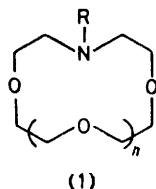


The Formation of Complexes between Aza-derivatives of Crown Ethers and Primary Alkylammonium Salts. Part 6.† Bis(mono-aza)crown Ethers

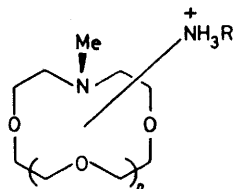
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The bis(mono-aza)-crown ethers (4) form 2 : 1 (G : H ratio) complexes with benzylammonium thiocyanate. In the case of the mono-aza-15-crown-5-derivatives (4a–g) the complexes have *cis,cis*-stereochemistry (10) but the 2 : 1 complexes of the mono-aza-18-crown-6 derivatives (4h–m) are mixtures of the *cis,cis*- (10), *cis,trans*- (11), and *trans,trans*- (12) isomers. The host molecules (4a–f) form 1 : 1 complexes with the bis(primary alkylammonium)thiocyanate (14); in the cases of (4a) and (4b) only a well-defined intramolecular complex (16) is formed but in the other cases both intramolecular and intermolecular (polymeric) complexes are formed. Hosts (4h–j) also form intramolecular complexes, with probably an increasing proportion of intermolecular complex as the distance between the macrocycles increases.

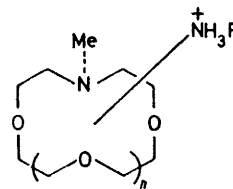
THE complexes of mono-aza-crown ethers (1) with primary alkylammonium thiocyanates have been discussed in the first paper of this series.¹ It was recognised that whereas the 15-crown-5 analogue (1a) formed



(1)
a; $n = 2$, $R = \text{Me}$
b; $n = 3$, $R = \text{Me}$
c; $n = 2$, $R = \text{H}$
d; $n = 3$, $R = \text{H}$



(2a)



(2b)

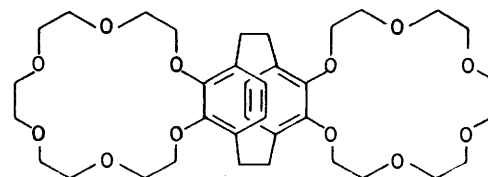
$n = 2$ or 3

complexes (2a) having only a *cis*-relationship between the N-Me substituent and the guest cation the 18-crown-6 analogue (1b) formed complexes having both *cis*- (2a) and *trans*- (2b) relationships between the N-Me substituent and the guest cation. These results were analogous to those found for various diaza-15-crown-5 and diaza-18-crown-6 hosts and various guest cations.^{2,3}

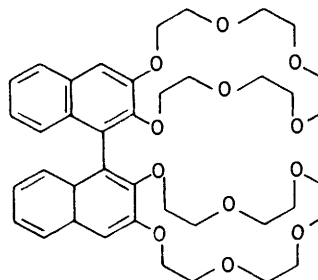
The extensive studies of complex formation by crown ethers and their aza-derivatives that have been reported⁴⁻⁷ have generally been concerned with binding involving only a single host site. A number of cases have been described⁸ in which a secondary binding site is involved but the nature of this secondary binding has usually been less well defined than that between the NH_3^+ group and the macrocyclic crown ether system. Furthermore it has been reported⁹ that the paracyclophanes (3a) form complexes with bis(primary alkylammonium)cations in an intermolecular, presumably polymeric, fashion because the two macrocycles are not suitably located to form monomeric complexes such as (5). It has been shown, however, that the analogous binaphthyl derivatives (3b), having the two crown ether systems closer together than in the case of (3a), forms 1 : 1 intramolecular complexes with some bis(primary alkylammonium)salts.¹⁰ The geometrical relationship

between the two crown ether rings of (3b) is controlled by the torsion angle about the bond between the two naphthyl units, resulting in some limitations in the variation of the distance between the two crown systems.

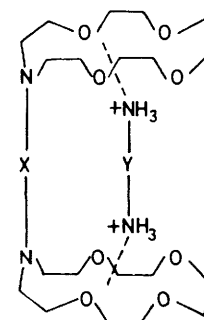
It was therefore of interest to examine bis(mono-aza)-crown ethers having the general structure (4) in the hope that a suitable bridge X between the macrocycles



(3a)



(3b)



(5)

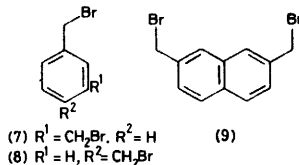
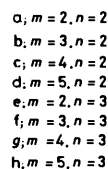
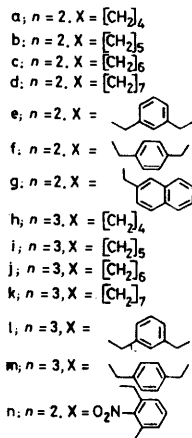
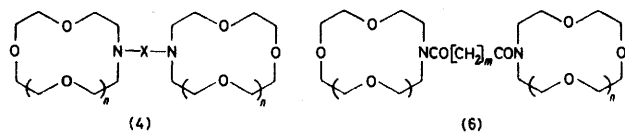
would produce host molecules capable of forming a 1 : 1 intramolecular complex [e.g. (5)] with a guest bis(primary

† Part 5, D. P. J. Pearson, S. J. Leigh, and J. O. Sutherland, *J.C.S. Perkin I*, 1979, 3113.

TABLE 1
Preparation of the diamides (6a—h)

Amine (1) (amount/g)	Diacid chloride ClCO[CH ₂] _n COCl n (amount/g)	Triethylamine		Reaction time	Product (6)	Yield (%)
		g	h			
(1c) (1.00)	2 (0.354)	0.461	4		(6a)	83
(1c) (1.00)	3 (0.386)	0.461	4		(6b)	84
(1c) (1.00)	4 (0.418)	0.461	1.5		(6c)	86
(1c) (1.00)	5 (0.450)	0.461	1.5		(6d)	87
(1d) (0.526)	2 (0.155)	0.202	1.5		(6e)	87
(1d) (0.526)	3 (0.169)	0.202	2		(6f)	95
(1d) (0.526)	4 (0.183)	0.202	2		(6g)	87
(1d) (0.790)	5 (0.295)	0.303	2		(6h)	88

alkylammonium)cation. Two general methods were used for the synthesis of the host compounds (4). Either a mono-aza-crown ether (1c) or (1d) was reacted with a



dicarboxylic acid chloride giving a diamide (6) which could be reduced with lithium aluminium hydride to the diamine (4), or the crown ether (1c) or (1d) was reacted

with one of the bis(bromomethyl)arenes (7)—(9). Using these methods the thirteen bis mono-aza-crown ethers (4a—m) were prepared (Experimental section). The functionalised bis(crown ether) (4n) was prepared by reaction of the aza-crown ether (1c) with 2,6-bis(bromomethyl)nitrobenzene. The n.m.r. spectra of the complexes formed by the host molecules (4) with benzylammonium thiocyanate and diamine thiocyanates are discussed in the final section of the paper.

EXPERIMENTAL

General.—See Part 2 of this series.^{2a}

N.M.R. Spectra.—These were determined using either a Varian EM390 (90 MHz) spectrometer or a Perkin-Elmer R34 (220 MHz) spectrometer and approximately 0.1M solutions in either deuteriomethylene chloride or deuteriochloroform. Temperatures were controlled within the range -110 to +25 °C and were calibrated using a methanol sample. Solutions of complexes with benzylammonium thiocyanate were prepared by dissolving the appropriate amounts of the two components in ca. 0.5 ml of solvent immediately prior to running the spectra. Solutions of the complexes with bis(primary alkylammonium)thiocyanates were prepared by adding a small quantity of deuterio-methanol to the appropriate amounts of the two components in deuteriomethylene chloride.

Preparation of the Diamides (6a—h).—The appropriate dicarboxylic acid dichloride (1 mol equiv.) and triethyl-

TABLE 2
Characterisation of the diamides (6a—h)

Compound	Formula	M.p. (°C)	Analysis (%) Found (Calc.)	N.m.r. spectrum (δ)
(6a)	C ₂₄ H ₄₄ N ₂ O ₁₀	87—88	C, 55.9; H, 8.9; N, 5.3 (C, 55.4; H, 8.5; N, 5.4)	2.68 (s, COCH ₂), 3.4—3.9 (m, OCH ₂ CH ₂ O + OCH ₂ CH ₂ N)
(6b)	C ₂₆ H ₄₆ N ₂ O ₁₀	Oil	C, 55.9; H, 8.8; N, 5.1 (C, 56.2; H, 8.6; N, 5.2)	1.98 (quintet, J 7 Hz, CH ₂ CH ₂ CH ₂), 2.41 (t, J 7 Hz, COCH ₂ CH ₂), 3.4—3.9 (m, OCH ₂ CH ₂ O + OCH ₂ CH ₂ N)
(6c)	C ₂₆ H ₄₈ N ₂ O ₁₀	67—70	M, 548.3285 (M, 548.3309)	1.63 (m, CH ₂ CH ₂ CH ₂ CH ₂), 2.32 (t, J 7 Hz, COCH ₂ CH ₂), 3.3—3.9 (m, OCH ₂ CH ₂ O + OCH ₂ CH ₂ N)
(6d)	C ₂₇ H ₅₀ N ₂ O ₁₀	Oil	C, 57.7; H, 9.2; N, 4.7 (C, 57.65; H, 8.9; N, 5.0)	1.47 (m, CH ₂ CH ₂ CH ₂), 1.65 (quintet, J 7 Hz, COCH ₂ CH ₂), 2.34 (t, J 7 Hz, COCH ₂ CH ₂), 3.3—3.9 (m, OCH ₂ CH ₂ O + OCH ₂ CH ₂ N)
(6e)	C ₂₈ H ₅₂ N ₂ O ₁₂	Oil	C, 55.4; H, 8.85; N, 4.2 (C, 55.3; H, 8.55; N, 4.6)	2.72 (s, COCH ₃), 3.3—4.0 (m, OCH ₂ CH ₂ O + OCH ₂ CH ₂ N)
(6f)	C ₂₉ H ₅₄ N ₂ O ₁₂	Oil	C, 55.2; H, 8.8; N, 4.4 (C, 55.95; H, 8.7; N, 4.5) M, 622.3753 (M, 622.3676)	1.95 (m, CH ₂ CH ₂ CH ₂), 2.40 (t, J 7 Hz, COCH ₂ CH ₂), 3.4—3.9 (m, OCH ₂ CH ₂ O + OCH ₂ CH ₂ N)
(6g)	C ₃₀ H ₅₆ N ₂ O ₁₂	Oil	M, 636.3797 (M, 636.3833)	1.71 (m, CH ₂ CH ₂ CH ₂ CH ₂), 2.40 (m, COCH ₂ CH ₂), 3.5—3.9 (m, OCH ₂ CH ₂ N + OCH ₂ CH ₂ O)
(6h)	C ₃₁ H ₅₈ N ₂ O ₁₂	Oil	M, 650.4036 (M, 650.3990)	1.2—1.8 (m, COCH ₂ CH ₂ CH ₂), 2.31 (t, J 7 Hz, COCH ₂ CH ₂), 3.4—3.9 (m, OCH ₂ CH ₂ N + OCH ₂ CH ₂ O)

amine (2 mol equiv.) were added to a solution of the azacrown ether, (1c) or (1d) (2 mol equiv.) in dichloromethane (50—100 ml). The solution was stirred for at least 1.5 h, washed with water (2 × 50 ml), and dried (MgSO₄). Evaporation gave the crude diamide (6) which was purified by

TABLE 3

Preparation of the diamines (4a—d) and (4h—k)

Amide (amount/g)	LiAlH ₄ / g	Reaction time h	Product	Yield (%)
(6a) (0.775)	0.460	20	(4a)	97
(6b) (0.790)	0.450	20	(4b)	100
(6c) (0.800)	0.500	70	(4c)	94
(6d) (0.900)	0.550	20	(4d)	71
(6e) (0.290)	0.250	4	(4h)	87
(6f) (0.450)	0.400	18	(4i)	95
(6g) (0.300)	0.200	2	(4j)	94
(6h) (0.380)	0.300	3.5	(4k)	85

column chromatography (Al₂O₃). Details of these preparations are given in Table 1 and the characterisation of the products is summarised in Table 2.

Preparation of the Diamines (4a—d) and (4h—k).—Lithium

aluminium hydride (≥ 10 mol equiv.) was added in portions to a solution of the diamide (6) (1 mol equiv.) in dry tetrahydrofuran (30—100 ml). The resulting suspension was stirred and heated under reflux for at least 2 h. Excess of lithium aluminium hydride was destroyed by the dropwise addition of water to the cooled reaction mixture, the resulting white suspension was filtered, and the residual solid washed with chloroform. The combined filtrate and washings were evaporated giving the crude diamine (4) which was purified by column chromatography (Al₂O₃) and/or short-path distillation. Details of these preparations are given in Table 3 and the characterisation of the products is summarised in Table 4.

Preparation of the Diamines (4e—g) and (4l and m).—The appropriate dibromide (7)—(9) (1 mol equiv.) was added to a solution of the amine, (1c) or (1d) (2 mol equiv.) in dry acetonitrile (30—100 ml) containing anhydrous potassium carbonate (≥ 5 mol equiv.). The reactants were heated under reflux with the exclusion of moisture for at least 2 h. The reaction mixture was cooled and filtered, and the filtrate evaporated, giving the crude diamine (4) which was purified by column chromatography (Al₂O₃) and/or short-path distillation. Details of these preparations are given in Table 5 and the characterisation of the products is summarised in Table 4.

Preparation of the Diamine (4n).—2,6-Bis(bromomethyl)-nitrobenzene (0.705 g) was added to a solution of the amine (1c) (1.000 g) in dry acetonitrile (50 ml) containing anhy-

TABLE 4
Characterisation of diamines (4a—n)

Compound	Molecular formula	B.p. °C (pressure/ Torr)	Analytical data Found (Calc.)	N.m.r. spectrum (δ)
(4a)	C ₂₄ H ₄₈ N ₂ O ₈	229—231 (0.01)	M, 492.3394 (M, 492.3411)	1.37 (m, NCH ₂ CH ₂ CH ₂ CH ₂ N), 2.43 (t, J 8 Hz, NCH ₂ CH ₂ CH ₂), 2.69 (t, J 6 Hz, NCH ₂ CH ₂ O), 3.4—3.8 (m, OCH ₂)
(4b)	C ₂₅ H ₅₀ N ₂ O ₈	235—242 (0.01)	M, 506.3583 (M, 506.3567)	1.28 (m, NCH ₂ CH ₂ CH ₂), 1.48 (m, NCH ₂ CH ₂ CH ₂), 2.55 (t, J 8 Hz, NCH ₂ CH ₂ CH ₂), 2.78 (t, J 6 Hz, NCH ₂ CH ₂ O), 3.5—3.8 (m, OCH ₂)
(4c)	C ₂₆ H ₅₂ N ₂ O ₈	210—220 (0.02)	M, 520.3712 (M, 520.3723)	1.1—1.7 (m, NCH ₂ CH ₂ CH ₂), 2.44 (t, J 8 Hz, NCH ₂ CH ₂ CH ₂), 2.69 (t, J 6 Hz, NCH ₂ CH ₂ O), 3.4—3.8 (m, OCH ₂)
(4d)	C ₂₇ H ₅₄ N ₂ O ₈	245—248 (0.05)	M, 534.3848 (M, 534.3880)	1.2—1.7 (m, NCH ₂ CH ₂ CH ₂ CH ₂), 2.68 (t, J 7 Hz, NCH ₂ CH ₂ CH ₂), 2.75 (t, J 6 Hz, NCH ₂ CH ₂ O), 3.4—3.9 (m, OCH ₂)
(4e)	C ₂₈ H ₄₈ N ₂ O ₈	240—245 (0.01)	C, 62.0; H, 8.7; N, 5.4 (C, 62.2; H, 8.9; N, 5.2) M, 540.3400 (M, 540.3411)	2.79 (t, J 6 Hz, NCH ₂ CH ₂ O), 3.65 (t, J 6 Hz, OCH ₂ CH ₂ N), 3.6—3.7 (m, OCH ₂ CH ₂ O + NCH ₂ Ar), 7.24 (s, aryl-H)
(4f)	C ₂₈ H ₄₈ N ₂ O ₈	258—262 (0.01)	C, 61.9; H, 8.8; N, 5.2 (C, 62.2; H, 8.9; N, 5.2) M, 540.3411 (M, 540.3411)	2.77 (t, J 6 Hz, NCH ₂ CH ₂ O), 3.62 (t, J 6 Hz, OCH ₂ CH ₂ N), 3.6—3.7 (m, OCH ₂ CH ₂ O + NCH ₂ Ar), 7.24 (s, aryl-H)
(4g)	C ₃₂ H ₅₀ N ₂ O ₈	230—240 (decomp.) (0.01)	M, 590.3586 (M, 590.3567)	2.82 (t, J 6 Hz, NCH ₂ CH ₂ O), 3.4—3.8 (m, OCH ₂), 3.81 (s, NCH ₂ Ar), 7.68 (s, aryl-H)
(4h)	C ₂₈ H ₅₆ N ₂ O ₁₀	m.p. 41—43 b.p. 244—246 (0.05)	M, 580.3886 (M, 580.3934)	7.4—7.8 (AB system, aryl-H) 1.44 (m, NCH ₂ CH ₂ CH ₂ CH ₂ N), 2.51 (t, J 8 Hz, NCH ₂ CH ₂ CH ₂), 2.76 (t, J 6 Hz, NCH ₂ CH ₂ O), 3.6—3.8 (m, OCH ₂)
(4i)	C ₂₈ H ₅₆ N ₂ O ₁₀	248—252 (0.04)	M, 594.4096 (M, 594.4090)	1.1—1.7 (m, NCH ₂ CH ₂ CH ₂), 2.48 (t, J 9 Hz, NCH ₂ CH ₂ CH ₂), 2.72 (t, J 6 Hz, NCH ₂ CH ₂ O), 3.58 (t, J 6 Hz, OCH ₂ CH ₂ N), 3.4—3.8 (m, OCH ₂)

TABLE 4 (Continued)

Compound (4j)	Molecular formula C ₃₀ N ₆₀ N ₂ O ₁₀	B.p. °C (pressure/Torr)	Analytical data Found (Calc.)	N.m.r. spectrum (δ)
		Oil	<i>M</i> , 608.4248 (1) (<i>M</i> , 608.4248)	1.29 (m, NCH ₂ CH ₂ CH ₂), 1.43 (m, NCH ₂ CH ₂ CH ₂), 2.47 (t, <i>J</i> 9 Hz, NCH ₂ CH ₂ CH ₂), 2.70 (t, <i>J</i> 6 Hz, NCH ₂ CH ₂ O), 3.5—3.7 (m, OCH ₂)
(4k)	C ₃₁ H ₆₂ N ₂ O ₁₀	Oil	<i>M</i> , 622.4376 (<i>M</i> , 622.4404)	1.1—1.7 (m, NCH ₂ CH ₂ CH ₂ CH ₂), 2.47 (t, <i>J</i> 8 Hz, NCH ₂ CH ₂ CH ₂), 2.73 (t, <i>J</i> 6 Hz, NCH ₂ CH ₂ O), 3.58 (t, <i>J</i> 6 Hz, NCH ₂ CH ₂ O), 3.5—3.8 (m, OCH ₂)
(4l)	C ₃₂ H ₆₆ N ₂ O ₁₀	Oil	<i>M</i> , 628.3905 (<i>M</i> , 628.3935)	2.75 (t, <i>J</i> 6 Hz, NCH ₂ CH ₂ O), 3.4—3.8 (m, OCH ₂ + ArCH ₂ N), 7.21 (s, aryl-H)
(4m)	C ₃₂ H ₆₆ N ₂ O ₁₀	Oil	<i>M</i> , 628.3924 (<i>M</i> , 628.3935)	2.79 (t, <i>J</i> 6 Hz, NCH ₂ CH ₂ O), 3.5—3.9 (m, OCH ₂ + ArCH ₂ N), 7.26 (s, aryl-H)
(4n)	C ₂₈ H ₄₇ N ₃ O ₁₀	225—235 (0.01)	C, 57.3; H, 7.6; N, 6.7 (C, 57.4; H, 8.0; N, 7.2) <i>M</i> , 585.3203 (<i>M</i> , 585.3262)	2.71 (t, <i>J</i> 6 Hz, NCH ₂ CH ₂ O), 3.4—3.8 (m, OCH ₂ + ArCH ₂ N), 7.1—7.6 (m, aryl-H)

drous potassium carbonate (1.60 g). The reactants were heated for 18 h with the exclusion of moisture. The cooled reaction mixture was filtered and the filtrate evaporated giving the crude diamine (4n) (1.30 g, 97%). The product

TABLE 5

Preparation of the diamines (4e—g) and (4l and m)

Amine (1) (amount/g)	Dibromide (7)—(9) (amount/g)	K ₂ CO ₃ g	Reaction time h	Product (4)	Yield (%)
(1c) (0.500)	(7) (0.301)	0.800	4	(4e)	88
(1c) (0.700)	(8) (0.421)	1.120	5	(4f)	89
(1c) (1.000)	(9) (0.717)	1.600	18	(4g)	99
(1d) (0.600)	(7) (0.300)	1.000	16	(4l)	98
(1d) (0.600)	(8) (0.300)	1.000	16	(4m)	97

was purified by column chromatography (Al₂O₃) and short-path distillation at 225—235 °C and 0.01 Torr. The characterisation of (4n) is summarised in Table 4.

RESULTS AND DISCUSSION

The host molecules (4a—n) were examined for the formation of complexes with (i) benzylammonium thiocyanate and (ii) bis(primary alkylammonium)thiocyanates. For convenience the n.m.r. spectral characteristics of ^{11,12} these two types of complex will be discussed separately.

(i) *Benzylammonium Thiocyanate as the Guest Molecule*.—The n.m.r. spectra of the complexes formed between the host molecules (4a—m) and 1 and 2 mol equiv. of benzylammonium thiocyanate are summarised in Table 6. The spectral characteristics of the complexes formed by the 15-crown-5 analogues (4a—g) and (4n) and the 18-crown-6 analogues (4h—m) were generally rather different, and typical examples from each group of host molecules will be discussed.

(a) *15-Crown-5 derivatives (4a—g) as host molecules*. The n.m.r. spectrum of the host (4b) showed significant chemical shift changes on the addition of 1 or 2 mol

* In formulae (10), (11), and (12), and similar representations of complexes, the circles represent either CH₂[CH₂OCH₂]₄CH₂ (15-crown-5) or CH₂[CH₂OCH₂]₅CH₂ (18-crown-6).

equiv. of benzylammonium thiocyanate [Table 6 and Figure 1(a)]; the spectrum of the 2 : 1 (G : H) complex will be discussed first. The sharp singlet (δ 3.40) associated with the OCH₂CH₂O groups of the host broadened as the solution was cooled and separated into two broad signals (δ 3.29, 3.52) below -35 °C. Similar changes were also observed in one other component of the OCH₂ signals. The n.m.r. spectrum showed no further changes, other than line broadening, as the temperature was lowered to -100 °C [Figure 1 (b) and (c)]. This behaviour is consistent with the formation of a 2 : 1 complex having the *cis,cis* stereochemistry shown diagrammatically in (10); * even at low temperatures, where guest-host exchange would be a slow process, there is no evidence for detectable amounts of the *cis,trans* (11) and *trans,trans* (12) complexes. The observation of a single complex could be consistent with the formation of only a *trans,trans* complex. This interpretation we reject since it would not be consistent with the results reported for monocyclic 15-membered aza-crown ether systems (ref. 1); the observed n.m.r. spectra are also considered to be inconsistent with a *trans,trans* complex. The failure of the spectra of the NCH₂ groups to show either substantial shifts to high field on complex formation or temperature dependence (Figure 1) contrasts with the spectral characteristics ¹ of the complex of (1a). This appears to be a consequence of the position of the phenyl group of the guest molecule in the complex; it is evidently situated in the vicinity of the OCH₂ groups rather than the NCH₂ groups. The temperature dependence indicates † that there is a substantial barrier (Δ*G*[‡] 12.0 kcal mol⁻¹) for the process *E* + *I*, which in this case involves dissociation and recombination of each of the guest molecules in turn, as outlined in Scheme 1. Thus each of the 15-crown-5 rings of (4b) behaves in an analogous manner to the monocyclic amine (1a).

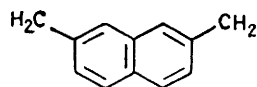
The n.m.r. spectrum of the same complex using a 1 : 1 (G : H) ratio of guest and host components showed

† Values for energy barriers (Δ*G*[‡]) cited in this paper are based upon the coalescence of signals in the n.m.r. spectra; the approximations described in ref. 12 were used to relate n.m.r. data to exchange rates at the coalescence temperatures. The derived values of Δ*G*[‡] are probably accurate to ±0.5 kcal mol⁻¹.

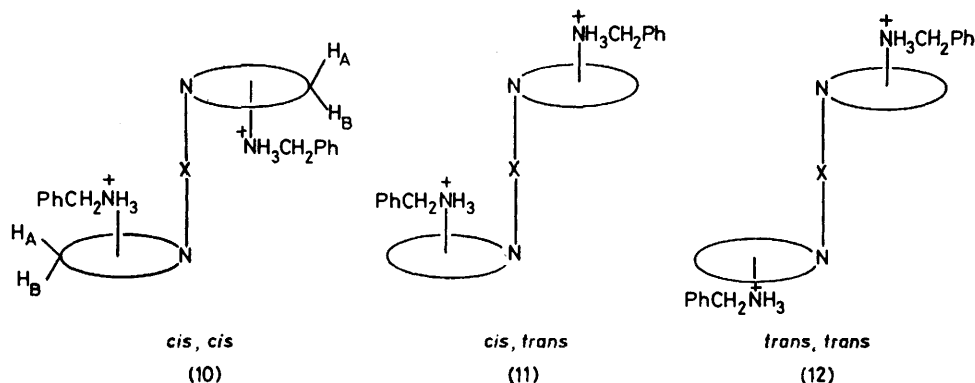
TABLE 6

N.m.r. spectra ^a of the complexes of the hosts (4a—g) with benzylammonium thiocyanate

Host	X in (4, n = 2)	G : H ratio	Temp. (°C)	Host spectrum						Guest spectrum		
				OCH ₂ ^{b,c}	NCH ₂ ^c	α ^d	β ^d or aryl	γ ^d or aryl	δ ^d	CH ₂	NH ₃ ⁺	
(4a)	[CH ₂] ₄	1 : 1	25	3.4—3.8(m)	2.69	2.43	1.37					
(4a)	[CH ₂] ₄	1 : 1	25	3.63(m), 3.51(s)	2.69	2.58	1.42				4.03	
			-60	^e	2.61(br)	ca. 2.6, 2.30	ca. 1.4	1.15,			3.98	8.31
(4a)	[CH ₂] ₄	2 : 1	25	3.63(m), 3.48(s)	2.69	2.63	1.40				4.03	
			-60	3.5—3.6(m) 3.53 3.32 } 3.78 3.60 }	ca. 2.60(br)	[2.6], ^f 2.23	1.18, [1.35] ^f				3.93	8.09
(4b)	[CH ₂] ₅	1 : 1	25	3.5—3.8(m)	2.78	2.55	1.48	1.28				
(4b)	[CH ₂] ₅	1 : 1	25	3.60(s), 3.49(s)	2.67	2.44	1.43	1.18			4.00	
			-60	^e 3.58(t)	2.67(br)	2.45, 2.28	1.42	ca. 1.2, ca. 1.0			3.97	8.33
(4b)	[CH ₂] ₅	2 : 1	25	3.61(m), 3.40(s)	2.67	2.42	1.43	1.12			4.00	
			-60	3.59(t) 3.52 3.29 } 3.82 3.52 }	2.59(br)	2.26(br)	1.40	0.97			3.97	8.30
(4c)	[CH ₂] ₆	1 : 1	25	3.60(m) 3.4—3.8(m)	2.69	2.44	1.1—1.7(m)					
(4c)	[CH ₂] ₆	1 : 1	25	3.58(s), 3.48(s)	2.62	2.37	1.40	1.18			4.00	
			-60	^e 3.53(t)				1.33, 1.20	1.20, 1.00		3.95	8.21, 8.35
(4c)	[CH ₂] ₆	2 : 1	25	3.63(s), 3.43(s)	2.65	2.38	1.42	1.18			4.00	
			-60	3.56(t) 3.60 3.33 } 3.76 3.46 }	2.52	2.03	1.31	1.00			3.93	8.29
(4d)	[CH ₂] ₇	1 : 1	25	3.4—3.9(m)	2.75	2.68	1.1—1.7(m)					
(4d)	[CH ₂] ₇	1 : 1	25	3.61(s), 3.49(s)	2.66	2.43	1.40	1.25	1.25		3.99	
			-60	^e 3.57(t)	2.60	2.45, 2.26	1.40	1.23	1.23		3.98	8.30
(4d)	[CH ₂] ₇	2 : 1	25	3.62(m), 3.40(s)	2.65	2.43	1.40	1.20	1.20		3.99	
			-60	3.57(t) 3.60 3.30 } 3.82 3.51 }	2.55	2.21	1.32	1.11	ca. 1.25		3.95	8.23
(4e)	<i>m</i> -CH ₂ C ₆ H ₄ CH ₂	1 : 1	25	3.67(m)	2.79	3.62	7.22(m)					
		2 : 1	25	3.63(m), 3.50(s)	2.71	3.63	^e				3.84	
			-60	3.46(s) 3.57 3.33 } 3.93 3.57 }	2.71, 2.50	^e	^e				ca. 3.75	8.25
(4f)	<i>p</i> -CH ₂ C ₆ H ₄ CH ₂	1 : 1	25	3.65(m)	2.79	3.65	7.22					
		2 : 1	25	3.60(m), 3.50(s)	2.65	3.60	7.25				3.89	
			-80	^e	2.63, 2.35	^e					ca. 3.8	8.20
		2 : 1	25	3.63(m), 3.45(s)	2.61	3.63	7.27				3.87	
			-60	3.55(s) 3.63, 3.35 } 3.50 }	2.63, 2.40	ca. 3.6	7.25				3.79	8.13
(4g)		1 : 1	25	3.4—3.8(m)	2.82	3.81	7.68(s)	7.4—7.8 (AB system)				
		2 : 1	25	3.60(m), 3.48(s)	2.70	3.76	7.83(s)	7.77, 7.35 (AB system)			3.83	
			-60	^e	2.70, 2.40	^e	^e	^e			ca. 3.7	8.22
		2 : 1	25	3.60(m), 3.42(s)	2.69	3.75	7.96(s)	7.82, 7.35 (AB system)			3.82	
			-60	ca. 3.6(m), 3.28 } 3.50 }	2.70, 2.41	^e	7.82(s)	7.80, ca. 7.4 (AB system)			3.72	8.15



^a Spectra run at 220 MHz for CD₂Cl₂ solutions unless otherwise stated, for ca. 0.1M solutions. ^b Signals bracketed together in low temperature data coalesce at higher temperatures (*E* + *I* fast). ^c Triplet signals from the system NCH₂CH₂O at 25 °C have *J* ca. 6 Hz. ^d α, β, γ, δ refer to the methylene groups in the bridge X in the sequence NCH₂(α)-CH₂(β)-CH₂(γ)-CH₂(δ). ^e Signals either too complex or obscured by other signals in the spectrum. ^f Minor signals, probably the result of imperfect 2 : 1 stoichiometry. ^g The spectrum was examined at -60 °C but was poorly defined.



chemical shifts intermediate between those of the free host and the 2 : 1 complex (Table 6). The temperature dependence of the n.m.r. spectrum could be associated with macrocycles that are complexed and free, but it is

not possible to judge whether the solution contains entirely the 1 : 1 complex (13), having one free crown ring and one complexed crown ring, or whether it consists of an equilibrium mixture of the free host, the 1 : 1 complex (13), and the 2 : 1 complex (10). The energy barrier for process *E*, involving guest exchange between free and complexed host macrocycles (ΔG^\ddagger 11.0 kcal mol⁻¹) is lower than that for the process *E* + *I*. This relationship is consistent with process *E* involving either intramolecular guest exchange, (13a) \rightleftharpoons (13b), or intermolecular guest exchange if the rate-determining process for the exchange is dissociation.

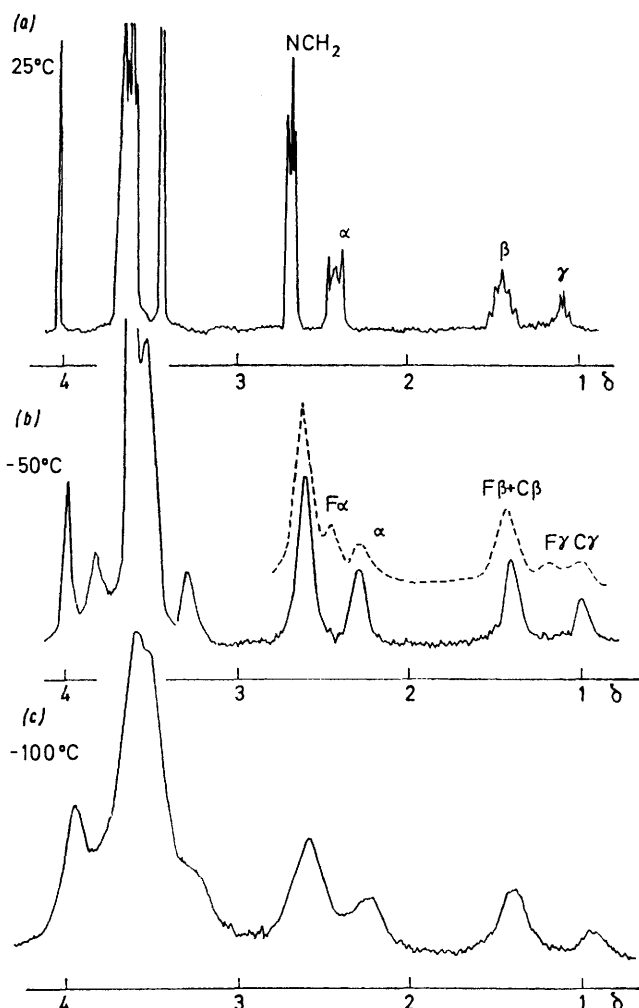
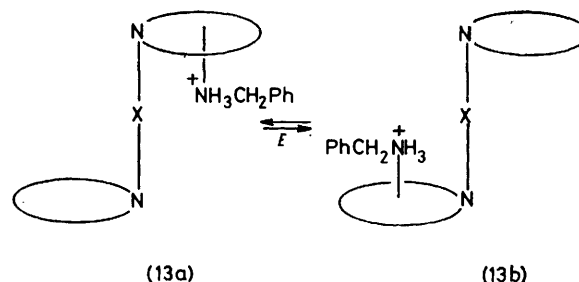


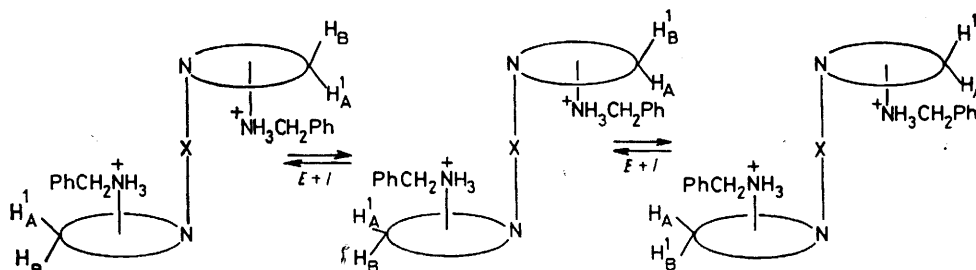
FIGURE 1. N.m.r. spectrum (220 MHz) of the OCH_2 , NCH_2 , and $\text{N}[\text{CH}_2]_5\text{N}$ protons of host (4b) complexed with 2 mol equiv. of benzylammonium thiocyanate at (a) 25, (b) -50 , and (c) -100 °C. The broken line in (b) shows the spectrum using 1 mol equiv. of benzylammonium thiocyanate; signals labelled F and C are associated with bridge methylene groups close to free and complexed macrocycles respectively.



The n.m.r. spectra of the other complexes of benzylammonium thiocyanate formed by the hosts (4a–g) show similar features (Table 6) to those described above for the complexes of the host (4b). This is particularly well illustrated by the host (4f). At low temperatures (< -40 °C) the n.m.r. spectrum of the 2 : 1 complex shows a clear separation of the NCH_2 signal into two broad signals, corresponding to H_A and H_B in the structure (10) and Scheme 1. The spectrum of a solution containing a 1 : 1 G : H ratio shows the same two signals at low temperatures, together with a third broad NCH_2 signal associated with an uncomplexed macrocycle. The temperature dependence of the n.m.r. spectra of solutions containing a 2 : 1 (G : H) ratio of guest and host components indicates in all cases (4a–g) that only a single type of complex is present in the solution. The process *E* + *I* becomes slow on the n.m.r. time scale for all the complexes studied at temperatures below *ca.* -30 °C, as indicated by line-shape changes in the OCH_2 and NCH_2 regions (Table 6). There is, however, no further signal separation at very low temperatures that can be assigned to slow conformational changes in the

fifteen-membered ring, with simultaneous hydrogen bond reorganisation, as found for the monocyclic systems.¹

The spectral behaviour of the solutions containing a 1 : 1 (G : H) ratio of the two components is more complex but in general it resembles that shown by the 1 : 1 complex of host (4b). It is consistent with the presence of free and complexed crown ether rings, but the distinction between a 1 : 1 complex (13) and an equilibrium mixture of 2 : 1 (10) and 1 : 1 (13) complexes and the free host is difficult to make. In the case of the host (4c),



SCHEME 1 The process $E + I$ for the 2 : 1 (G : H) complex of a bis(mono-aza)crown ether. Hydrogen atoms in a ring methylene group are identified as H and H¹ so that the inversion process can be recognised

however, the presence of two signals at -60°C , assignable to the NH_3^+ group of the guest cation, indicates the presence of at least two types of complex, possibly (10) and (13). The diamides (6a) and (6b) were also examined but no positive evidence was obtained indicating complex formation with benzylammonium thiocyanate.

(b) 18-Crown-6 derivatives (4h—m) as host molecules. The spectral behaviour of the complexes of the 18-crown-6 analogues (4h—m) with benzylammonium thiocyanate was generally more complex than that of the 15-crown-5 derivatives (4a—g) (Table 7). Thus the spectra of solutions containing a 2 : 1 (G : H) ratio of the two components showed complex changes at low temperatures in signals assignable to the protons of the macrocycles and the bridging groups (Table 7). Some of the changes in the spectrum of the macrocycle are assignable to the process $E + I$, but other spectral changes, particularly those associated with the protons of the bridging group, must be assigned to the interconversion of the three diastereoisomeric complexes (10), (11), and (12). The signal assignments are, however, less straightforward than those made previously for complexes of mono-aza¹ and di-aza-18-crown-6 systems³ and it is not, for example, possible to detect the four sets of guest signals expected from the three complexes. The energy barrier for the process $E + I$, in cases where it is detectable from changes in the signals from the OCH_2 and NCH_2 groups of the macrocycle, is higher than the barrier associated with the interconversion of the three types of complex. The latter process presumably involves guest exchange and inversion at the nitrogen atom of the macrocycle.

The spectra of solutions containing a 1 : 1 (G : H) ratio of ammonium salt to host are very complex at low temperatures. This behaviour is not surprising, since the solutions might be expected to contain free host

molecules together with a mixture of the diastereoisomeric 2 : 1 complexes (10), (11), and (12) and the two possible diastereoisomeric 1 : 1 complexes.

The above results establish that both macrocycles in the bis(crown ethers) (4a—m) are available for complex formation with a guest primary alkylammonium cation. On the basis of approximate energy barriers for the processes $E + I$ and E the free energy of association for each molecule of the guest cation is similar to that observed¹ for complex formation by the monocyclic

aza-crown ethers examined in our earlier work.* It was therefore reasonable to expect that the host systems (4) would prove to be excellent hosts for bis(primary alkylammonium)salts and an investigation of complexes of this type is described in the next section of this paper.

(ii) Bis(primary alkylammonium) Thiocyanates as Guest Molecules.—Most studies of this type were carried out using the dithiocyanate salt (14) of *meta*-xylylene diamine. This was chosen both as an analogue of benzylammonium thiocyanate, which was used in the first part of our investigation, and also because it acts as a 'shift reagent' due to the well known magnetic anisotropy of the aromatic ring. A few investigations were also made using the dithiocyanates (15) of polymethylene diamines, but in general the results for guest salts of this type were more satisfactory when the bridging group, X, of the host (4) included an aromatic ring. The results of studies using the guest (15) will be presented in a future paper when related studies using polycyclic host molecules will be described.¹³ Although the complexes of benzylammonium thiocyanate were freely soluble in deuteriomethylene chloride the salt (14) proved to be rather insoluble. Complexes were therefore prepared using deuteriomethylene chloride containing a little deuteriomethanol. The spectroscopic results did not appear to be critically dependent upon the deuteriomethanol concentration, provided that sufficient was added to maintain a homogeneous solution over the temperature range used in the study.

The spectra of the complexes of the hosts (4a—f) with the salt (14) will be discussed first. The n.m.r. spectra of these complexes and their temperature dependence proved to be strikingly different from those of the benzyl-

* For a discussion on the relationship between the energy barriers for these processes and the association energy of the complex see Part 3 of this series (ref. 2b).

ammonium thiocyanate complexes (Tables 6 and 8, Figures 1 and 2). Thus the spectrum of the host molecule (4a) in the complex with the salt (14) (1 : 1, G : H ratio) at 25 °C showed marked shifts to high field of the signals of the bridging groups (α -CH₂, 1.89;

that a conformational change in the complex became slow on the n.m.r. time scale [Figure 2(d) and Table 8]. There was, however, no sign of more than one species of complex on the basis of the n.m.r. spectrum of the guest molecule. These changes, at low temperatures, in the

TABLE 7
N.m.r. spectra ^a of the complexes of the hosts (4h—m) with benzylammonium thiocyanate

Host	X in (4; n = 3)	G : H ratio	Temp. (°C)	Host spectrum					Guest spectrum		
				OCH ₂ ^{b,c}	NCH ₂ ^e	α ^d	β ^d or aryl	γ ^d or aryl	δ ^d	CH ₂	NH ₃ ⁺
(4h)	[CH ₂] ₄		25	3.6—3.8(m)	2.76	2.51	1.44				
(4h)	[CH ₂] ₄	1 : 1	25 ^e	3.5—3.7(m)	2.70	2.41	1.31			4.00	
(4h)	[CH ₂] ₄	2 : 1	25	3.55—3.8(m)	2.72	2.57	1.30			4.00	
			−80	3.5(m) ca. 3.6, ca. 3.4 ca. 3.6		ca. 2.6, 1.98, 2.18	1.15, 0.95, 0.80			3.94, ca. 4.00 (−70 °C)	8.05, 7.95 (−70 °C)
(4i)	[CH ₂] ₅		25	3.4—3.8(m)	2.72	2.48	1.1—1.7(m)				
(4i)	[CH ₂] ₅	1 : 1	25	3.60(s), 3.55(m)	2.67	2.44	1.35	1.27		3.96	
			−80			2.35(F) ca. 1.9(C)	1.45(F) 1.15(C)	ca. 1.2(F) 0.8(C)		3.90	8.00
(4i)	[CH ₂] ₅	2 : 1	25	3.55—3.7(m) 3.48(m)	2.69	2.48	1.30	1.10		3.98	
			−65		2.54, 2.65	ca. 2.5, 1.93, 1.83	ca. 1.1, 0.8, 0.5	ca. 1.0, 0.8, 0.5		3.86, 3.93	7.95
(4j)	[CH ₂] ₆		25	3.4—3.7(m)	2.70	2.47	1.43	1.29			
(4j)	[CH ₂] ₆	1 : 1	25 ^e	3.64(s), 3.60(m)	2.71	2.49	1.39	1.27		4.00	
(4j)	[CH ₂] ₆	2 : 1	25 ^e	3.55—3.80(m) 3.50(m)	2.70	2.50	1.30	1.22		4.00	
			−75		2.5—2.8 (br m)	ca. 2.6, [ca. 2.3] 1.95	1.28	1.16, 0.93 0.80		3.94(br)	8.04
(4k)	[CH ₂] ₇		25	3.5—3.8(m)	2.73	2.47	1.1—1.7(m)				
(4k)	[CH ₂] ₇	1 : 1	25 ^e	3.58(t), 3.59(s), 3.55(s)	2.70	2.45	1.32	1.23	1.23	3.95	
(4k)	[CH ₂] ₇	2 : 1	25	3.55—3.75(m) 3.50(m)	2.70	2.45	1.30	1.23	1.23	3.97	
			−70		2.69, 2.55	ca. 2.55, 1.90	1.20	ca. 1.20, 0.82		3.90(br)	8.00
(4l)	<i>m</i> -CH ₂ C ₆ H ₄ CH ₂	1 : 1	25	3.4—3.8(m)	2.75		7.21				
			25 ^e	3.5—3.7(m)	2.68		7.1— 7.35(m)			3.99	
		2 : 1	25	3.79(m), 3.57(m)	2.65		7.05— 7.35(m)			4.01	
			−70							3.93(br)	7.80, 7.95
			−90							3.91(br)	7.98, 7.83 7.77
(4m)	<i>p</i> -CH ₂ C ₆ H ₄ CH ₂	1 : 1	25	3.5—3.9(m)	2.79		7.26				
			25 ^e	3.60(m), 3.55(m)	2.70		7.23			3.99	
		2 : 1	25	3.5—3.7(m)	2.65		7.18			4.02	
			−80				7.11, 7.02			ca. 3.91, ca. 4.10(br)	7.97, 7.82

^{a-d} See Table 6. ^e The spectra of all 1 : 1 complexes were run at low temperatures. The observed signals were consistent with complexed and free macrocycles but were not sufficiently well resolved for the details to be reported.

β -CH₂, δ 0.90) as compared with the analogous chemical shifts for the complex with benzylammonium thiocyanate (2 : 1, G : H ratio) [α -CH₂, 2.63; β -CH₂, δ 1.40, see Figure 2(a) and (b)]. As the temperature was lowered small changes in the OCH₂ region suggested that inversion of the complexed macrocycles became slow on the n.m.r. time scale. Finally at very low temperatures (< −80 °C) a complex series of changes in the spectrum of the NCH₂ groups and the bridging β -CH₂ groups suggested

spectrum of the host were observed only for the complex with the salt (14) (see below for further examples) and were not observed for the complex with benzylammonium thiocyanate [Figure 2(c)].

The spectrum of the complex formed by the host (4b) with the salt (14) showed rather similar characteristics (Table 8). Thus at 25 °C the signals assignable to the bridging polymethylene chain (α -CH₂, 2.10; β -CH₂, 0.89; δ -CH₂, δ 0.89) were at significantly higher fields

TABLE 8
N.m.r. spectra ^a (220 MHz) of the complexes of the hosts (4a—f) with the salt (14)

Host (4a)	X in (4) [CH ₂] _n	G : H ratio	Temp. (°C)	Host spectrum					Guest spectrum			
				OCH ₂	NCH ₂ ^b	α ^c	β ^c or aryl	γ ^c or aryl	δ ^c	aryl-H	NH ₃ ⁺	
(4a)	[CH ₂] ₄	1 : 1	25	3.68(s), 3.58(t)	2.53	1.89	0.90			4.08(s), 7.56(m), 7.90(s)		
			-80	3.2—3.9(br)	2.48	1.72	0.89			4.00(br), 7.5—7.7(m)	8.29	
			-100			2.60(br), 2.40(br) <i>ca.</i> 1.5	1.82(br) <i>ca.</i> 0.8	1.0(br) <i>ca.</i> 0.8			7.80(s)	
(4b)	[CH ₂] ₅	1 : 1	25	3.68 (s), 3.54(t)	2.55	2.10	0.89	0.89		4.06(s), 7.48, 7.58 (AB ₂ system), 7.74(s)		
			-40	3.4—4.0(m)	2.49	2.00	0.69	0.83		4.04(s), 7.50, 7.64 (AB ₂ system), 7.62(s)	8.07	
			-105			2.98, 2.80 <i>ca.</i> 2.3, 2.05	2.06, 1.75	<i>ca.</i> 0.9	<i>ca.</i> 0.9		7.53, 7.72 (AB ₂ system)	8.07
(4b)	[CH ₂] ₅	0.5 : 1	25	3.65(s), 3.60(s) 3.56(t)	2.64	2.32	<i>ca.</i> 1.20	<i>ca.</i> 1.20		7.56(s) 4.08(s), 7.48, 7.58 (AB ₂ system)		
			-40 ^d			2.71(F)	2.51(F)	1.50(F)	1.20(F)		7.79(s) 4.06(s), 7.50, 7.66 (AB ₂ system), 7.64(s)	8.09
						2.51(C)	2.02(C)	0.72(C)	0.85(C)		4.06(s), 7.47(s) 7.69(s)	
(4c)	[CH ₂] ₆	1 : 1	25	3.66(s), 3.63(s) 3.55(t)	2.61	2.30	1.05	1.05		4.03(s), 7.52(s)	8.25 } 8.40 }	
			-60	<i>ca.</i> 3.7(m), 3.50(m)	2.58	2.19		0.95 } ^e 1.25 }		7.2(s) } ^e 7.72(s) }		
(4d)	[CH ₂] ₇	1 : 1	25	3.66(s), 3.60(s) 3.54(t)	2.66	2.42	1.39	1.20	1.20	4.06(s), 7.44(s) 7.69(s)		
			-70	3.70(m), 3.53(m)	2.65	2.40	1.39	<i>ca.</i> 1.21	<i>ca.</i> 1.21	4.03(s) } ^f 4.06(s) } 7.52(m) } ^f 7.60(m) } 7.60(s) } ^f 7.71(s) }	8.35 } 8.45 }	
(4e)	<i>m</i> -CH ₂ C ₆ H ₄ CH ₂	1 : 1	25	3.66(s), 3.58(m)	2.70		7.19, 7.34 (AB ₂ system) 7.06(s)			4.01(s), 7.50(s) 7.71(s)		
			-70 ^g			2.80(br) 2.50(br)						
(4f)	<i>p</i> -CH ₂ C ₆ H ₄ CH ₂	1 : 1	25	3.65(m), 3.70(s)	2.71		7.20(s)			4.07(s), 7.50(m) 7.73(s)		
			-70 ^g			2.76(br) 2.50(br)					<i>ca.</i> 4.0(br), 7.60(m) <i>ca.</i> 7.5(br) } <i>ca.</i> 7.8(br) }	

^a For *ca.* 0.1M solutions in CD₂Cl₂ containing a little CD₃OD. ^b t, *J ca.* 6 Hz at 25 °C; broad signals at low temperatures. ^c α, β, γ, δ refer to the methylene groups of X labelled as NCH₂(α)CH₂(β)CH₂(γ)CH₂(δ) ^d Signals labelled (F) and (C) assignable to free and complexed host respectively. ^e Upper signal for major species, lower signal for minor species. ^f Signals for two species in *ca.* 1 : 1 ratio. ^g Signals not listed are too broad for confident assignment.

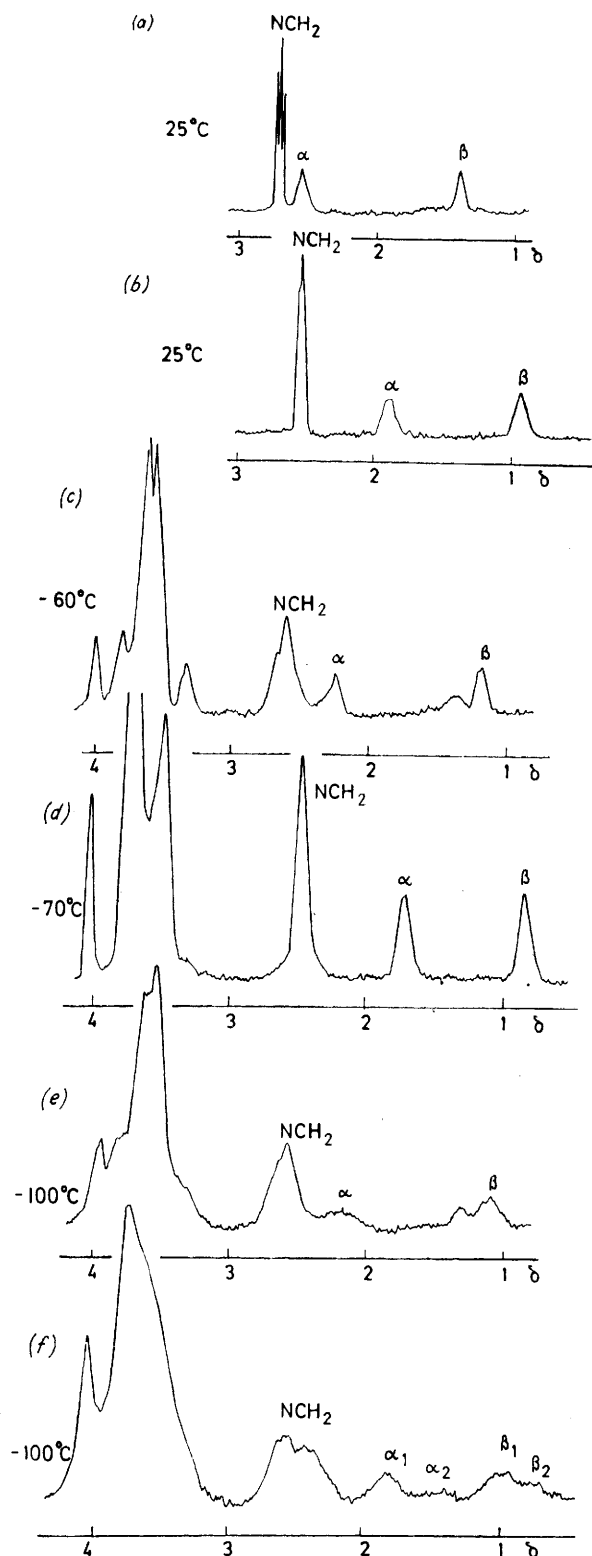


FIGURE 2 N.m.r. spectrum (220 MHz) of the NCH_2 and $\text{N}[\text{CH}_2]_4\text{N}$ protons of host (4a) complexed with the bis-(primary alkylammonium) thiocyanate (14) at (a) 25, (d) -70, and (f) -100°C; and with benzylammonium thiocyanate (2:1, G:H ratio) at (a) 25, (c) -60, and (e) -100°C

than those of the analogous signals in the spectrum of the complex with benzylammonium thiocyanate ($\alpha\text{-CH}_2$, δ 2.42; $\beta\text{-CH}_2$, 1.43; $\gamma\text{-CH}_2$, δ 1.12). As the temperature was decreased the OCH_2 region showed considerable changes [Figure 3(a-c)] and it was evident that ring inversion became slow on the n.m.r. time scale. Finally

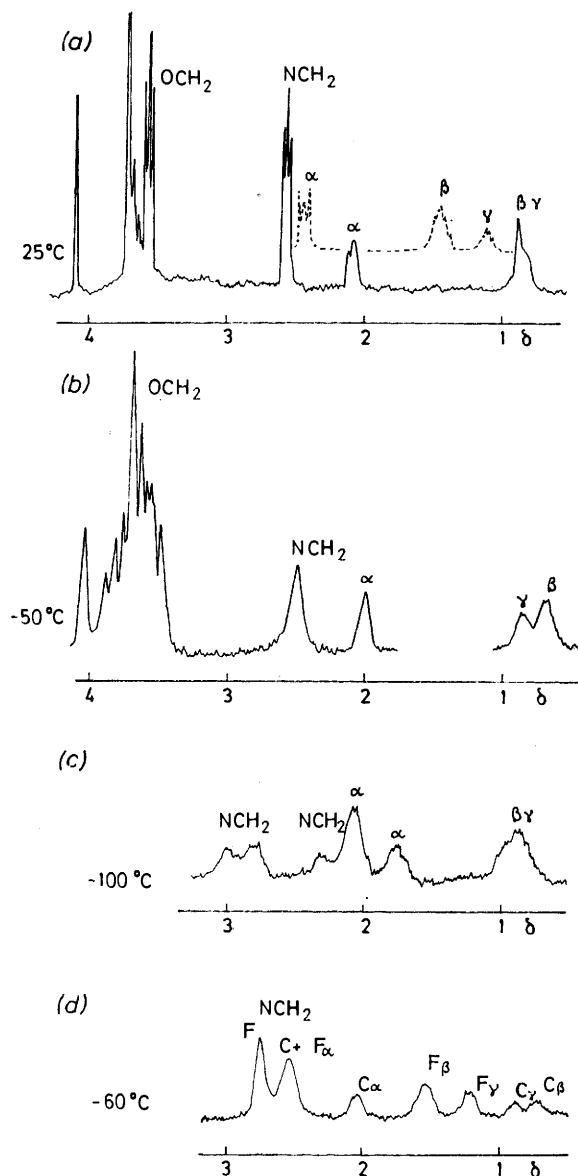


FIGURE 3 N.m.r. spectrum (220 MHz) of OCH_2 , NCH_2 , and $\text{N}[\text{CH}_2]_5\text{N}$ protons of host (4b) complexed with the bis-(primary alkylammonium) thiocyanate (14) at (a) 25, (b) -50, and (c) -100°C. Spectrum (d) is for a sample containing host (4b) and 0.5 mol equiv. of the guest (14) at -60°C. The broken line above spectrum (a) is the spectrum of the benzylammonium thiocyanate complex (2:1, G:H ratio)

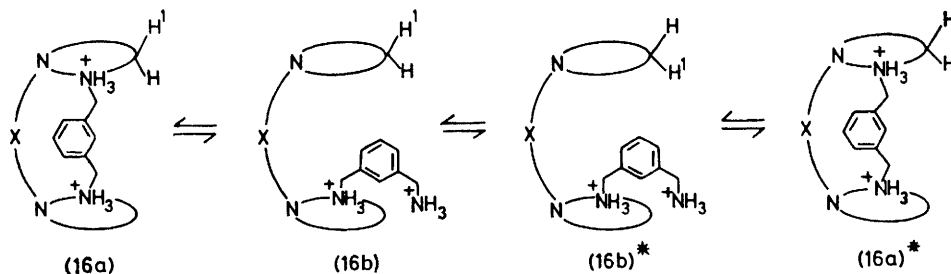
at very low temperature ($< -80^\circ\text{C}$) the spectrum of the host showed further changes, analogous to those shown by the complex of host (4a), probably indicating hindered conformational changes within the complex.

The interpretation of this spectral behaviour in the terms of a strongly-bound complex, having a substantial

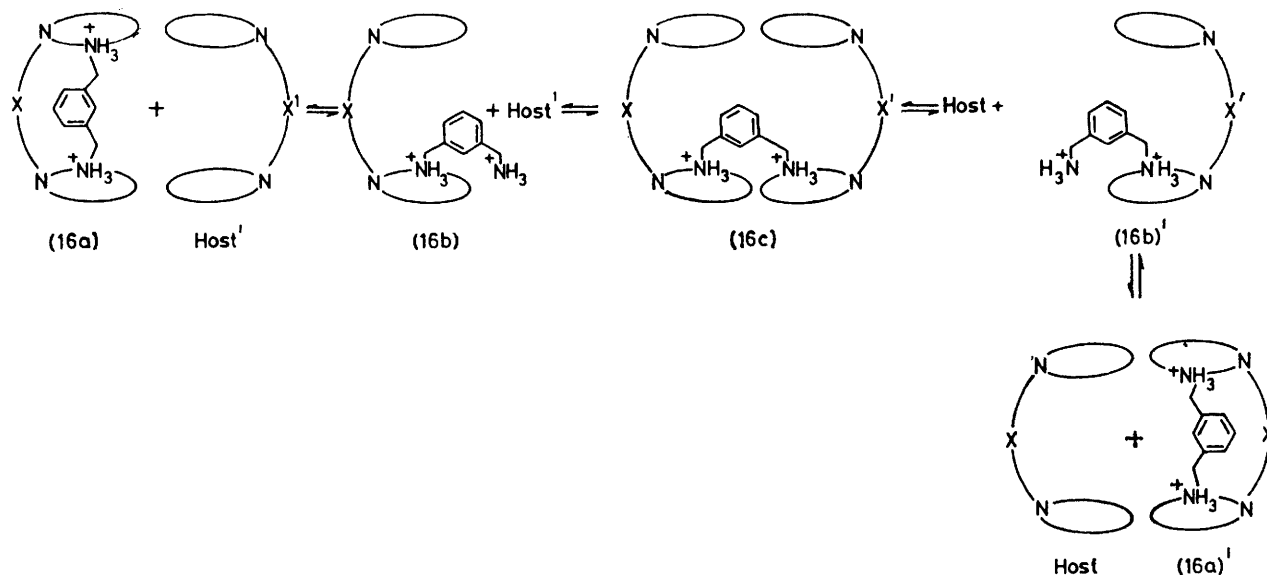
barrier to the ring-inversion process † involving the sequence $(16a) \rightleftharpoons (16b) \rightleftharpoons (16b)^* \rightleftharpoons (16a)^*$ (Scheme 2), was supported by examining the spectrum of the same complex, using an excess of the host molecule

molecule between two different host molecules involves a substantial energy barrier (ΔG^\ddagger 12.5 kcal mol⁻¹), of the same order as that found for the ring-inversion process $(16a) \rightleftharpoons (16a)^*$.

(a) Host inversion

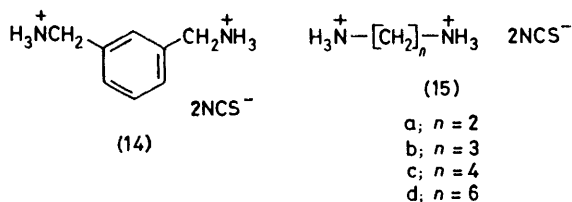


(b) Host exchange



SCHEME 2

(0.5 : 1, G : H ratio). At 25 °C the chemical shifts of the host molecule were intermediate between those of the complex (1 : 1, G : H ratio) and the free host, but at



temperatures below 0 °C separate signals were observed for the free and complexed host (4b) [Figure 3(d)]. This result indicates that the exchange of the guest

† The process $(16a) \rightleftharpoons (16a)^*$ involves inversion of only a single ring of the host, the process observed spectroscopically corresponds to the inversion of both rings by the stepwise process $(16a) \rightleftharpoons (16a)^* \rightleftharpoons (16a)^{**}$.

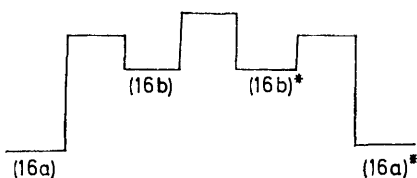
This is consistent with the same intermediate (16b) being involved in both processes, as outlined in Scheme 2‡, with the exchange pathway, $(16a) + \text{Host}' \rightleftharpoons (16b) + \text{Host}' \rightleftharpoons (16c) \rightleftharpoons (16b)' + \text{Host} \rightleftharpoons (16a)' + \text{Host}$, involving a further intermediate (16c) in which the guest dication is bound to two host molecules. The actual relationship between the free energies of activation measured for these two pathways and the free energy of association at each of the two binding

‡ Scheme 2 is an attempt to show the relationship between these two processes. The individual formulae (16a–c) are only intended to indicate guest–host binding in the various species and do not have conformational significance. The symbols H and H', X and X' are used to distinguish between different hydrogen atoms and bridging groups involved in the site-exchange process. (16a) and (16a)' are used to denote the complex before and after guest exchange from Host to Host'. (16a) and (16a)* are used to denote the complex before and after inversion of one of the host macrocycles.

sites is difficult to assess; some of the measured activation energy must correspond to the activation energy for either of the association processes $(16b) \rightarrow (16a)$ and $(16b) + \text{Host}' \rightarrow (16c)$. Diagrams giving free energy profiles for both processes are shown in Figure 4.

The process $(16a) \rightleftharpoons (16a)^*$ has some similarity to the process $E + I$, recognised¹⁻³ for complexes of simple monocyclic hosts, but the process $(16a) \rightleftharpoons (16a)'$ has, of course, no analogy in any of the processes studied in our earlier work. The relative energies of the intermediate states, $(16b) + \text{Host}$ and $(16c)$, are obviously as

(a) Host inversion



(b) Host exchange

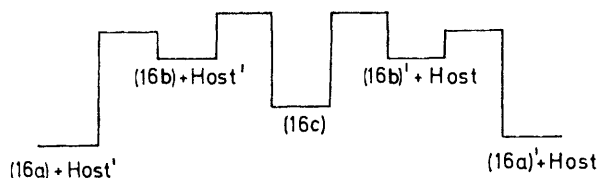


FIGURE 4 Free-energy profiles for the processes outlined in Scheme 2. (a) $(16a) \rightleftharpoons (16a)^*$ and (b) $(16a) + \text{Host}' \rightleftharpoons (16a)' + \text{Host}$

shown in Figure 4(b) and the spectroscopic results indicate that the state $(16a) + \text{Host}'$ is at a lower energy than $(16c)$. The relationship between the two types of transition state is not available readily from the experimental results but in view of the measured activation energy the relationship appears to be as depicted in Figure 4(b). These considerations also indicate clearly that the total binding energy in the 1:1 complex [*cf.* $(16a)$] is substantial.

The spectrum of the complex of the host (4c) with the salt (14) at 25 °C showed high-field chemical shifts for some of the protons of the bridging methylene groups ($\alpha\text{-CH}_2$, 2.30; $\beta\text{-CH}_2$, 1.05; $\gamma\text{-CH}_2$, δ 1.05) as compared with the chemical shifts of the analogous protons in the benzylammonium thiocyanate complex ($\alpha\text{-CH}_2$, 2.38; $\beta\text{-CH}_2$, 1.42; $\gamma\text{-CH}_2$, δ 1.18). The changes were more marked for the β - and $\gamma\text{-CH}_2$ groups, in contrast to the hosts (4a) and (4b) in which the $\alpha\text{-CH}_2$ groups were also affected. As the temperature of the solution was lowered to -60 °C the spectrum showed changes consistent with the presence of two different types of com-

plex (Table 8). The major complex was associated with high-field signals (δ 0.95) for the β - and $\gamma\text{-CH}_2$ groups of the bridge and the minor complex showed a signal at lower field (δ 1.25) for these groups. On the basis of these chemical shifts it seems likely that the major complex is an intramolecular complex, similar to those formed by the hosts (4a) and (4b), and the minor complex is a polymeric complex involving complexation of each dication by a macrocycle from each of two host molecules. The presence of two different complexes was also indicated by two pairs of signals at -60 °C from the guest NH_3^+ group and H-2 of the aromatic ring of the guest (Table 8). The spectrum showed no further changes, other than line-broadening, as the temperature was lowered to -100 °C in contrast with the spectra of the complexes formed by hosts (4a) and (4b).

The complex of the host (4d) with the dication (14) showed similarities in its spectral behaviour to the complex of host (4c). In particular, at -70 °C the guest molecule gave signals corresponding to two different complexes in approximately a 1:1 ratio (Table 8). The spectrum of the host system at 25 °C showed chemical shifts for the bridging methylene groups ($\alpha\text{-CH}_2$, 2.40; $\beta\text{-CH}_2$, 1.39; $\gamma\text{-CH}_2$, *ca.* 1.21; $\delta\text{-CH}_2$, δ *ca.* 1.21) similar to those of the analogous groups in the complex of (4d) with benzylammonium thiocyanate ($\alpha\text{-CH}_2$, 2.43; $\beta\text{-CH}_2$, 1.40; $\gamma\text{-CH}_2$, *ca.* 1.20; $\delta\text{-CH}_2$, δ *ca.* 1.20). The spectrum of this complex showed no further changes, other than line-broadening, as the temperature was lowered to -100 °C.

The n.m.r. spectra of the complexes formed by the hosts (4e) and (4f) with the salt (14) were less informative because the spectral lines became very broad at low temperatures. The chemical shifts of the host components (4e) and (4f) in these complexes were not very different from those of the same hosts in the complexes with benzylammonium thiocyanate. The spectra of the complexes at -70 °C showed two sets of signals for the CH_2N groups of the macrocycle indicating that the ring inversion process [*cf.* $(16a) \rightleftharpoons (16a)^*$, Scheme 2] was slow on the n.m.r. time scale at low temperatures (ΔG^\ddagger 10.5 kcal mol⁻¹). In the case of the host (4f) there was some evidence for more than one type of complex but the spectral lines at low temperatures were not sufficiently well resolved to be definitive.

The above results indicate that the formation of an intramolecular complex, shown diagrammatically in $(16a)$, requires a good fit between the guest and host components. This fit appears to be almost equally good for the hosts (4a) and (4b) with the guest (14), but it deteriorates rapidly along the series (4b), (4c), and (4d). The changes observed in the n.m.r. spectra of the complexes of (4a) and (4b) at very low temperatures appear to be characteristic of intramolecular complexes in which the guest and host components fit together well. It is not possible to determine which of the possible conformational changes should be associated with these changes. These conclusions are supported by studies using CPK space-filling molecular models; assuming that hydrogen

bonding between the guest and host components involves the nitrogen atom of the macrocycle and one of the oxygen atoms, as believed to be the case for the monocyclic mono-aza-15-crown-5 system,¹ the hosts (4a) and (4b) provide crown rings at a suitable spacing to interact with both of the $-\text{NH}_3^+$ groups of the salt (14). The hosts (4c) and (4d) have bridges that are too long, in an extended conformation, to fit the salt (14) and evidently

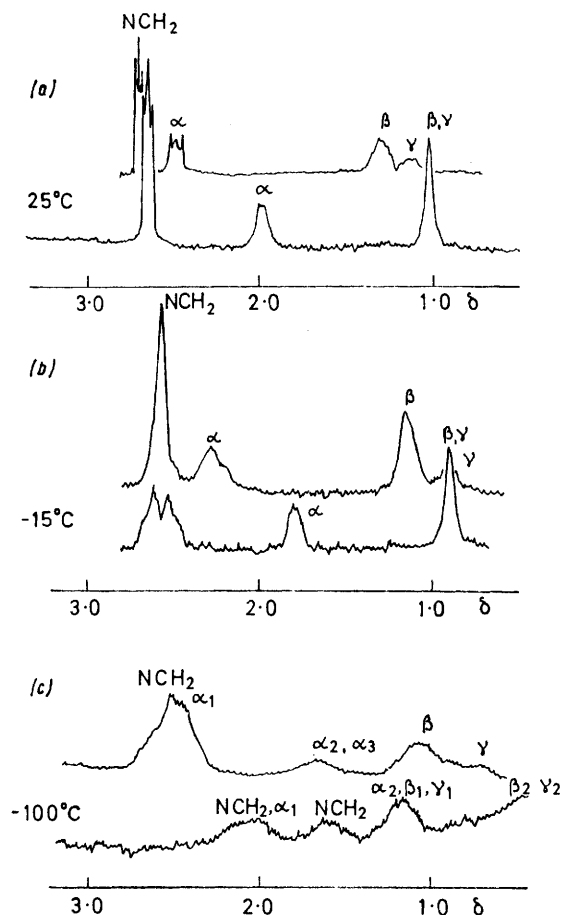


FIGURE 5 N.M.R. spectrum (220 MHz) of NCH_2 and $[\text{CH}_2]_5\text{N}$ protons of host (4i) complexed with the bis(primary alkylammonium) thiocyanate (14) at (a) 25, (b) -15 , and (c) -100 °C. In each case the upper spectrum is the spectrum of the benzylammonium thiocyanate complex (2 : 1, G : H ratio)

in these cases the intermolecular complex competes with the intramolecular complex.

In spite of the substantial binding energy associated with the two binding sites utilised in the formation of an intramolecular complex (16a) it is not possible, on the basis of the kinetic studies reported in this paper, to observe directly the consequences of this high binding energy. Due to the stepwise nature of both the exchange and inversion processes, which is evident from Scheme 2 and Figure 4, the kinetic results are more directly related to the binding energy for a single complexed NH_3^+ group. This is clearly of the same order as that found for the complexes of a mono-aza-15-crown-5 system with a simple primary alkylammonium salt. These con-

clusions also imply that secondary binding interactions⁸ are not generally detectable by kinetic methods unless they are so strong that they lead to slow dissociation, on the n.m.r. time scale, at the secondary binding site as well as at the primary binding site. The implications of these results will be further explored.

The 18-crown-6 derivatives (4h) and (4i) were not expected to be so effective as the 15-crown-5 derivatives in forming intramolecular complexes with the dication (14). An intramolecular complex [cf. (16a)] clearly requires a *cis*-relationship between the guest and the bridge at each of the macrocycles; although this *cis*-relationship is usually found for 15-crown-5 systems both *cis*- and *trans*-complexes are found for aza-derivatives of 18-crown-6 systems.

The n.m.r. spectra of complexes formed between hosts (4h-i) and the salt (14) were not completely definitive, but the spectral evidence suggested that both (4h) and (4i) formed at least some intramolecular complex. Thus the spectrum of the complex of the host (4h) with the salt (14) at 25 °C showed significant upfield shifts of the signals assignable to the protons of the bridging methylene groups ($\alpha\text{-CH}_2$, 1.98; $\beta\text{-CH}_2$, δ 1.17) as compared with the analogous signals in the complex with benzylammonium thiocyanate ($\alpha\text{-CH}_2$, 2.51; $\beta\text{-CH}_2$, δ 1.44). At lower temperatures the signal from the NCH_2 group of the host macrocycle split into two signals, indicating that the process analogous to (16a) \rightleftharpoons (16a)* had become slow on the n.m.r. time scale. The other signals assignable to the host molecule broadened at low temperatures but did not show any other recognisable temperature dependence; however, the guest NH_3^+ signal appeared as two broad singlets at low temperatures. This result is consistent with the presence of two types of complex but the difference between the two types cannot be identified on the basis of the available evidence. The spectrum of the complex of the host (4i) with the salt (14) also showed significant upfield shifts of the signals assignable to the bridging group ($\alpha\text{-CH}_2$, 2.00; $\beta\text{-CH}_2$, 1.01; $\gamma\text{-CH}_2$, δ 1.01) as compared with the complex with benzylammonium thiocyanate ($\alpha\text{-CH}_2$, 2.48; $\beta\text{-CH}_2$, 1.30; $\gamma\text{-CH}_2$, δ 1.10). At lower temperatures (< -5 °C) the process analogous to (16a) \rightleftharpoons (16a)* became slow on the n.m.r. time scale and two signals were observable for the NCH_2 groups of the macrocycle. At very low temperatures (< -80 °C) rather more profound changes appeared in the spectrum of the host, similar to those observed in the spectrum of the analogous complex of the 15-crown-5 derivative (4b). This appears to be a consequence of hindered conformational changes in a complex analogous to (16a) but the presence of the two NH_3^+ signals at these very low temperatures is difficult to explain. On the basis of these results it appears that the 18-crown-6 derivatives (4h) and (4i) are able to form intramolecular complexes with the dication (14). There is no satisfactory explanation for the doubling of the NH_3^+ signals for these complexes at very low temperatures, but the behaviour of the signals assignable to the host macrocycle is not consistent with a mixture

TABLE 9

N.m.r. spectra ^a (220 MHz) of the complexes of the hosts (4h—j) with the salt (14)

Host	X in (4)	G : H ratio	Temp. (°C)	Host spectrum					Guest spectrum	
				OCH ₂	NCH ₂ ^b	α ^c	β ^c	γ ^c	arylH	NH ₃ ⁺
(4h)	[CH ₂] ₄	1 : 1	25	3.65—3.8(m) 3.57(t)	2.65	1.98	1.17		4.21(s), 7.59(s), ^d 7.68(s)	
			-60	3.5—3.9(m)	2.68, 2.60	1.78	1.18		4.21(s), 7.62(s), ^d 7.55(s)	8.28, 8.38
(4i)	[CH ₂] ₅	1 : 1	25	3.75(m), 3.72(m) 3.68(m)	2.64	2.00	1.01	1.01	4.22(s), 7.61, 7.48 (AB ₂ system), 7.59(s)	
			-60	3.4—3.85(m)	2.63, 2.50	1.73	0.85	0.85	4.19(s), 7.59, 7.38 (AB ₂ system), 7.40(s)	8.25(br)
			-100	3.3—4.2 (v br)	ca. 3.4, ^e 2.05	ca. 2.05	1.2, ^f 0.5 ^f		7.60, 7.30 (AB ₂ system), ca. 7.4(s)	8.29, 8.37
(4j)	[CH ₂] ₆	1 : 1	25 ^g	3.68(s), 3.61(m) 3.56(m)	2.73	2.43	1.28(br)	1.28(br)	4.13(s), 7.51(s), ^d 7.60(s)	

^a For ca. 0.1M solutions in CD₂Cl₂ containing a little CD₃OD. ^b t, *J* ca. 6 Hz at 25 °C; broad signals at low temperatures. ^c α, β, γ refer to the methylene groups of X labelled as NCH₂(α)CH₂(β)CH₂(γ). ^d 3-aryl-H corresponding to AB₂ system for complex of (4i). ^e Obscured by OCH₂ signals. ^f Signals not individually assignable to β or γ groups. ^g Spectrum at low temperatures very broad.

of intramolecular and intermolecular complexes. The spectrum of the complex between the host (4j) and the dication (14) did not show significant upfield shifts of the signals assignable to the bridging methylene groups.

TABLE 10

Comparison of chemical shifts (δ) of [CH₂]_n bridge of hosts (4a—d) and (4h—j) in complexes with the bis(ammonium) salt (14) and benzylammonium thiocyanate

Host	X in (4)	Chemical shifts ^a			δ
		α	β	γ	
(4a)	[CH ₂] ₄	1.89 (2.63)	0.90 (1.40)		
(4b)	[CH ₂] ₅	2.10 (2.42)	0.89 (1.43)	0.89 (1.12)	
(4c)	[CH ₂] ₆	2.30 (2.38)	1.05 (1.42)	1.05 (1.18)	
(4d)	[CH ₂] ₇	2.42 (2.43)	1.39 (1.40)	1.20 (1.20)	1.20 (1.20)
(4h)	[CH ₂] ₄	1.98 (2.57)	1.17 (1.30)		
(4i)	[CH ₂] ₅	2.00 (2.48)	1.01 (1.30)	1.01 (1.10)	
(4j)	[CH ₂] ₆	2.43 (2.50)	1.28 (1.30)	1.28 (1.22)	

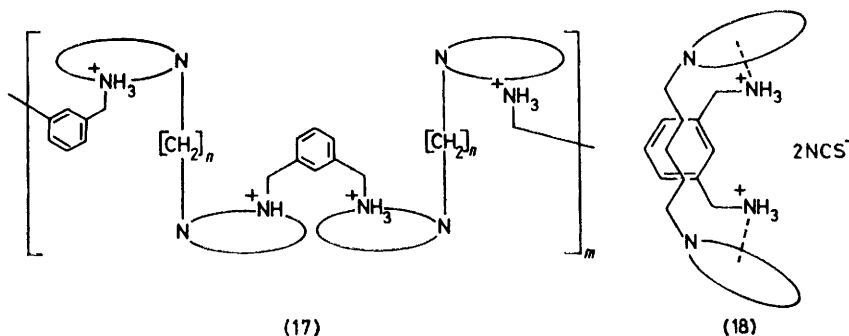
^a Data refer to solutions in CD₂Cl₂ at 25 °C; α, β, γ, and δ refer to the methylene groups of X labelled as NCH₂(α)CH₂(β)-CH₂(γ)CH₂(δ). The figures in parentheses refer to the benzylammonium thiocyanate complex (2 : 1, G : H ratio).

Furthermore the spectrum of this complex was poorly defined at low temperatures. The available spectroscopic evidence suggests that in this case the complex is

not intramolecular, presumably a consequence of poor guest-host fit.

The different chemical shifts of the N[CH₂]_nN protons of the hosts (4a—d) and (4h—j) in complexes with benzylammonium thiocyanate (2 : 1 G : H ratio) and the bis(ammonium)salt (14) deserve further comment; the relevant data are summarised in Table 10. The chemical shifts of these [CH₂]_n protons are similar for both types of complex. In contrast the complexes of the hosts (4a—c) and (4h and i) show significant differences for the chemical shifts of the [CH₂]_n bridge in the two series of complexes. Since the complexes of the bis(ammonium) salt (14) show high-field shifts relative to the complexes of benzylammonium thiocyanate we deduce that the restricted motion of the aromatic ring in an intramolecular complex (16) places it in a special relationship to some, or all, of the CH₂ groups of the bridge X and hence causes shifts to high field. The well known shielding effects of aromatic rings¹⁴ indicate that this relationship must be that shown diagrammatically in (18) for the complex between (4b) and the salt (14).

Shielding of 1.0 p.p.m. is considered¹⁵ to be associated with a proton lying only 3—4 Å above the plane of a benzene ring. Since it is likely that only one proton of each methylene group of the [CH₂]_n bridge lies in the shielding zone of the aromatic ring of the guest dication [*cf.* (18)] the recorded shifts (Table 10) are in accord with



distances of this order. In general shifts are maximum for the α -CH₂ and β -CH₂ groups but decrease, particularly for the α -CH₂ group, as the length of the bridge increases. This indicates that the shorter [CH₂]_n bridges are more rigidly held in close proximity to the aromatic ring of the guest. If intermolecular complexes (17) are formed this shielding relationship between the aromatic ring and the [CH₂]_n bridge, shown in (18), is no longer enforced and for complexes believed to be of this type there is no evidence that shifts to high field are greater than those for benzylammonium thiocyanate complexes.

Some of the results described in this paper were briefly discussed in a preliminary communication.¹⁶ The bis(monoaza)crown systems [cf. (4)] are potentially versatile host molecules since a wide range of compounds having different bridges, and hence different relationships between the two crown macrocycles, can readily be synthesised. These results, and those reported¹⁰ in an earlier study by Professor Cram's group, establish the possibility of binding polyfunctional guest molecules by synthetic host molecules that contain suitably located binding sites based upon crown ether systems. Compounds analogous to (4) should provide suitable hosts for the formation of complexes with a wide variety of guest alkylammonium cations in which the substituents are capable of hydrogen-bond formation.

[9/516 Received, 2nd April, 1979]

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