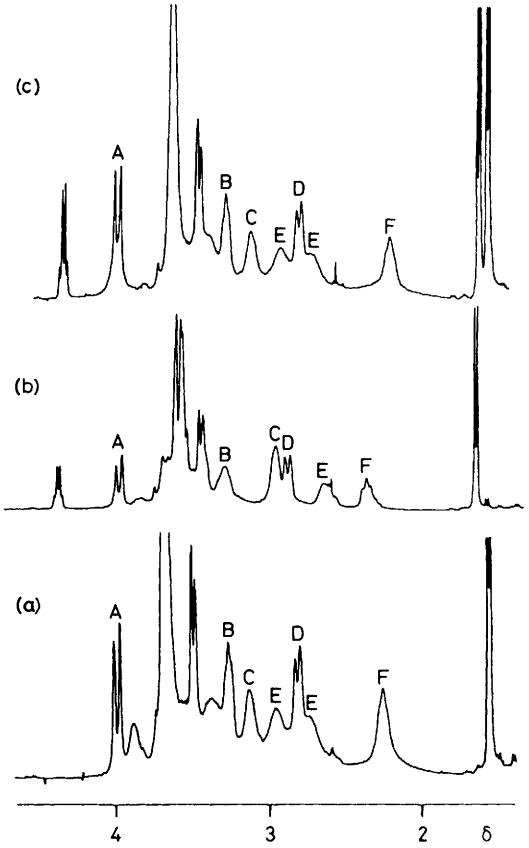


Figure 2. ^{1}H N.m.r. spectrum (400 MHz) of diaza-18-crown-6 derivative (**21b**) with 1-phenylethylammonium thiocyanate in CD_2Cl_2 at 0 °C. (a) (*R*)-guest and (b) (*S*)-guest, 1:1 G:H ratio, and (c) (*R,S*)-guest 2:1 G:H ratio. Host signals are labelled A—F in accord with Table 5.

Enantioselectivity was also checked using the two-phase methods that have been described by Cram and co-workers.[22] Thus either (*R*)- or (*S*)-phenylethylammonium thiocyanate was extracted from water into deuteriochloroform by the host (**20b**) to give a 1:1 complex in the organic layer. However, the n.m.r. spectrum of the complex formed under these conditions showed two sets of guest signals, corresponding to two types of complex. The major species was identical (n.m.r. spectrum, see Table 2) with the corresponding 1:1 complex formed by mixing host and guest in a single-phase system ($CDCl_3$ or CD_2Cl_2) but the minor species had a distinct and different spectrum [guest CMe signal at δ 1.22 and 1.25 for the (*R*)- and (*S*)-salts respectively]. A similar spectrum could be obtained by adding one equivalent of the guest amine to a solution of the hydrated salt (**20b**), H_3O^+ ClO_4^- in deuteriochloroform and it was concluded that the minor species was probably the hydrated complex (**20b**), D_2O, $PhCHMeNH_3NCS^-$. Extraction experiments using the (*R,S*)-guest salt showed only a very slight

Table 4. ^{1}H N.m.r. spectra (400 MHz) of complexes of diaza-18-crown-6 derivative (**21c**) with 1-phenylethylammonium thiocyanate in CD_2Cl_2

Ratio R:S:H	Temp. (°C)	Spectrum of host[a] H_A	H_B	H_C	H_D	H_E	H_F	Me_A[g]	Me_B[g]	Spectrum of guest *CH*	*CHMe*
1:0:1	0	3.84[b]	3.23[c]	2.87[d]	2.63[e]	2.47	1.88[f]	0.94	0.90	4.14	1.58
0:1:1	0	3.82[h], 3.77	3.32	2.88	2.88	2.54	1.90[f]	0.98	0.90	4.31	1.59
0.5:0.5:1	0	3.76	3.27[c]	2.87[d]	2.76	2.48	1.88[f]	0.96	0.90	4.16, 4.32	1.58, 1.60
1:1:1	0	3.87[b]	3.23[c]	2.90[d]	2.68	2.51	1.91[f]	0.94	0.90	4.19, 4.33	1.59, 1.61
1:0:1	−20	3.87[b]	3.08, 3.12	2.83	2.38	2.38	1.85[f]	0.87	0.87	3.99	1.56
0:1:1	−20	3.73[i]	3.24	2.81	2.81	2.48	1.88	0.95	0.88	4.31	1.58
0.5:0.5:1	−20	3.78[b]	3.18	2.79	2.57	2.42	1.85[f]	0.91	0.87	3.99, 4.32	1.56, 1.59
1:1:1	−20	3.91[b]	3.09, 3.12	2.84	2.42	2.42	1.87[f]	0.87	0.87	4.05, 4.32	1.57, 1.60

[a] Signals for complexes of (**21c**) labelled in accord with Figure 1. Chemical shifts (δ) in p.p.m. relative to $SiMe_4$. [b] Doublet, *J* 14 Hz, H_A of $PhCH_AH_B$. [c] Triplet, *J ca.* 5 Hz. [d] Doublet triplet, *J* 12, 6, Hz. [e] Broad doublet, *J* 12 Hz. [f] Octet, *J* 6.5 Hz, $CHCHMe_2$. [g] Doublet, *J* 6.5 Hz. [h] AB system, *J* 14 Hz, $PhCH_AH_B$. [i] Broad singlet.

Table 5. ^{1}H N.m.r. spectra (400 MHz) of complexes of diaza-18-crown-6 derivative (**21b**) with 1-phenylethylammonium thiocyanate in CD_2Cl_2 at 0 °C

Ratio R:S:H	Spectrum of host[a] H_A[a]	H_B	H_C	H_D[c]	H_E	H_F	Spectrum of guest *CH*	*CHMe*
0:1:1	3.96	3.28	2.95	2.87	2.59	2.34	4.36	1.63
1:0:1	3.98	3.26	3.11	2.81	2.95, 2.73	2.24	3.72[d]	1.55
1:1:1	4.00	3.30	3.13	2.82	2.93, 2.75	2.22	4.36 *e*	1.64, 1.57

[a] Signals for complexes of (**21b**) labelled in accord with Figure 2. Chemical shifts (δ) in p.p.m. relative to $SiMe_4$. [b] Doublet, *J* 14 Hz, H_A of $PhCH_AH_B$. [c] Doublet, *J* 13 Hz. [d] Broad signal probably assignable to C*H*Me of guest. [e] Broad signal *ca.* δ3.7, possibly corresponding to C*H*Me of (*R*)-guest.

Table 6. ^{1}H N.m.r. spectra (220 MHz) of the $CDCl_3$ layer obtained by distribution of 1-phenylethylammonium thiocyanate between $CDCl_3$ and D_2O in the presence of hosts (**20b**) and (**21c**) at room temperature.

Host	Configuration of guest salt	Scale[a]	G:H in[b] $CDCl_3$ layer	Spectrum of guest CH*Me*
(**20b**)	(*R*)	A	1.0	1.57, 1.22[c]
(**20b**)	(*S*)	B	1.0	1.52, 1.25[c]
(**20b**)	(*R,S*)	A	1.0	1.57, 1.51, 1.22[c]
(**21c**)	(*R*)-	D	0.51 (1.05)	*ca.* 1.5[d]
(**21c**)	(*S*)-	C	0.44 (0.76)	*ca.* 1.5[d]

[a] Scale A: 0.1M-solution of guest salt in D_2O (1.6 ml), 0.15M-solution of host in $CDCl_3$ (0.6 ml). Scale B: 0.35M-solution of guest salt in D_2O (0.6 ml), 0.15M-solution of host in $CDCl_3$ (0.6 ml). Scale C: 0.52M-solution of guest salt in D_2O (0.6 ml), 0.04M-solution of host in $CDCl_3$ (0.6 ml). Scale D: 1.05M-solution of guest salt in D_2O (0.3 ml), 0.04M-solution of host in $CDCl_3$ (0.6 ml). [b] From integration of Me signals of guest and host, the values in parentheses refer to calculated extraction coefficients (ref. 9). [c] The lowfield signal is assigned to the complex H, G and the highfield signal to the complex, H, D_3O^+, G. [d] A broad signal with no distinction between the (*R*)- and (*S*)-guest salt, *cf.* Table 4.

preferential extraction of the (*S*)-guest by the host (**20b**) in accord with the conclusions based upon n.m.r. studies in a single-phase system.

Similar extraction experiments with the more sterically hindered host (**21c**) showed that extraction of the (*R*)- or (*S*)-guest salt from D_2O by a deuteriochloroform solution of (**21c**) required higher concentrations of the guest salt in the D_2O layer than were used for the host (**20b**). Furthermore, the molar ratios of guest to host in the organic phase were significantly less than 1:1 (Table 6). The extraction coefficients for the (*R*)- and (*S*)-guest salts indicated a slight preference for the (*R*)-guest but the n.m.r. spectra of the organic layer indicated that the complexes obtained under these conditions were different from those obtained in a water-free single phase system by the addition of guest salt to host. It is therefore not possible to compare the results of the two methods for estimating enantioselectivity. We conclude that the *N,N*-dibenzyl derivatives, (**21b**) and (**21c**), of the chiral diaza-18-crown-6 systems (**19b**) and (**19c**) show significant enantioselectivity in the complexation of 1-phenylethylammonium thiocyanate in an anhydrous organic solvent. However, the successful exploitation of this result, for example for enantiomer separation, would require the attachment of the host molecule to a suitable polymer support.[23]

Experimental

General.—See Part 2 of this series.[24]

N.M.R. Spectra.—These were determined using either a Perkin-Elmer R34 (220 MHz, CW) spectrometer or a Bruker WH 400 (400 MHz, FT) spectrometer* and approximately

* We thank the S.E.R.C. 400 MHz n.m.r. service at Sheffield for running these spectra.

0.1M-solutions in either deuteriomethylene chloride or deuteriochloroform. Temperatures were controlled within the range −110 to +25 °C and were calibrated using either a thermocouple or a methanol sample. Solutions of complexes were prepared as described in earlier parts of this series.[1]

(S)-13-[2-(*Benzyloxycarbonylamino*)*propanoyl*]-1,4,7,10-*tetra-oxa*-13-*azacyclopentadecane* (**11a**).—Diphenylphosphinyl chloride (0.486 g) in dry methylene chloride (4 ml) was added to a solution of (*S*)-*N*-benzyloxycarbonylalanine (0.458 g) and *N*-methylmorpholine (2 ml) in dry methylene chloride (4 ml) at −23 °C. The mixture was stirred for 20 min at −23 °C, the aza crown ether (**9**) (0.450 g) was added, and the solution was allowed to warm to room temperature and stirred for 22 h. The resulting solution was diluted with methylene chloride (88 ml), washed with 0.1M-HCl (3 × 40 ml) and 0.1M-NaOH (3 × 30 ml), dried ($MgSO_4$), and evaporated to give the amide (**11a**) (0.859 g, 99%) as a yellow oil which crystallised with time (Found: M^+, 424.2190. $C_{21}H_{32}N_2O_7$ requires M, 424.2210); $\nu_{max.}$ 3 415, 1 717, and 1 647 cm^{-1}; δ 7.31 (m, C_6H_5), 5.95 (d, J 8 Hz, NH), 5.07 (s, $PhCH_2$), 4.71 (m, CH), 3.57 (m, OCH_2 and NCH_2), and 1.31 (d, J 6 Hz, CH_3); $[\alpha]_D^{21}$ −47.7° (*c* 0.1 in $CHCl_3$).

(S)-13-[2-(*t-Butyloxycarbonylamino*)*propanoyl*]-1,4,7,10-*tetraoxa*-13-*azacyclopentadecane* (**11c**). This compound was prepared in a similar manner from (*S*)-*N*-t-butyloxycarbonylalanine and the aza crown ether (**9**). 10% Citric acid was substituted for 0.1M-HCl in the isolation procedure. The *product* (**11c**) was obtained as a yellow oil (80%) (Found: M^+, 390.2387. $C_{18}H_{34}N_2O_7$ requires M, 390.2366); $\nu_{max.}$ 3 010, 1 703, and 1 639 cm^{-1}; δ 5.70 (br s, NH), 4.65 (br m, CH), 3.90—3.40 (m, OCH_2 and NCH_2), 1.41 (s, CMe_3), and 1.27 (d, J 7 Hz, CH_3); $[\alpha]_D^{22}$ −10.4° (*c* 0.5 in $CHCl_3$).

(S)-13-[2-(*Ethoxycarbonylamino*)*propanoyl*]-1,4,7,10-*tetraoxa*-13-*azacyclopentadecane* (**11b**). This compound was prepared in a similar manner from (*S*)-*N*-ethoxycarbonylalanine and the aza crown ether (**9**). The product was purified by chromatography (silica gel, $CHCl_3$–MeOH) to give the *amide* (**11b**) (76%) as a yellow oil (Found: M^+, 362.2017. $C_{16}H_{30}N_2O_7$ requires M, 362.2053); $\nu_{max.}$ 3 425, 1 707, and 1 638 cm^{-1}; δ 5.90 (d, NH), 4.69 (br m, CH), 4.08 (br m, CH_3CH_2O), 4.00—3.45 (m, OCH_2 and NCH_2), 1.29 (d, J 6 Hz, CH_3CH), and 1.17 (br t, CH_3CH_2O).

(S)-13-[2-(*Methylamino*)*propyl*]-1,4,7,10-*tetraoxa*-13-*azacyclopentadecane* (**12a**).—A solution of the amide (**11a**) (0.250 g) in dry tetrahydrofuran (20 ml) was treated with lithium aluminium hydride (0.179 g) and the mixture heated under reflux for 18 h. Excess of hydride was destroyed by the addition of ice–water and the precipitated alumina was removed by filtration. The residual alumina was washed with $CHCl_3$–EtOH (1:1) and the combined filtrate and washings were evaporated to give a yellow oil which was dissolved in ethyl acetate (10 ml) and extracted with 3M-HCl (3 × 2 ml). The aqueous extract was evaporated and the residual yellow solid hydrochloride salt of (**12a**) converted into the free base using ion exchange resin (Amberlite IRA-402, OH^-; ethanol as solvent) to give the amine (**12a**) (0.105 g, 60%) as a yellow oil [Found: M^+, 290 (M − C_3H_8N, 232.1555). $C_{14}H_{30}N_2O_4$ requires M, 290 (M − C_3H_8N, 232.1549)]; $\nu_{max.}$ 3 320 cm^{-1}; δ 3.67 (m, OCH_2), 2.85—2.30 (m, NCH_2 and CH), 2.40 (s, NMe), and 0.96 (d, J 7 Hz, CH_3); $[\alpha]_D^{20}$ +18.9° (*c* 4.7 in $CHCl_3$). The amine (**12a**) could also be prepared (87% yield) by reduction of the amide (**11b**) with lithium aluminium hydride in hot tetrahydrofuran.

(S)-13-(2-*Aminopropyl*)-1,4,7,10-*tetraoxa*-13-*azacyclopentadecane* (**12b**).—The amide (**11c**) (2.161 g) was stirred for 75 min with 6M-HCl in 1,4-dioxane (25 ml). The solution was poured into ether (300 ml) and the precipitated hydrochloride removed by filtration. The amide (**11d**) was liberated from the salt by ion-exchange chromatography (Amberlite IRA-402, OH^-; ethanol as solvent) to give a yellow oil (1.446 g, 90%) (Found: M^+, 290.1872. $C_{13}H_{26}N_2O_5$ requires M, 290.1842); $\nu_{max.}$ 1 638 cm^{-1}; $[\alpha]_D^{22}$ +6.9° (*c* 0.3 in $CHCl_3$). A solution of the amide (**11d**) (1.400 g) in dry tetrahydrofuran (100 ml) was treated with lithium aluminium hydride (1.460 g) and the mixture heated under reflux for 18 h. Excess of hydride was destroyed by the addition of ice–water and the residual alumina extracted in a Soxhlet apparatus with ethanol. The extract was evaporated and the residual oil dissolved in methylene chloride; the solution was filtered and evaporated to give the impure amine (**12b**) as a yellow oil (1.301 g, 98%); $\nu_{max.}$ 2 860 cm^{-1}; δ 4.00—3.48 (m, OCH_2), 2.95—2.75 (m, NCH), 2.54 (br d, J 12 Hz, NCH), 2.37 (dd, J 11, 3 Hz, NCH), and 1.19 (d, J 6 Hz, $CHCH_3$); $[\alpha]_D^{20}$ +20.4° (*c* 9.6 in $CHCl_3$). The N-*acetyl derivative* (**12c**) (acetyl chloride) was obtained as an oil which was purified by short-path distillation at 200—240 °C, 0.08 mmHg (84% yield) (Found: C, 56.3; H, 9.3; N, 8.7. $C_{15}H_{30}N_2O_5$ requires C, 56.6; H, 9.5; N, 8.8%); $\nu_{max.}$ 1 657 cm^{-1}; δ 3.88 (m, CH); 3.17 (m, OCH_2), 2.76 (t, J 5 Hz, NCH_2CH_2O), 2.55 (m, NCH_2CHN), 1.96 (s, $COCH_3$), and 1.16 (d, J 7 Hz, $CHCH_3$); $[\alpha]_D^{18}$ −4.5° (*c* 2.2 in $CHCl_3$).

(S,S)-7,13-*Bis*[2-(*t-butyloxycarbonylamino*)*propanoyl*]-1,4,10-*trioxa*-7,13-*diazacyclopentadecane* (**13a**).—*Method* A. *N,N*-Dicyclohexylcarbodi-imide (0.174 g) in acid-free methylene chloride (5 ml) was added dropwise to (*S*)-*N*-t-butyloxycarbonylalanine (0.319 g) in acid free methylene chloride (2 ml). The solution was stirred for 1 h, treated with the diaza-crown ether (**10**) (0.184 g) in acid free methylene chloride (4 ml) and left at room temperature for a further 70 h. The reaction mixture was diluted with methylene chloride, filtered, and evaporated. The residue was extracted with ethyl acetate (50 ml), the extract washed (aqueous $NaHCO_3$ and aqueous NaCl), dried ($MgSO_4$), and evaporated to give the diaza-crown ether derivative (**13a**) as a yellow oil (0.363 g, 77%) (Found: M^+, 560.3408. $C_{26}H_{48}N_4O_9$ requires M, 560,3421); $\nu_{max.}$ 1 703 and 1 645 cm^{-1}; δ 5.35 (br, NH), 4.70 (br m, CH), 3.85—3.55 (br m, 6 × OCH_2 + 4 × NCH_2), 1.43 (s, CMe_3), and 1.29 (d, J 7 Hz, CH_3).

Method B. A similar procedure using isolated (*S,S*)-*N*-t-butyloxycarbonylalanine anhydride[25] gave the crown ether derivative (**13a**) in 95% yield.

The diaza-crown ether derivative (**13a**) was treated with methanolic HCl for 2 h at room temperature and the basic reaction product isolated by ion exchange chromatography [Amberlite resin IRA-402 (OH^-), ethanol as solvent] to give the diamine (**13b**) as an oil (95%) which was only partly characterised; $\nu_{max.}$($CHCl_3$) 2 920 and 1 636 cm^{-1}; δ 3.95—3.20 (br m, 6 × OCH_2 + 4 × NCH_2 + 2 × CH), 2.26 (br s, NH_2), and 1.22 (br d, J 6 Hz, CH_3); *m/z* 360 (M^+, <1%), 149 (34), and 56 (100).

(*R*)-2-*Chloroacetamido*-2-*phenylethanol* (**14a**).—A vigorously stirred solution of (*R*)-2-amino-2-phenylethanol (5.505 g) in water (25 ml) at 0 °C was treated successively with 2.5 ml of a solution of chloroacetyl chloride (4.79 ml) in methylene chloride (25 ml) and 6 ml of 1M-NaOH, ten such additions being made over a period of 90 min. The volume of the mixture was reduced by evaporation to 70 ml and the aqueous residue extracted with ethyl acetate. The extracts were washed (aqueous $NaHCO_3$ and water), dried ($MgSO_4$), and evaporated. The residual oil slowly solidified and was recrystallised from ethyl acetate–cyclohexane to give the *product* (**14a**) (6.496 g, 76%), m.p. 103—105 °C (Found: C, 56.1; H, 5.5; N, 6.4. Calc. for $C_{10}H_{12}ClNO_2$: C, 56.2; H, 5.7; N, 6.6%); $\nu_{max.}$ 3 590, 3 410, and 1 668 cm^{-1}; δ 7.26 (m,

C_6H_5 and NH), 5.09 (br m, CH), 4.09 (s, CH_2Cl), 3.91 (br m, OCH_2), and 2.60 (br s, OH); $[\alpha]_D^{18}$ −32.7° (*c* 2.2 in $CHCl_3$).

(S)-2-*Chloroacetamido*-3-*phenylpropanol* (**14b**).—A vigorously stirred solution of (*S*)-2-amino-3-phenylpropanol (3.032 g) in water (40 ml) was treated portionwise at 0 °C with chloroacetyl chloride (2.4 ml) in methylene chloride (50 ml) and aqueous sodium hydroxide (1M; 30 ml) as in the preceding experiment. The product was isolated in a similar manner to give the *chloroacetyl derivative* (**14b**) (3.351 g, 74%), m.p. 58—79 °C (Found: C, 58.1; H, 6.2; N, 6.0. $C_{11}H_{14}ClNO_2$ requires C, 58.0; H, 6.2; N, 6.15%); $\nu_{max.}$ 3 615, 3 400, and 1 665 cm^{-1}; δ 7.20 (m, C_6H_5), 6.96 (d, *J* 8 Hz, NH), 4.17 (m, CH), 3.93 (s, CH_2Cl), 3.57 (br m, CH_2O + OH), and 2.86 (d, *J* 7 Hz, $C_6H_5CH_2CH$); $[\alpha]_D^{19}$ −34.5° (*c* 4.1 in $CHCl_3$).

(S)-2-*Chloroacetamidopropanol* (**14c**).—A vigorously stirred solution of (*S*)-2-aminopropanol (3.174 g) in water (20 ml) was treated portionwise at 0 °C with chloroacetyl chloride (5.04 ml) in methylene chloride (50 ml) and aqueous sodium hydroxide (1M; 63 ml) as in the previous experiments. The product was isolated to give the chloroacetyl derivative (**14c**) (5.017 g, 78%) as yellow oil (Found: M^+ + 1, 154.0400 and 152.0447. $C_5H_{11}{}^{37}ClNO_2$ requires *m/z* 154.0449; $C_5H_{11}{}^{35}ClNO_2$ requires *m/z* 152.0478); $\nu_{max.}$ 3 600, 3 405, and 1 660 cm^{-1}; δ 2.54 (d, *J* 8 Hz, NH), 4.69 (br s, OH), 4.06 (s, CH_2Cl), 4.05 (m, CH_3CH), 3.59 (m, CH_2O), and 1.19 (d, *J* 6.5 Hz, CH_3CH); $[\alpha]_D^{19}$ −12.5° (*c* 13.2 in $CHCl_3$).

(R,R)-7,13-*Bis*(5-*hydroxy*-2-*oxo*-4-*phenyl*-3-*azapentyl*)-1,4,10-*trioxa*-7,13-*diazacyclopentadecane* (**15a**).—A stirred solution of the diaza crown ether (**10**) (0.184 g) and the chloroacetamide (**14a**) (0.901 g) in acetonitrile (4.5 ml) containing anhydrous potassium carbonate (0.582 g) was heated under reflux for 21 h. The reaction mixture was cooled, diluted with ethyl acetate (50 ml), and filtered. The filtrate was extracted with hydrochloric acid (1M; 3 × 30 ml), the aqueous extracts were washed with ethyl acetate, made basic (Na_2CO_3), and evaporated to dryness. The residue was extracted with methylene chloride and the extract dried and evaporated; the residual white solid was purified by chromatography (alumina, methylene chloride–ethanol, 50:1 to 4:1) to give the bisalkylated diaza crown ether (**15a**) as a colourless oil (0.220 g, 46%) (Found: M^+, 572.3249. $C_{30}H_{44}N_4O_7$ requires *M*, 572.3210); $\nu_{max.}$ 3 300 and 1 658 cm^{-1}; δ 8.35 (d, *J* 7 Hz, NH), 7.28 (m, 2 × C_6H_5), 5.08 (m, 2 × CH), 3.78 (br m, 2 × CH_2OH), 3.58 (s, OCH_2CH_2O), 3.47 (br m, 4 × OCH_2), 3.10 (s, NCH_2CO), and 2.65 (br m, 4 × NCH_2); $[\alpha]_D^{21}$ −17.9° (*c* 0.8 in $CHCl_3$).

(S,S)-7,13-*Bis*(4-*benzyl*-5-*hydroxy*-2-*oxo*-3-*azapentyl*)-1,4,10-*trioxa*-7,13-*diazacyclopentadecane* (**15b**). This compound was prepared by a similar procedure from the diaza crown ether (**10**) (0.393 g) and the chloroacetamide (**14b**) (1.230 g) in acetonitrile (6 ml) containing anhydrous potassium carbonate (0.995 g). The diaza crown ether derivative (**15b**) was obtained as a colourless oil (0.473 g, 44%) (Found: M^+, 600.3506. $C_{32}H_{48}N_4O_7$ requires *M*, 600.3528); $\nu_{max.}$ 3 390 and 1 654 cm^{-1}; δ 7.88 (br d, *J* 8 Hz, NH), 7.20 (m, 2 × C_6H_5), 4.16 (br m, 2 × CH), 3.60—3.35 (m, 6 × OCH_2 + 2 × CH_2OH), 3.07 (s, 2 × NCH_2CO), 2.87 (d, *J* 7 Hz, 2 × $PhCH_2CH$), and 2.65 (m, 4 × NCH_2); $[\alpha]_D^{21}$ −26.4° (*c* 1.0 in $CHCl_3$).

(S,S)-7,13-*Bis*(5-*hydroxy*-4-*methyl*-2-*oxo*-3-*azapentyl*)-1,4,10-*trioxa*-7,13-*diazacyclopentadecane* (**15c**). This compound was prepared by a similar procedure from the chloroacetamide (**14c**) (1.414 g) and the diaza crown ether (**10**) (0.491 g) in acetonitrile (15 ml) containing anhydrous potassium carbonate (1.288 g). The diaza crown ether derivative (**15c**) was obtained as a yellow oil (0.723 g, 72%) (Found: M^+, 448.2908. $C_{20}H_{40}N_4O_7$ requires *M*, 448.2897); $\nu_{max.}$ 3 290 and 1 652 cm^{-1}; δ 7.85 (br d, *J* 8 Hz, 2 × NH), 4.02 (m, 2 × CH), 3.65 (s, OCH_2CH_2O), 3.55 (m, 4 × OCH_2 + 2 × CH_2OH), 3.11 (s, 2 × NCH_2CO), 2.75 (m, 4 × NCH_2), and 1.15 (d, *J* 7 Hz, 2 × CH_3); $[\alpha]_D^{21}$ −12.2° (*c* 3.3 in $CHCl_3$).

(R,R)-1,11-*Diamino*-1,11-*diphenyl*-3,6,9-*trioxaundecane* (**17a**).—The (*R*)-amino alcohol (**16a**) (0.466 g) in dry tetrahydrofuran (10 ml) was added dropwise at 0 °C to a stirred suspension of sodium hydride (55—60% in oil; 0.259 g) in dry tetrahydrofuran (10 ml) (N_2 atmos.). The mixture was stirred at room temperature for 2 h, treated with diethylene glycol bistoluene-*p*-sulphonate (0.703 g) in dry tetrahydrofuran (10 ml), and stirred at room temperature for a further 72 h. The reaction mixture was treated with water (30 ml) and the solution concentrated by evaporation to *ca.* 20 ml. The concentrate was acidified (10M-HCl), washed with ethyl acetate (3 × 50 ml), made basic (Na_2CO_3), and extracted with ethyl acetate (3 × 50 ml). This extract was dried and evaporated to give the crude diamine (**17a**) as an oil which was suitable for use as described below. A sample was purified by chromatography (alumina, methylene chloride–ethanol, 20:1) to give the *diamine* (**17a**) as an oil (Found: M^+ + 1, 345.2197. $C_{20}H_{29}N_2O_3$ requires *M*, 245.2178); $\nu_{max.}$ 3 360 cm^{-1}; δ 7.45—7.19 (m, 2 × C_6H_5), 4.20 (m, 2 × NCH), 3.65—3.40 (m, 6 × OCH_2) and 2.68 (br s, 2 × NH_2); $[\alpha]_D^{22}$ −43.5° (*c* 3.3 in $CHCl_3$).

(S,S)-2,12-*Diamino*-1,13-*diphenyl*-4,7,10-*trioxatridecane*(**17b**). This compound was prepared in a similar manner from the (*S*)-amino alcohol (**16b**) (1.832 g) and diethylene glycol bistoluene-*p*-sulphonate (2.502 g). The product (**17b**) was obtained as a yellow oil (1.501 g, 67%) which was converted into the amide (**18b**) without further purification; $\nu_{max.}$ 3 350 cm^{-1}; δ 7.15 (m, 2 × C_6H_5), 3.59 (m, 2 × OCH_2CH_2O), ABMXY system, δ_A 3.45, δ_B 3.31, δ_M 3.19, δ_X 2.72, δ_Y 2.57 (J_{AB} 9.3, J_{AM} 3.7, J_{BM} 7.4, J_{MX} 5.5, J_{MY} 7.9, J_{XY} 13.3 Hz, 2 × $OCH_AH_BCH_MCH_XH_Y$), and 2.88 (br s, 2 × NH_2).

(S,S)-3,13-*Diamino*-2,14-*dimethyl*-5,8,11-*trioxapentadecane* (**17c**). This compound was prepared in a similar manner from the (*S*)-amino alcohol (**16c**) (4.892 g) and diethylene glycol bistoluene-*p*-sulphonate (9.815 g). The product was isolated from the dihydrochloride salt by ion-exchange chromatography [Amberlite resin IRA-402 (OH), ethanol] to give the diamine (**17c**) as an oil (5.089 g, 78%) (Found: M^+, 276.2329. $C_{14}H_{32}N_2O_3$ requires *M*, 276.2413); $\nu_{max.}$ 3 370 cm^{-1}; δ 3.68 (m, 2 × OCH_2CH_2O), ABMNX$_6$ system, δ_A 3.51, δ_B 3.28, δ_M 2.93, δ_N 1.63, δ_X 0.89 {J_{AB} 8.9, J_{AM} 3.6, J_{BM} 8.0, J_{MN} 6.2, J_{NX} 6.7 Hz, $OCH_AH_BCH_MCH_N$ [$C(H_X)_3$]$_2$}, and 2.11 (br s, 2 × NH_2); $[\alpha]_D^{21}$ 16.0° (*c* 2.8 in $CHCl_3$).

(R,R)-9,17-*Diphenyl*-1,4,7,13-*tetraoxa*-10,16-*diazacyclo-octadecane*-11,15-*dione* (**18a**).—Solutions of the diamine (**17a**) (1.267 g) in toluene–methylene chloride (3:1, 100 ml) and diglycollyl chloride (0.693 g) in toluene (100 ml) were added dropwise and simultaneously to a vigorously stirred solution of triethylamine (1.13 ml) in toluene (500 ml) over a period of 6 h. The mixture was stirred for a further 14 h, filtered, and the filtrate evaporated to give the crude product as a yellow solid (1.611 g). Purification by column chromatography (alumina, methylene chloride–ethanol, 100:1) gave the diamide (**18a**) as an oil (0.288 g, 18%) (Found: M^+, 442.2119. $C_{24}H_{30}N_2O_6$ requires *M*, 442.2104); $\nu_{max.}$ 3 410 and 1 669 cm^{-1}; δ 7.54 (br d, *J* 7 Hz, 2 × NH), 7.33 (m, 2 × C_6H_5), 5.25 (m, 2 × CH), AB system, δ_A 4.26, δ_B 3.90 (J_{AB} 14.7 Hz, OCH_AH_BCO), and 3.85—3.51 (m, 2 × $CH_2OCH_2CH_2O$); $[\alpha]_D^{22}$ −48.1° (*c* 1.1 in $CHCl_3$).

(S,S)-9,17-*Dibenzyl*-1,4,7,13-*tetraoxa*-10,16-*diazacyclo-octadecane*-11,15-*dione* (**18b**).—Solutions of the diamine (**17b**) (1.472 g) in toluene (100 ml) and diglycollyl chloride (0.744 g) in

toluene (100 ml) were added dropwise and simultaneously to a vigorously stirred solution of triethylamine (1.2 ml) in toluene (500 ml) over 6 h. The mixture was stirred for 2 days, treated with saturated aqueous sodium hydrogencarbonate (100 ml), and heated under reflux for 0.5 h. The resulting mixture was evaporated to dryness and the residue extracted with methylene chloride (500 ml). The extract was dried and evaporated to give a yellow oil (1.860 g) which was purified by column chromatography (alumina, methylene chloride–ethanol, 60:1) to yield the *diamine* (**18b**) (0.551 g, 30%), m.p. 117—119 °C (Found: C, 66.3; H, 7.4; N, 5.8. $C_{26}H_{34}N_2O_6$ requires C, 66.4; H, 7.4; N, 5.95%); $\nu_{max.}$ 3 410 and 1 668 cm^{-1}; δ 7.34—7.15 (m, 2 × C_6H_5), 6.98 (br d, *J* 8.3 Hz, 2 × NH), AB system, δ_A 4.09, δ_B 3.84 (J_{AB} 16.3 Hz, OCH_AH_BCO), AMNXY system, δ_A 4.36, δ_M 3.49, δ_N 3.31, δ_X 2.94, δ_Y 2.88 (J_{AM} 2.9, J_{AN} 3.1, J_{AX} 6.2, J_{AY} 8.5, J_{MN} 9.4, J_{XY} 13.3 Hz, 2 × $OCH_MH_NCH_ACH_XH_Y$), and 3.72—3.55 (m, 2 × OCH_2CH_2O); $[\alpha]_D^{18}$ −65.7° (*c* 0.9 in $CHCl_3$).

(S,S)-9,17-*Di-isopropyl*-1,4,7,13-*tetraoxa*-10,16-*diazacyclo-octadecane*-11,15-*dione* (**18c**). This compound was prepared by an analogous procedure using the (*S,S*)-diamine (**17c**) (1.879 g) and diglycollyl chloride (1.164 g). The product was purified by column chromatography (alumina, methylene chloride–ethanol, 100:1) to give the *diamide* (**18c**) (0.565 g), 22%) as an oil (Found: M^+, 374.2381. $C_{18}H_{34}N_2O_6$ requires *M*, 374. 2417); $\nu_{max.}$ 3 405 and 1 664 cm^{-1}; δ 6.86 (br d, *J* 8 Hz, 2 × NH), AB system, δ_A 4.22, δ_B 3.92 (J_{AB} 14.9 Hz, 2 × OCH_AH_BCO), 3.83 (m, 2 × NCH), 3.70—3.40 (m, 2 × OCH_2CH_2O + 2 × OCH_2), 1.93 (octet, *J* 7 Hz, 2 × $CHCHMe_2$), 0.92 (d, *J* 7 Hz, 2 × $CHCH_3$), and 0.89 (d, *J* 7 Hz, 2 × $CHCH_3$).

(R,R)-9,17-*Diphenyl*-1,4,7,13-*tetraoxa*-10,16-*diazacyclo-octadecane* (**19a**).—Lithium aluminium hydride (0.45 g) was added to a solution of the amide (**18a**) (0.288 g) in tetrahydrofuran (40 ml) and the mixture heated under reflux for 18 h. Excess of hydride was destroyed by the dropwise addition of water (0.5 ml), aqueous sodium hydroxide (1M; 1 ml), and water (1.5 ml) and the precipitate was removed by filtration and washed with methylene chloride (4 × 40 ml). The combined filtrate and washings were evaporated to dryness and the residue extracted with methylene chloride. The extract was dried and evaporated to give the diaza crown ether (**19a**) as an oil (0.263 g, 97%); δ 7.45—7.15 (m, 2 × C_6H_5), 3.97 (m, 2 × NC*H*Ph), 3.80—3.40 (m, 2 × OCH_2CH_2O + 4 × OCH_2), and 2.83—2.39 (m, 2 × NCH_2); *m/z* 414 (M^+, 1%). The *N,N'*-dimethyl derivative was prepared by Eschweiler-Clark methylation (40% aqueous formaldehyde, formic acid, heated under reflux for 18 h) followed by purification by solvent extraction.

(R,R)-10,16-*Dimethyl*-9,17-*diphenyl*-1,4,7,13-*tetraoxa*-10,16-*diazacyclo-octadecane* (**20a**) was obtained as an oil (82% yield) (Found: M^+, 442. $C_{26}H_{38}N_2O_4$ requires *M*, 442); δ 7.28 (m, 2 × C_6H_5), 3.98 (m, 2 × NC*H*Ph), 3.80—3.50 (m, 2 × OCH_2CH_2O + 4 × OCH_2), 2.81 (m, 2 × NCH_2), and 2.20 (s, 2 × NMe); $[\alpha]_D^{20}$ −35.3° (*c* 0.6 in $CHCl_3$).

(S,S)-9,17-*Dibenzyl*-1,4,7,13-*tetraoxa*-10,11-*diazacyclo-octadecane* (**19b**).—A solution of the amide (**18b**) (4.034 g) in tetrahydrofuran (500 ml) containing lithium aluminium hydride (3.26 g) was heated under reflux for 20 h. The product was isolated as in the previous experiment to give the *diaza crown ether* (**19b**) as an oil (3.79 g, 99%) (Found: M^+, 442.2918. $C_{26}H_{38}N_2O_4$ requires *M*, 442.2831); $\nu_{max.}$ 3 300 cm^{-1}; δ 7.16 (m, 2 × C_6H_5) and 5.71—2.42 (m, 2 × $C_6H_5CH_2$ + 2 × OCH_2CH_2N + 2 × OCH_2CH_2O + 2 × OCH_2CHN); $[\alpha]_D^{20}$ + 45.0° (*c* 0.9 in $CHCl_3$). The N,N'-*dimethyl derivative* (**20b**) was prepared by Eschweiler-Clark methylation as a yellow oil (99% yield) (Found: M^+, 470.3146. $C_{28}H_{42}N_2O_4$ requires *M*, 470.3144); δ 7.18 (m, 2 × C_6H_5), 3.63—3.32 (m, 3 × CH_2OCH_2), 3.11 (br m, 2 × NCH), 3.00—2.45 (2 × $CH_2C_6H_5$ + 2 × CH_2N), and 2.39 (s, 2 × NCH_3); $[\alpha]_D^{20}$ +17.9° (*c* 0.4 in $CHCl_3$).

(S,S)-9,17-*Di-isopropyl*-1,4,7,13-*tetraoxa*-10,16-*diazacyclo-octadecane* (**19c**).—A solution of the amide (**18c**) (0.560 g) in tetrahydrofuran (100 ml) containing lithium aluminium hydride (1.13 g) was heated under reflux for 18 h. The product was isolated as in the previous experiment to give the diaza crown ether (**19c**) as an oil (0.45 g, 87%); $\nu_{max.}$ 3 300 cm^{-1}; δ 3.80—3.50 (m, CH_2OCH_2 + 2 × CHO + 2 × OCH_2CH_2O), 3.31 (t, *J* 9 Hz, 2 × $OCHHCHN$), 2.33 (ddd, *J* 12, 8, 4.5 Hz, 2 × $NCHHCH_2O$), 2.18 (dt, *J* 12, 3.5 Hz, 2 × $NCHHCH_2O$), 2.55 (m, 2 × OCH_2CHCH), 1.80 (octet, *J* 6.5 Hz, 2 × $CHCHMe_2$), 0.92 (d, *J* 7 Hz, 2 × CH_3), and 0.85 (d, *J* 7 Hz, 2 × CH_3); $[\alpha]_D^{18}$ +23.2° (*c* 0.2 in $CHCl_3$). This product did not give a molecular ion in its mass spectrum but could be characterised as the N,N'-*dimethyl derivative* (**20c**), prepared by Eschweiler-Clark methylation as a yellow oil (92% yield) (Found: M^+, 374.3154. $C_{20}H_{42}N_2O_4$ requires *M*, 374.3144); δ 3.68—3.45 [m, $CH_2O(CH_2CH_2O)_2CH_2$ + CH_2OCH_2], 2.83 (m, 2 × NCH_2), 2.40 (m, 2 × NCH), 2.32 (s, 2 × NCH_3), 1.76 (octet, *J* 7 Hz, 2 × $CHCHMe_2$), 0.92 (d, *J* 7 Hz, 2 × $CHCH_3$), and 0.86 (d, *J* 7 Hz, 2 × $CHCH_3$); $[\alpha]_D^{18}$ −15.4° (*c* 0.4 in $CHCl_3$).

(S,S)-9,10,16,17-*Tetrabenzyl*-1,4,7,13-*tetraoxa*-10,16-*diaza-cyclo-octadecane* (**21b**).—A solution of the amine (**19b**) (0.339 g) in methyl cyanide (2 ml) containing dry potassium carbonate (0.3 g) was treated with benzyl bromide (0.2 ml) and the mixture stirred at room temperature for 64 h. The resulting mixture was treated with hydrochloric acid (0.2M; 50 ml), washed with ether (4 × 10 ml), made basic (Na_2CO_3), and extracted with ether (3 × 50 ml). The ether extract was dried and evaporated to give the *product* (**21b**) as a yellow oil (0.440 g, 91%) (Found: M^+, 622.3736. $C_{40}H_{50}N_2O_4$ requires *M*, 622.3770); δ 7.19 (m, 4 × C_6H_5) and 3.75—2.62 (complex m, 4 × CH_2Ph + 2 × NCH + 2 + NCH_2 + 8 × OCH_2).

(S,S)-10,16-*Dibenzyl*-9,17-*di-isopropyl*-1,4,7,13-*tetraoxa*-10,16-*diazacyclo-octadecane* (**21c**).—A solution of the amine (**19c**) (0.245 g) in methyl cyanide (5 ml) containing dry potassium carbonate (0.3 g) was treated with benzyl bromide (0.2 ml) and heated under reflux for 14 h. The *product* (**21c**), isolated as in the previous experiment, was obtained as a yellow oil (0.286 g, 77%) (Found: M^+, 526.3755. $C_{32}H_{50}N_2O_4$ requires *M*, 526.3770); δ 7.35—7.12 (m, 2 × C_6H_5), 3.84 (d, *J* 14 Hz, 2 × PhCH*H*), 3.72—3.54 (m, 6 × OCH_2 + 2 × PhC*H*H), 3.32 (t, *J* 6.7 Hz, 2 × OCH_2), 2.82 (m, 2 × NCH_2), 2.46 (dt, *J* 10.5 Hz, 2 × $NCHCH_2O$), 1.79 (m, 2 × $CHCHMe_2$), 0.95 (d, *J* 6.5 Hz, 2 × $CHCH_3$), and 0.86 (d, *J* 6.5 Hz, 2 × $CHCH_3$).

References

1 Part 6, M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1979, 586.

2 D. J. Cram and J. M. Cram, *Acc. Chem. Res.*, 1978, **11**, 8; J. M. Timko, R. C. Helgeson, and D. J. Cram, *J. Am. Chem. Soc.*, 1978, **100**, 2828; S. C. Peacock, L. A. Domeier, F. C. A. Gaeta, R. C. Helgeson, J. M. Timko, and D. J. Cram, *J. Am. Chem. Soc.*, 1978, **100**, 8190; S. C. Peacock, D. M. Walba, F. C. A. Gaeta, R. C. Helgeson, and D. J. Cram, *J. Am. Chem. Soc.*, 1980, **102**, 2043.

3 W. Hain, R. Lehnert, H. Rottele, and G. Schroder, *Tetrahedron Lett.*, 1978, 625; J. F. Stoddart, *Chem. Soc. Rev.*, 1979, **8**, 85; T. Matsui and K. Koga, *Tetrahedron Lett.*, 1978, 1115; N. Ando, Y. Yamamoto, J. Oda, and Y. Inoue, *Synthesis*, 1978, 688; J. P. Behr, J. M. Lehn, D. Moras, and J. C. Thierry, *J. Am. Chem. Soc.*, 1981, **103**, 701.

4 D. J. Cram, R. C. Helgeson, M. Newcomb, and J. L. Toner, *J. Am. Chem. Soc.*, 1979, **101**, 4941.

5 D. J. Cram and G. D. Y. Sogah, *J. Am. Chem. Soc.*, 1979, **101**, 3035.

6 M.R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1979, 357.
7 L. C. Hodgkinson, M. R. Johnson, S. J. Leigh, N. Spencer, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2193.
8 M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 309; R. Mageswaran, S. Mageswaran, and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1979, 722.
9 D. P. J. Pearson, S. J. Leigh, and I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1979, 3113.
10 F. Gaeta and F. Wudl, *J. Chem. Soc., Chem. Commun.*, 1972, 107.
11 B. Bosnic-Kasnar, D. Kolbah, and M. Zinic, *Tetrahedron Lett.*, 1980, **21**, 1365.
12 R. M. Kellogg and J. D. de Vries, *J. Am. Chem. Soc.*, 1979, **101**, 2759; P. Jouin, R. M. Kellogg, and C. B. Troostwijk, *J. Am. Chem. Soc.*, 1981, **103**, 2091.
13 J. M. Lehn, *Acc. Chem. Res.*, 1978, **11**, 49; *Pure Appl. Chem.*, 1978, **50**, 871; 1979, **51**, 979; J. M. Lehn and C. Sirlin, *J. Chem. Soc., Chem. Commun.*, 1978, 949.
14 R. C. Sheppard in 'Comprehensive Organic Chemistry Vol. 5,' ed. D. H. R. Barton and W. D. Ollis, Pergamon, Oxford, 1979, p. 339.
15 A. G. Jackson, G. W. Kenner, G. A. Moore, R. A. Ramage, and W. D. Thorpe, *Tetrahedron Lett.*, 1976, 3627.
16 D. F. De Tar, R. Silverstein, and F. F. Rogers, *J. Am. Chem. Soc.*, 1966, **88**, 1024.
17 For a preliminary communication describing part of this work see D. J. Chadwick, I. A. Cliffe, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1981, 992.
18 M. J. Bovill, D. J. Chadwick, M. R. Johnson, N. F. Jones, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 1065.
19 J. C. Metcalfe and J. F. Stoddart, *J. Am. Chem. Soc.*, 1977, **99**, 8317; J. Krane and O. Aune, *Acta Chem. Scand.*, 1980, **34B**, 397.
20 G. Binsch, *Topics Stereochem.*, 1968, **3**, 97; I. O. Sutherland, *Annu. Rev. NMR Spectrosc.*, 1971, **4**, 71.
21 J. J. Christensen, B. L. Haymore, and R. M. Izatt, *J. Chem. Soc., Chem. Commun.*, 1972, 1308; B. J. Garcia and G. W. Gokel, *Tetrahedron Lett.*, 1977, 317.
22 D. J. Cram, P. C. Hilberty, S. S. Moore, J. M. Timko, and D. M. Walba, *J. Am. Chem. Soc.*, 1977, **99**, 4207; D. J. Cram, G. W. Gokel, R. C. Helgeson, E. P. Kyba, K. Madan, S. S. Moore, and T. L. Tarnowski, *J. Am. Chem. Soc.*, 1977, **99**, 2564.
23 For examples see G. W. Gokel and S. H. Korzeniowski, Macrocyclic Polyether Syntheses,' Springer-Verlag, Berlin, Heidelberg, 1982, pp. 276—279.
24 S. J. Leigh and I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1089.
25 C. Birr, F. Flor, and T. Wieland, *Angew. Chem. Int. Ed. Engl.*, 1971, **10**, 336.

Received 27*th* October 1983; *Paper* 3/1909