The Formation of Complexes between Aza-derivatives of Crown Ethers and Primary Alkylammonium Salts. Part 3.[1] Monobenzo-derivatives of Diaza-analogues and Diazametacyclophanes

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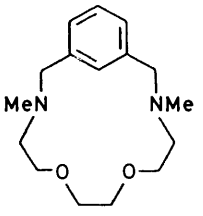
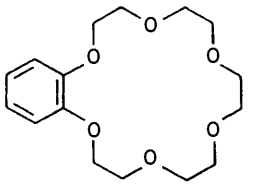
The diaza-analogues of crown ethers (3b and e—g) form complexes with primary alkylammonium thiocyanates in non-polar solvents in which the binding energy is comparable with that found for the complexes of the analogous host molecules lacking the fused benzene ring substituent. These relative binding energies are based upon a kinetic method using n.m.r. line-shape techniques. The host molecule (6b) forms complexes with primary alkylammonium thiocyanates in which guest–host binding energy is significantly greater than for the [12]metacyclophane derivatives (3).

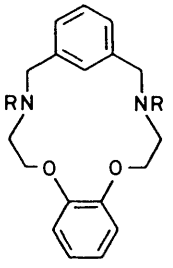
In Part 2[1] we discussed the formation of complexes by some diazametacyclophanes [*e.g.* (1)] having structures analogous to those of crown ethers. It has been shown[2,3] that benzo-derivatives of crown ethers [*e.g.* (2)] have an



(1)

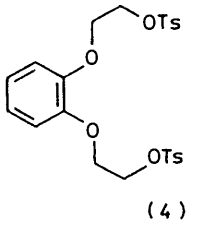


(2)

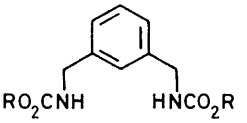


(3)

a; R = CO_2Et
b; R = Me
c; R = CO_2CH_2Ph
d; R = H
e; R = CH_2CH_2OH
f; R = $CH_2CONHMe$
g; R = CH_2CONMe_2



(4)



(5)

a; R = Et
b; R = CH_2Ph

ability to form complexes with primary alkylammonium salts that is similar to that of the parent crown ethers and it was anticipated[4] that this would also be the case with the benzo-derivatives (3) of the host molecule (1). The advantages of benzo-substitution include potentially greater ease of synthesis, increased solubility of host compounds in organic solvents, and simpler n.m.r. spectra of the host macrocycles and their complexes.

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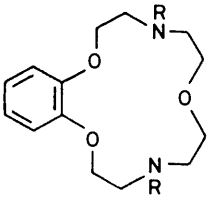
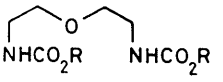
The macrocycle (3a) was readily prepared by the reaction of the bis(toluene-*p*-sulphonate) (4) with the dianion from the bisethoxycarbonyl derivative of αα′-*m*-xylylenediamine (5a). Reduction of the carbamate (3a) with lithium aluminium hydride gave the *N*-methyl derivative (3b). The benzyloxycarbonyl derivative (3c) of the metacyclophane was readily prepared by an analogous cyclisation reaction and debenzylation (HBr–HOAc) gave the diamine (3d). The cyclophane derivatives (3e—g) were readily prepared from the diamine (3d) by reaction with ethylene oxide or the appropriate chloroacetamide.

The host macrocycle (3b) formed moderately strong complexes with primary alkylammonium thiocyanates but in order to increase the strength of guest–host binding a further oxygen atom was introduced into the 15-membered ring. The required macrocycle (6b) was readily synthesised, using a route analogous to that used for the preparation of (3b), from the dianion of the biscarbamate (7) and the bis(toluene-*p*-sulphonate) (4).



(6)

a; R = CO_2Et
b; R = Me
c; R = CO_2CH_2Ph



(7)

a; R = Et
b; R = CH_2Ph

The formation of complexes with primary alkylammonium salts by the host molecules (3b and e—g) and (6b) is described in the last section of this paper.

EXPERIMENTAL

For general details see Part 2.[1]

N.M.R. Spectra.—These were determined using Varian HA 100 or JEOL PFT 100 spectrometers and *ca.* 0.1M solutions in either deuteriochloroform or deuteriomethylene chloride. Temperatures were controlled within the range −80 to +30° and were calibrated using either a methanol

sample or a thermocouple. Solutions of complexes were prepared by dissolving the appropriate amounts of the two components in solvent (*ca.* 0.5 ml) immediately prior to running the spectra. Thiocyanate salts of primary amines were prepared as described in earlier papers of this series.

1,2-*Bis*-(2-p-*tolylsulphonylethoxy*)*benzene* (4).—Diethyl (*o*-phenylenedioxy)diacetate (23.5 g, 0.083 mol) was added dropwise over 3 h to a rapidly stirred suspension of lithium aluminium hydride (13 g, 0.33 mol) in dry ether (250 ml). The mixture was stirred at room temperature for 16 h, excess of hydride was destroyed by careful addition of water, the solution was filtered, and the residue washed with ethyl acetate. The combined filtrate and washings were dried (Na_2SO_4) and evaporated and the residue crystallised from light petroleum (b.p. 40—60°) giving 1,2-*bis*-(2-*hydroxyethoxy*)*benzene* (13.2 g, 78%) as crystals, m.p. 93—94° (Found: C, 60.4; H, 7.2. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.1%); $\nu_{max.}$ 3 430 cm^{-1}; $\delta(CDCl_3)$ 7.10 (4 H, s, ArH), 4.35—3.8 (m, 2 × OCH_2CH_2O + 2 × OH). The bis-(toluene-*p*-sulphonate) was prepared using toluene-*p*-sulphonyl chloride in pyridine at 0 °. The *product* (4) (57% yield) had m.p. 95.5—97° (Found: C, 57.1; H, 5.4; S, 12.6. $C_{24}H_{26}O_6S_2$ requires C, 56.9; H, 5.2; S, 12.65%); $\delta(CDCl_3)$ δ_A 7.78 and δ_B 7.28 (8 H, 2 × AA'BB', J_{AB} 8 Hz, ArH), 6.80 (4 H, s, ArH), 4.47—3.99 (m, 2 × A_2B_2 system, 2 × OCH_2CH_2O), and 2.40 (s, 2 × $ArCH_3$).

NN'-*Bisethoxycarbonyl*-2,11-*diaza*-5,8-*dioxa*-(6,7)-*benzo*-[12]*metacyclophan*-6-*ene* (3a).—Sodium hydride * (1.0 g, 0.04 mol) was added to a solution of *NN'*-bisethoxycarbonyl-αα'-diamino-*m*-xylene (5a) (5.6 g, 0.02 mol) in dimethyl sulphoxide (70 ml) and the mixture left under dry nitrogen for 3 h. This mixture was then added dropwise over 1 h to stirred dimethyl sulphoxide (100 ml) simultaneously with a solution of the catechol derivative (4) (10.16 g, 0.02 mol) in dimethyl sulphoxide (70 ml). The mixture was stirred at room temperature for 24 h, diluted with water (300 ml), and the product extracted into chloroform (2 × 200 ml). The chloroform extract was washed with water (3 × 500 ml), dried, and evaporated and the residual oil purified by column chromatography on silica gel. The product crystallised from light petroleum (b.p. 40—60°) giving the [12]*metacyclophane* (3a) as a solid (2.8 g, 33%), m.p. 102° (Found: C, 65.3; H, 7.0; N, 6.2. $C_{24}H_{39}N_2O_6$ requires C, 65.1; H, 6.8; N, 6.3%); $\nu_{max.}$ 1 680 cm^{-1}; $\delta(CDCl_3)$ 7.81br (s, 18-H), 7.46—7.10 (m, 14-, 15-, 16-H), 6.88 (s, 4 aromatic H), 4.62 (s, 2 × $ArCH_2N$), 4.22 (q, *J* 7 Hz, 2 × OCH_2CH_3), 4.16 (m, 2 × CH_2O), 3.74 (t, *J* 5 Hz, 2 × CH_2N), and 1.25 (t, *J* 7 Hz, 2 × CH_2CH_3).

NN'-*Bisbenzyloxycarbonyl*-2,11-*diaza*-5,8-*dioxa*-(6,7)-*benzo*[12]*metacyclophan*-6-*ene* (3c).—This compound was prepared, using a method similar to that used for the [12]-metacyclophane (3a), from *NN'*-bisbenzyloxycarbonyl-αα'-diamino-*m*-xylene (5b) (6.06 g, 0.015 mol), sodium hydride (0.75 g), and the catechol derivative (4) (7.58 g, 0.015 mol). The [12]*metacyclophane* (3c) crystallised from chloroform–ether as a solid (3.8 g, 45%), m.p. 135—138° (Found: C, 71.9; H, 6.4; N, 5.1. $C_{34}H_{34}N_2O_6$ requires C, 72.1; H, 6.1; N, 4.9%); $\nu_{max.}$ 1 700 cm^{-1}; $\delta(CDCl_3)$ 7.90br (s, 18-H), 7.32 (s, 13 aromatic H), 6.83br (s, 4 aromatic H), 5.15 (s, 2 × OCH_2Ph), 4.69 (s, 2 × $ArCH_2N$), 4.15br (m, 2 × OCH_2), and 3.70br (t, *J* 5 Hz, 2 × NCH_2).

NN'-*Dimethyl*-2,11-*diaza*-5,8-*dioxa*-(6,7)-*benzo*-[12]*metacyclophan*-6-*ene* (3b).—The bisethoxycarbonyl[12]metacyclophane (3a) (1.70 g, 3.9 mmol) was reduced using lithium aluminium hydride (0.57 g, 15 mmol) in dry ether (60 ml) at room temperature for 24 h. Excess of hydride was destroyed by the addition of water and the mixture was filtered. The filtrate, combined with ethyl acetate washings of the precipitated solid, was dried and evaporated giving the *product* (3b) as an oil which slowly crystallised (1.30 g, 96%). A sample, purified by short-path distillation at 230—236° and 0.4 Torr, had m.p. 76—78° (Found: C, 73.8; H, 8.1; N, 8.5. $C_{20}H_{26}N_2O_2$ requires C, 73.6; H, 8.0; N, 8.6%); $\lambda_{max.}$ 237 (ε 6 600) and 279.5 nm (3 300); $\delta(CDCl_3)$ 8.15br (s, 18-H), 7.0—7.3 (m, 16-, 15-, 14-H), 6.84 (s, 4 aromatic H), 4.02 (t, *J* 5 Hz, 2 × OCH_2), 3.66 (s, 2 × $ArCH_2N$), 2.77 (t, *J* 5 Hz, 2 × NCH_2), and 2.44 (s, 2 × NMe).

2,11-*Diaza*-5,8-*dioxa*-(6,7)-*benzo*-[12]*metacyclophan*-6-*ene* (3d).—The *NN'*-bisbenzyloxycarbonyl[12]metacyclophane (3c) (56.6 mg, 1 mmol) was heated with hydrogen bromide in acetic acid (2 ml, 45%) at 100° for 2.5 min. The mixture was diluted with water (20 ml), washed with chloroform (10 ml), and the aqueous layer made basic (10N aqueous NaOH) and extracted with chloroform (2 × 20 ml). The chloroform extract was dried (Na_2SO_4) and evaporated giving the *diamine* (3d) as a solid (298 mg, 100%), m.p. 119—122°; *M*, 298; $\delta(CDCl_3)$ 7.85br (s, 18-H), 7.25—7.10 (m, 16-, 15-, 14-H), 6.88 (s, 4 aromatic H), 4.13 (t, *J* 4.5 Hz, 2 × OCH_2-CH_2N), 3.95 (s, 2 × $ArCH_2$), 3.05 (t, *J* 4.5 Hz, 2 × OCH_2-CH_2N), and 2.70br (s, 2 × NH).

NN'-*Bis*-(2-*hydroxyethyl*)-2,11-*diaza*-5,8-*dioxa*-(6,7)-*benzo*-[12]*metacyclophan*-6-*ene* (3e).—Ethylene oxide (1 ml, 20 mmol) was added to a solution of the diamine (3d) (298 mg, 1 mmol) in ethanol (2 ml) containing a little water. The mixture was left at room temperature for 16 h, evaporated, and the residue purified by column chromatography (alumina) to give the *diol* (3e) as an oil (232 mg, 60%) [Found: *M*, 355.201. $C_{11}H_{27}N_2O_3$ (loss of CH_2OH) requires *M*, 355.202]; $\nu_{max.}$ 3 460 cm^{-1}; $\delta(CDCl_3)$ 8.16—8.08 (s, 18-H), 7.22—6.96 (m, 14-, 15-, 16-H), 4.02 (t, *J* 4.5 Hz, 2 × OCH_2CH_2N), 3.68 (s, 2 × $ArCH_2N$), 3.46 (t, *J* 5.0 Hz, 2 × $HOCH_2$), 2.90 (t, *J* 4.5 Hz, 2 × NCH_2), and 2.68 (t, *J* 5.0 Hz, 2 × NCH_2). The diol formed a dibenzoate, m.p. 115—117° (Found: *M*, 594.2715. $C_{36}H_{38}N_2O_6$ requires *M*, 594.2730).

NN'-*Bis*-(NN'-*dimethylacetamido*)-2,11-*diaza*-5,8-*dioxa*-(6,7)-*benzo*-[12]*metacyclophan*-6-*ene* (3f).—The diamine (3d) (270 mg, 0.9 mmol) was stirred with anhydrous potassium carbonate (400 mg, 3 mmol) and *NN'*-dimethyl-2-chloroacetamide (276 mg, 2.2 mmol) in acetonitrile (5 ml) at room temperature for 48 h. The solvent was evaporated and the product extracted into chloroform followed by work-up for basic material (soluble in 2N-HCl). The crude product was purified by column chromatography (alumina) to give the *diamide* (3c) as an oil (242 mg, 65%) (Found: *M*, 468.2762. $C_{26}H_{36}N_4O_4$ requires *M*, 468.2737); $\nu_{max.}$ 1 630 cm^{-1}; $\delta(CDCl_3)$ 8.21br (s, 18-H), 7.33—6.98 (m, 16-, 15-, 14-H), 6.83 (s, 4 aromatic H), 4.02 (t, *J* 4.5 Hz, 2 × OCH_2), 3.81 (s, 2 × $ArCH_2N$), 3.40 (s, 2 × NCH_2CO), 2.99 (t, *J* 4.5 Hz, 2 × NCH_2), 3.00 (s, 2 × NMe), and 2.79 (s, 2 × NMe).

NN'-*Bis*-(N-*methylacetamido*)-2,11-*diaza*-5,8-*dioxa*-(6,7)-*benzo*-[12]*metacyclophan*-6-*ene* (3g).—The diamine (3d) (270 mg, 0.9 mmol) and *N*-methyl-2-chloroacetamide (233 mg, 2.2 mmol) reacted under similar conditions to those used for the diamide (3f) to give the *diamide* (3g) as an oil (218 mg, 50%) (Found: *M*, 440.2422. $C_{24}H_{32}N_4O_4$ requires *M*, 440.2424); $\nu_{max.}$ 1 660 cm^{-1}; $\delta(CDCl_3)$ 8.21br (s, 18-H), 7.70br (s, 2 × NH), 7.37—6.97 (m, 16-, 15-, 14-H), 6.90 (s,

* Used as a 50% dispersion in oil, washed with n-pentane before use; the stated quantity refers to the residual hydride.

4 aromatic H), 4.11 (t, J 4.5 Hz, 2 × OCH_2), 3.78 (s, 2 × $ArCH_2N$), 3.19 (s, 2 × NCH_2CO), 2.98 (t, J 4.5 Hz, 2 × NCH_2), 2.43 (d, J 5.0 Hz, 2 × MeN).

NN′-*Bisethoxycarbonyl*-4,10-*diaza*-1,7,13-*trioxa*[13]*orthocyclophane* (6a).—This compound was prepared, using a method similar to that used for the [12]metacyclophane (3a), from *NN*′-bisethoxycarbonyl-1,5-diamino-3-oxapentane (7a) (2.48 g, 0.01 mol), the catechol derivative (4) (5.06 g, 0.01 mol), and sodium hydride (0.96 g) in dry dimethyl sulphoxide (140 ml). The *product* (6a) was purified by column chromatography (silica gel) giving an oil (2.2 g, 55%), b.p. 265—270° at 0.3 Torr (Found: C, 58.8; H, 7.5; N, 7.0. $C_{20}H_{30}N_2O_7$ requires C, 58.5; H, 7.4; N, 6.8%); $\nu_{max.}$ 1 680 cm^{-1}; δ($CDCl_3$) 6.90 (s, 4 aromatic H), 4.40—3.40 (m, 4 × NCH_2 + 6 × OCH_2), and 1.24 (t, J 7 Hz, 2 × $CO_2CH_2CH_3$).

NN′-*Dimethyl*-4,10-*diaza*-1,7,13-*trioxa*[13]*orthocyclophane* (6b).—This compound was prepared by reduction of the corresponding ethoxycarbonyl derivative (6a) (1.10 g, 2.7 mmol) by lithium aluminium hydride (0.38 g, 10 mmol) in ether (20 ml) over 16 h. The product (6b) was obtained as an oil (624 mg, 77%) purified by short-path distillation at 210° and 0.4 Torr (Found: M, 294.1944. $C_{16}H_{26}N_2O_3$ requires M, 294.1943); $\lambda_{max.}$ 237 (ε 7 100) and 279.5 nm (3 900); δ($CDCl_3$) 6.83 (s, 4 aromatic H), 3.97 (t, J 4.5 Hz, 2 × $ArOCH_2$) ,3.58 (t, J 5.0 Hz, 2 × OCH_2), 2.79 (t, J 4.5 Hz, 2 × NCH_2), 2.64 (t, J 5.0 Hz, 2 × NCH_2), and 2.31 (s, 2 × NCH_3).

NN′-*Bisbenzyloxycarbonyl*-4,10-*diaza*-1,7,13-*trioxa*[13]-*orthocyclophane* (6c).—This compound was prepared, using a method similar to that used for the [12]metacyclophane (3a), from *NN*′-bisbenzyloxycarbonyl-1,5-diamino-3-oxapentane (7b) (1.20 g, 3.2 mmol), the catechol derivative (4) (1.60 g, 3.2 mmol), and sodium hydride (0.3 g) in dry dimethyl sulphoxide (70 ml). The *product* (6c) was purified by column chromatography (silica gel) giving an oil (900 mg, 55%), b.p. *ca.* 320° at 0.2 Torr (Found: C, 67.4; H, 6.8; N, 5.7. $C_{30}H_{34}N_2O_7$ requires C, 67.4; H, 6.5; N, 5.4%); $\nu_{max.}$ 1 700 cm^{-1}; δ($CDCl_3$) 7.37 (s, 10 aromatic H), 6.88 (s, 4 aromatic H), 5.17 (s, 2 × $PhCH_2O$), and 4.27—3.47 (m, 4 × OCH_2CH_2N).

RESULTS AND DISCUSSION

The macrocyclic diamines (3b and e—g) and (6b) form complexes with a variety of primary alkylammonium thiocyanates when the two components of the complex are dissolved in a non-polar solvent such as chloroform or methylene chloride. Evidence for complex formation is to some extent based upon the increased solubility of the guest salt and changes in the chemical shift in the ^1H n.m.r. spectrum of the host macrocycle. Rather more compelling evidence for complex formation has been obtained, as in other cases reported previously,[1,3,5] by a detailed study of the n.m.r. spectra of the complexes. Details of this spectroscopic behaviour are summarised in Tables 1—3 and the energy barriers and processes associated with the temperature dependence are summarised in Table 4.

The n.m.r. spectra of the complexes of the [12]metacyclophane (3b) with achiral guests, such as benzylammonium thiocyanate, showed an AB system for the

TABLE 1

N.m.r. spectra [a] of complexes of [12]metacyclophane (3b) with primary alkylammonium salts

Guest	Ratio G : H	T/°C	Chemical shift of host (δ) 18-H	$ArCH_2N$ [b]	OCH_2 [c]	NCH_2 [c]	NMe	Aryl H	Chemical shift of guest (δ)
		35	8.00	3.58	3.93	2.68	2.42	6.79(s)	
$PhCH_2\overset{+}{N}H_3NCS^-$	1 : 1	35	7.78	3.52	3.79	2.56		6.7—7.0(m)	3.69
		−70		3.90(A)		2.82br(m)	2.12		
				3.14(B)		2.2br			
(*R*)-$PhCHMe\overset{+}{N}H_3NCS^-$	1 : 1	20	7.83	3.54	3.6—4.0(m)	2.54	2.18		3.72 (q, J 7 Hz),
		−60					2.65(Me1)		1.52 (d, J 7 Hz)
							1.55(Me2)		
(*R*)-$PhCHMe\overset{+}{N}H_3NCS^-$	2 : 1	20	7.78	3.53	3.6—3.9(m)	2.55	2.15		4.06 (q, J 7 Hz),
									1.66 (d, J 7 Hz)
		−70					2.63(Me1)		4.1br(F) [d]
							1.55(Me2)		3.8br(C) [d]
									1.55br (F + C)
$Me_3C\overset{+}{N}H_3NCS^-$	1 : 1	35	7.96	3.59	3.96	2.69	2.45	6.83(s)	1.29
		−94		~3.75(A)					
				3.17(B)					
$Me_2CH\overset{+}{N}H_3NCS^-$	1 : 1	35	7.78	3.60	3.93	2.65	2.50	6.85(m)	
									2.91 (septet,
									J 6.5 Hz),
		−82		4.02(A)		2.91 (t,			1.20 (d, J 6.5 Hz)
						$J \sim 11$ Hz)			
				3.15(B)		2.28 (d,			
						$J \sim 11$ Hz)			
$MeCH_2\overset{+}{N}H_3NCS^-$	1 : 1	35	7.73	3.59	3.95	2.68	2.50	6.85(m)	2.63 (q, J 7 Hz),
									1.13 (t, J 7 Hz)
		−92		3.96(A)					
				3.21(B)					
$Me\overset{+}{N}H_3NCS^-$	1 : 1	35	7.68	3.58	4.00	2.72	2.49	6.88(m)	2.28
$\overset{+}{N}H_4NCS^-$	1 : 1	35 [e]	7.81	3.64	3.99	2.73	2.47	6.85(s)	
$PhCH\overset{+}{N}H_3CO_2MeNCS^-$	1 : 1	35 [e]	8.20	3.82	4.05	2.84	2.48	6.85(s)	4.53 (CH),
									3.62 (OMe)

[a] All spectra run at 100 MHz for CD_2Cl_2 solutions *ca.* 0.1M. Low-temperature data for well resolved, temperature-dependent signals only. [b] Singlet at 35°, AB system at low temperatures, J_{AB} *ca.* 12 Hz. [c] t, J *ca.* 5 Hz at 35°. [d] F refers to free guest, C to complexed guest. [e] Spectrum at 35° only; low-temperature spectra not well resolved.

TABLE 2

N.m.r. spectra [a] of complexes of [12]metacyclophanes (3e, f, and g) with primary alkylammonium salts

Host	Guest	T/°C	18-H	ArCH$_2$N [b]	OCH$_2$ [c]	NCH$_2$ [c]	Side chain [d]	Aryl H	Chemical shift of guest (δ)
				Chemical shift of host (δ)					
(3e)			8.12	3.68	4.02	2.90	3.46, 2.68	6.83(m)	
(3e)	$PhCH_2\overset{+}{N}H_3NCS^-$	35	8.42	3.44	3.90	2.58	3.82, 2.49	6.82(m)	4.02
		−40		~4.05(A) 2.92(B)					
(3e)	$PhCH\overset{+}{N}H_3CO_2MeNCS^-$	35	7.67	3.55	3.98	2.64 or 2.59 [b]	3.85, 2.59 or 2.64 [e]	6.91	4.92 (CH), 3.67 (OMe)
(3g)		35	8.20	3.81	4.02	2.96	3.40, 2.99, 2.78	6.83(s)	
(3g)	$PhCH_2\overset{+}{N}H_3NCS^-$	35	7.95	3.43	3.78	2.72	3.33, 3.04,		3.78
		−30		3.90(A) ~3.0(B)			3.02		
(3g)	(*R*,*S*)-$PhCHMe\overset{+}{N}H_3NCS^-$	20	7.70	3.42	3.77	2.72	3.10, 3.08, 3.05		4.23 (q, *J* 7 Hz) 1.45 (d, *J* 7 Hz)
		−40					3.10,[e] 2.95 [e] 3.14,[e], 3.08 [e]		
(3g)	$PhCH\overset{+}{N}H_3CO_2MeNCS^-$	40	7.82	3.54		2.84	3.06, 2.97	6.85(m)	4.82 (CH), 3.52 (OMe)
		−30					3.08,[f] 3.26,[f] 3.83 [f]		
(3f)		35 [g]	8.21	3.78	4.11	2.99	3.19, 2.44 (d, 5 Hz)		
(3f)	$PhCH_2\overset{+}{N}H_3NCS^-$	35 [g]	7.96	3.55	4.09	2.96	3.19, 2.65 (d, *J* 5 Hz)		3.95

[a-c] As footnotes *a*—*c* of Table 1. [d] For (3e) both signals triplets, *J ca.* 6 Hz, for (3g) singlets, for (3f) singlet CH_2 and doublet NH*Me*. [e] Both NMe singlets at 20° give two signals at −40°. [f] NMe signal at δ 3.06 does not show temperature dependence, NMe signal at δ 2.97 gives two singlets at −30°. Remainder of host spectrum rather poorly resolved. [g] Spectra show temperature dependence but low-temperature spectra poorly resolved.

TABLE 3

N.m.r. spectra [a] of complexes of diaza-15-crown-5 analogue (6b) with primary alkylammonium salts

Guest	Ratio G : H	T/°C	ArH	ArOCH$_2$ [b]	OCH$_2$ [b]	CH$_2$N [b]	CH$_2$N [b]	NMe	Chemical shift of guest (δ)
				Chemical shift of host (δ)					
		35	6.83	3.97	3.58	2.78	2.64	2.18	
$PhCH_2\overset{+}{N}H_3NCS^-$	1 : 1	35	6.95	3.93 (t, *J* ~ 5 Hz)	3.53	2.65br	2.65br	1.96	3.67
		−30 [c]	6.98	3.92 (d, *J* ~ 7 Hz)	~3.5(m)	3.16 (dd, *J* 14, 7 Hz) 2.14 (d, *J* 14 Hz)	2.93 (t, *J* ~ 12 Hz) 2.35 (d, *J* ~ 13 Hz)	1.87	
(*R*)-$PhCHMe\overset{+}{N}H_3NCS^-$	2 : 1	35	6.98	3.98(m)	3.58	~2.70br	~2.70br	2.02	4.12 (q, *J* 7 Hz), 1.57 (d, *J* 7 Hz)
		−20 [d]						2.41 (Me1) 1.29 (Me2)	1.55br(d)
		−60 [d]						2.47 (Me1) 1.15 (Me2)	1.63br(F) [e] 1.44br(C) [e]
(*R*,*S*)-$PhCHMe\overset{+}{N}H_3NCS^-$	1 : 1	20	6.93	3.98br	3.61	~2.70br	~2.70br	1.96br	3.86 (q, *J* 7 Hz), 1.53 (d, *J* 7 Hz)
		−60 [d]						2.47 (Me1) 1.14 (Me2)	1.41 (d, *J* 7 Hz)
(*R*,*S*)-$PhCHMe\overset{+}{N}H_3NCS^-$	2 : 1	20	6.87	3.96(br)	3.54	~2.70br	~2.70br	1.96br	4.13 (q, *J* 7 Hz), 1.56 (d, *J* 7 Hz)
		−60 [d]						2.43 (Me1) 1.13 (Me2)	1.62br(F) [e] 1.42br(C) [e]
(*R*)-$PhCH\overset{+}{N}H_3CO_2Me$-NCS$^-$	1 : 2	20	6.91	4.01	3.60	2.79	2.71	2.23	4.58(CH), 3.65(OMe)
		−70 [d]	7.04 (C) [e] 6.86 (F) [e]					2.63 (C,Me1) [e] 1.48 (C,Me2) [e] 2.26(F) [e]	

[a] As Footnote *a*, Table 1. [b] Observed as triplets at highest temperature, *J ca.* 5 Hz. [c] The groups ArOCH$_2$CH$_2$N and OCH$_2$CH$_2$N constitute two ABCD systems at low temperatures; the reported coupling constants are based on first-order analysis. [d] Only the signals showing simple temperature dependence are reported, the NCH$_2$ and OCH$_2$ signals are highly complex at low temperatures. [e] The labels F and C refer to free and complexed guest or host species respectively.

ArC*H*$_2$N protons when the exchange process E + I * became slow on the n.m.r. time scale. This study was extended to a variety of guest salts and on the basis of the collapse of the AB system to a singlet as the temperature was raised the free energy barriers for the site exchange process could be calculated in the usual way.[6] As found for the [12]metacyclophane (1) these free energy barriers were reduced by bulky alkyl substituents in the guest salt, as in t-butylammonium thiocyanate, and also reduced when the alkyl substituent was small, as in methylammonium thiocyanate. These results indicate a close similarity in the behaviour of the host systems (1) and (3b), and the similar values of the energy

* Processes are described using the nomenclature adopted in Part 1 (ref. 5). The labelling of n.m.r. sites in Schemes and Tables also follows the system adopted in Part 1.

TABLE 4

Free energy barriers associated with the processes E + I and E for the complexes of the crown ether analogues (3) and (6b) with primary alkylammonium thiocyanates in CD_2Cl_2

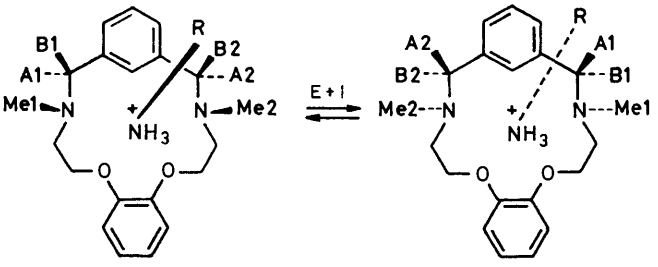
Host	Guest	Ratio G : H	Signal [a]	Spectral changes [b]	T_c/°C (±5 °C)	$\Delta G^{\ddagger}$ [c]/kcal mol^{-1} ±0.5	Process
(3b)	$PhCH_2\overset{+}{N}H_3NCS^-$	1 : 1	$ArCH_2N$	A + B→AB,	−40	11.1	E + I
(3b)	(*R*)-$PhCHMe\overset{+}{N}H_3NCS^-$	1 : 1	NCH_3	Me1 + Me2→Me12	−40	11.0	E + I
(3b)	(*R*)-$PhCHMe\overset{+}{N}H_3NCS^-$	2 : 1	NCH_3	Me1 + Me2→Me12	−35	11.2	E + I
(3b)	$Me_3C\overset{+}{N}H_3NCS^-$	1 : 1	$ArCH_2N$	A + B→AB	−82	9.1	E + I
(3b)	$Me_2CH\overset{+}{N}H_3NCS^-$	1 : 1	$ArCH_2N$	A + B→AB	−57	10.2	E + I
(3b)	$MeCH_2\overset{+}{N}H_3NCS^-$	1 : 1	$ArCH_2N$	A + B→AB	−62	10.0	E + I
(3b)	$Me\overset{+}{N}H_3NCS^-$	1 : 1	$ArCH_2N$	A + B→AB	−68	9.7	E + I
(3e)	$PhCH_2\overset{+}{N}H_3NCS^-$	1 : 1	$ArCH_2N$	A + B→AB	−15	12.1	E + I
(3g)	$PhCH_2\overset{+}{N}H_3NCS^-$	1 : 1	$ArCH_2N$	A + B→AB	−5	12.8	E + I
(3g)	(*R*)-$PhCHMe\overset{+}{N}H_3NCS^-$	1 : 1	$CON(CH_3)_2$	Me1 + Me2→Me12 [d]	−5	13.7	E + I
(3g)	(*R*)-$PhCHCO_2Me\overset{+}{N}H_3NCS^-$	1 : 1	$CON(CH_3)_2$	Me1 + Me2→Me12 [d]	−20	12.9	E + I
(6b)	$PhCH_2\overset{+}{N}H_3NCS^-$	1 : 1	NCH_2	A + B→AB	0	13.1	E + I
(6b)	(*R,S*)-$PhCHMe\overset{+}{N}H_3NCS^-$	1 : 1	NCH_3	Me1 + Me2→Me12	−15	12.1	E + I/E1 [e]
(6b)	(*R,S*)-$PhCHMe\overset{+}{N}H_3NCS^-$	2 : 1	NCH_3 CCH_3	Me1 + Me2→Me12 F + C→FC	−21 −47	11.8 11.4	0.5E1 E1/E
(6b)	(*R*)-$PhCHMe\overset{+}{N}H_3NCS^-$	2 : 1	NCH_3 CCH_3	Me1 + Me2→Me12 F + C→FC	−5 −47	12.6 11.4	E + I E
(6b)	(*R*)-$PhCHCO_2Me\overset{+}{N}H_3NCS^-$	1 : 2	NCH_3	F + C→FC	−55	10.2	E + I/E

[a] All signals refer to the host molecule with the exception of CCH_3 which refers to the guest molecule. [b] The labels A, B, Me1, Me2, *etc.*, are those used in Tables 1—3 and in Schemes 1—3. [c] Calculated using the approximations referred to in ref. 6 for coalescing AB systems and pairs of singlets. [d] Me1 and Me2 here refer to the two diastereotopic CONMe groups; see footnotes *f* and *g* of Table 2. [e] The rate determining process may be E1 or E + I.

barriers for the process E + I indicate that the fused benzene ring of compound (3b) only has a slight effect upon the ability of the macrocycle to form complexes with primary alkylammonium salts.

Further similarities in the behaviour of the complexes of (1) and (3b) were noted when the guest salt contained a chiral alkyl substituent. At low temperatures the n.m.r. spectrum of the complex of (3b) with (*R*)-phenylethylammonium thiocyanate showed two NMe signals, as expected on the basis of the site labelling of Scheme 1. The addition of an excess of guest (up to a 2 : 1 molar ratio of guest : host) did not significantly affect the host n.m.r. spectrum or its temperature dependence, but at low temperatures separate signals were observable for the >C*H* proton of free and complexed guest. The energy barrier for the exchange of free and complexed guest cations (process E) could not be calculated reliably from the coalescence data for this pair of signals due to poor resolution of the signals but this second energy barrier appeared to be significantly lower than that associated with the process E + I (Scheme 1); this point will be developed later in this paper.

The effects of introducing side chains other than methyl into the host macrocycle were also studied. The results of these studies are presented in Tables 2 and 4. Although the temperature dependence of the n.m.r. spectra is not as clearly defined for the complexes of the hosts (3e, f, and g) the substituents in the side chains have a significant effect upon the energy barrier for the process E + I. Thus the complex of the diol (3e) with benzylammonium thiocyanate shows an increased energy barrier and this is presumably an effect of the side chain upon the binding between the macrocycle and the guest $\overset{+}{N}H_3$ group. The host (3e) also forms a strong complex with the thiocyanate of methylphenylglycinate and in this case secondary binding interactions between the side chain and the guest CO_2Me group may also be involved. The increased energy barriers associated with complexes



SCHEME 1 Site exchanges associated with the process E + I for complexes of the [12]metacyclophane (3b). For cases in which the guest cation $R\overset{+}{N}H_3$ is achiral the distinction between sites with the labels 1 and 2 disappears

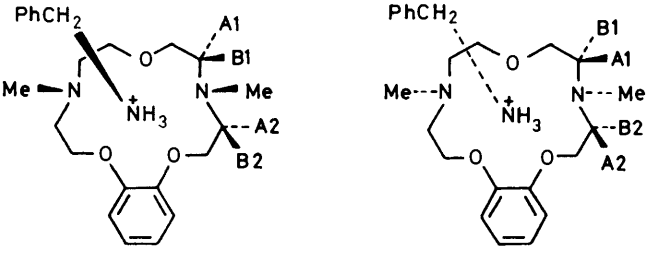
of the host (3f) are presumably associated with the participation of the amide side chain in binding to the $\overset{+}{N}H_3$ group of the guest molecules. In the absence of precise data, such as crystal structure data, concerning the nature of the complexes of (3e and f) it is not possible to comment in detail upon the effects of the side chain substituents.

The n.m.r. spectra of the complexes of the host (3g) are unfortunately poorly resolved at low temperatures and it is not possible to calculated precise values for energy barriers associated with the process E + I.

Qualitatively it appears that in this case the energy barrier for the complex with benzylammonium thiocyanate is similar in magnitude ($\Delta G^{\ddagger}$ *ca.* 12 kcal mol^{-1}) to that found for the analogous complexes of (3e and f).

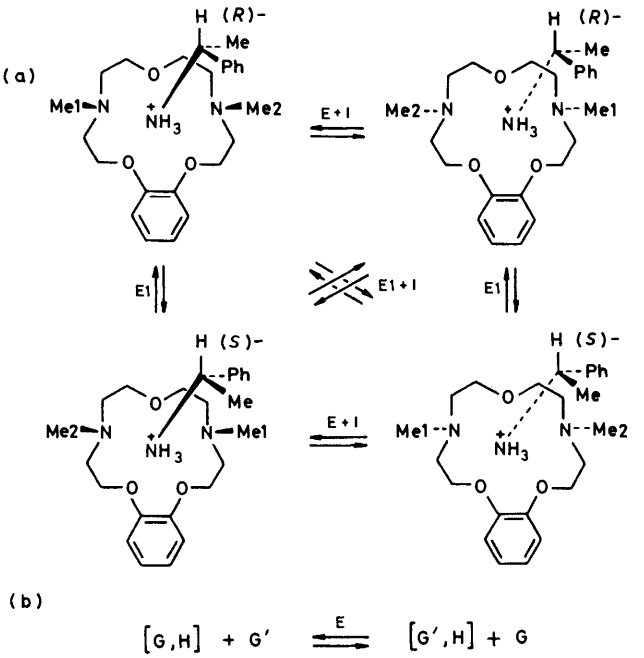
The macrocycle (6b), in which the *m*-xylylene system of (3b) is replaced by a $CH_2CH_2OCH_2CH_2$ system, hereby providing an additional binding site, shows the expected higher energy barrier for both the processes E and E + I. Consequently the associated changes in the n.m.r. spectra occur in a higher temperature range at which spectra are more clearly resolved. For an achiral guest, such as benzylammonium thiocyanate, the NCH_2 signals are observable as the AB portions (A1 and B1 and A2 and B2) of ABCD systems at low temperatures. The free energy barrier, obtained from the collapse of the AB systems to the triplet observable at higher temperatures (Tables 3 and 4) corresponds to the process E + I (Scheme 2) and is significantly higher than that associated with the complex of the analogous metacyclophane systems (1) and (3b).

The n.m.r. spectrum of the complex of (6b) with (*R*,*S*)-phenylethylammonium thiocyanate showed complex changes in the OCH_2 and NCH_2 regions at low temperatures, but the NMe groups were observed as two separate signals which were well resolved. This non-equivalence of the two NMe groups at low temperatures indicates that the processes E + I and E1 (see Scheme 3) are slow on the n.m.r. time scale. At higher temperatures the two NMe signals collapse to a singlet when either E + I or E1 become fast on the n.m.r. time scale. Re-examination of these spectral changes in the presence



SCHEME 2 Site exchange processes associated with the process E + I for complexes of the diaza 15-crown-5 system (6b) with an achiral guest (*cf.* Scheme 1 of ref. 5)

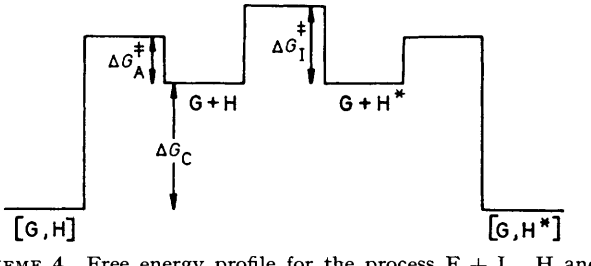
of one molar equivalent excess of guest salt shows that the collapse of the two NMe signals and the collapse of the two guest CMe signals observable at low temperatures involve processes with almost the same free energy of activation (Tables 3 and 4). Consideration of Scheme 3 shows that under these conditions, if process E1 involves dissociation and recombination with little change of host geometry, in the presence of an excess of (*R*,*S*)-guest recombination is equally likely to involve an (*R*)- or an (*S*)-guest species so that the process E1 is expected to occur at one half the rate of the process E whereby the complexed and free guest species are exchanged. This factor of 2 is in good agreement with the calculated activation energies for the two types of exchange process, and it is concluded that under these conditions the



SCHEME 3 (a) Site exchange processes for complexes of the diaza-15-crown-5 system (6b) with a chiral guest (*cf.* Scheme 2 of ref. 5). (b) Guest exchange in the presence of an excess of guest molecules, the square brackets indicate a complex and G and G' are used to differentiate two different guest molecules

processes E1 and E are responsible for the temperature dependence of the n.m.r. spectra.

The spectral behaviour of the complex of (6b) with (*R*)-phenylethylammonium thiocyanate, in the presence of one molar equivalent excess of the guest salt, is significantly different from that of the complex of the (*R*,*S*)-salt. Reference to Scheme 3 shows that under these conditions collapse of the host NMe signals can only involve the process E + I, whereas collapse of the guest CMe signals involves the simple exchange process E. The energy barriers found for these two processes under these conditions are significantly different (Table 4), consistent with the view that the process E + I involves consecutive dissociation of the complex, inversion of the host macrocycle, and recombination at the opposite face of the macrocycle. The free energy profile for this process is shown diagramatically in Scheme 4, which shows how the height of the free energy barrier for the overall process is determined by the sum of the free energy barrier for inversion of the host ($\Delta G_I^{\ddagger}$) and the



SCHEME 4 Free energy profile for the process E + I. H and H* refer to the two conformations of the host molecule related by inversion and the square brackets indicate a complex

free energy of complex formation (ΔG_C). If it is further assumed that guest–host recombination is diffusion-controlled [3] then the activation energy for recombination ($\Delta G_A^{\ddagger}$) would lie in the range *ca.* 3 kcal mol^{-1}, by analogy with the results obtained for the complex of 18-crown-6 with the t-butylammonium cation. Thus in the case of the host (6b) the value for $\Delta G_I^{\ddagger}$ is *ca.* 5 kcal mol^{-1} which is in reasonably good agreement for a process involving either nitrogen inversion or rotation about a C–C bond as the rate-determining step.[7] The value for $\Delta G_I^{\ddagger}$ obtained in this way is a minimum value since it is possible that there may be some bonding between guest and host components during the inversion process (*cf.* ref. 1). Furthermore the exchange process E (Scheme 3) may involve a bimolecular component (*cf.* ref. 3) but our results are not sufficiently precise to comment upon this possibility.

The spectral behaviour of the complexes of the host macrocycle (6b) is typical of the behaviour of aza-derivatives of crown ethers and forms a useful basis for the examination of the relative strengths of a related series of complexes, particularly where the value of the association constant K_a is large. The relationship between exchange processes that do not involve a major conformational change of the host macrocycle and those, slower, processes that do is of general interest and complementary to the observations of rapid conformational changes of some host macrocycles without major loss of complex binding energy which were reported in Part 1.[5] In none of the examples of complex formation reported in this paper was there any evidence for the formation of more than one type of complex and this behaviour contrasts with the behaviour of aza 18-crown-6 analogues reported in Part 1 and in the next paper of this series.

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