The Formation of Complexes between Aza-derivatives of Crown Ethers and Primary Alkylammonium Salts. Part 2.[1] Diaza-derivatives of Meta-cyclophanes

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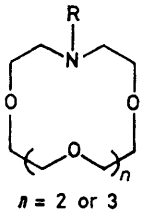
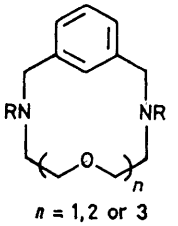
The diazametacyclophanes (6) and the derivatives (15) have been synthesised and the formation of complexes between these host macrocycles and guest primary alkylammonium salts in CD_2Cl_2 has been examined using n.m.r. line-shape methods. In general the strengths of the complexes for any particular guest are in the order (6b) > (6c) ⩾ (6a). A detailed examination of the complexes of (6b) shows that binding is affected adversely by steric interactions between guest and host, by the presence of certain additional functional groups in the guest cation, and by the lack of lipophilic shielding of the guest $\overset{+}{N}H_3$ group. Complex formation by the derivatives (15) is affected by the side chains containing functional groups, and in some cases the binding energy is significantly increased relative to complex formation by the diazametacyclophane (6b).

In Part 1 of this series [1] we described the preparation of mono-aza analogous of crown ethers (1) and discussed the formation of complexes with primary alkylammonium salts. Prior to this work we had investigated some diaza-analogues of crown ethers and had presented our results in preliminary form.[2] In this paper we discuss the synthesis of a series of crown ether analogues (2) based upon various diazametacyclophane systems and we discuss the ability of these compounds to form complexes with primary alkylammonium salts. The



n = 2 or 3

(1)



n = 1,2 or 3

(2)

metacyclophane system (2) was chosen as a basic structural unit since it was felt (*i*) that compounds of this type would be synthetically readily accessible; (*ii*) that the interruption of the crown ether system by a *meta*-substituted aromatic ring would not have a serious effect on the required crown-like geometry of the macrocycle but would decrease the tendency of the ring system to form complexes with metal cations; and (*iii*) the n.m.r. spectra of compounds of this type would be more readily interpreted than those of the analogous crown ether systems. It was additionally anticipated that the presence of two nitrogen atoms in the ring system would permit the synthesis of a wide range of polyfunctional derivatives by the suitable choice of the group R in (2), and allow the possibility of the synthesis of bridged and polycyclic compounds as in the elegant studies of bicyclic and polycyclic cryptands by J. M. Lehn and his co-workers [3] (see also ref. 2 of Part 1 for important related work on monocyclic crown ether derivatives).

The bis-phthaloyl diamines (3) were synthesised by literature procedures [4] from the corresponding polyethylene glycols and were converted by hydrazinolysis into the corresponding diamines from which the bis-alkoxycarbonyl derivatives (4) could readily be obtained. The dianions generated from the bis-amides (4) using sodium hydride in dimethyl sulphoxide reacted with *m*-xylylene dibromide giving the series of metacyclophanes (5) in moderate yields. The use of high dilution procedures for this reaction, (4)→(5), proved to be unnecessary and in all cases the monomeric cyclisation product (5) was the major reaction product. Reduction of the *N*-ethoxycarbonyl derivatives (5) with lithium aluminium hydride gave the *N*-methyl derivatives (6) in good yield. The diamines (6) formed complexes with primary alkylammonium cations and an examination of complex formation is reported below (Results and Discussion Section). The analogous metacyclophanes (7) and (8) were required for comparison and they were readily synthesised from the appropriate diamine by an analogous procedure.

In order to prepare a series of compounds based upon the metacyclophane system (2,n = 2) having different side chains on the nitrogen atoms containing a variety of functional groups the parent diamine (2, n = 2, R = H) was required. Preliminary experiments showed that the benzyloxycarbonyl derivatives of diazametacyclophanes [*e.g.* (9c)] could be obtained by reaction of the appropriate bis(amide)dianion with *m*-xylylene dibromide and this makes the series of diazametacyclophanes (10) potentially readily available. The cyclophane (11b) could be obtained in moderate yields either by reaction of *m*-xylylene dibromide with the dianion from (4d) or, more conveniently, by the reaction of the dianion from the *m*-xylylene diamine derivative (13) with the triethylene glycol derivatives (14a or b). Reaction of the cyclophane (11b) with HBr in acetic acid, under carefully controlled conditions, gave the required diamine (12b) in excellent yield.

A wide variety of compounds (15) are obviously available from the diamine (12b) and some examples of alkylation (restricted to reactive halides) and acylation procedures are outlined in Scheme 1.

EXPERIMENTAL

General.—^{1}H N.m.r. spectra were determined using a Varian HA 100 spectrometer; temperatures were calibrated in the usual way using a methanol sample and are probably accurate to ±2 °C. Solutions of complexes were prepared by adding the appropriate quantity of the guest ammonium

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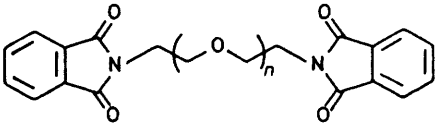
salt to a solution (generally *ca.* 0.2M) of the host diamine. Chemical shifts are given in p.p.m. (δ) relative $SiMe_4$ and the symbols s, d, t, q have the usual meaning.

I.r. spectra were recorded for chloroform solutions using a Perkin-Elmer 157G spectrometer. Low-resolution mass spectra were recorded using an A.E.I. MS 12 spectrometer and although details are not give in all cases mass spectra were in accord with the assigned structure. High-resolution mass spectra quoted for measurement of *M* were obtained by the PCMU, Harwell. Microanalytical data were determined by the University of Sheffield microanalytical service. Melting points were determined using a Kofler hot stage apparatus. The temperatures quoted for short-path distillation refer to the temperature of the heating block and do not represent the boiling points of the oils concerned.

Solvents were purified by standard procedures. Solutions were dried using either anhydrous sodium sulphate ($CHCl_3$, CH_2Cl_2) or anhydrous magnesium sulphate (Et_2O). Anhydrous potassium carbonate was dried by heating over a flame for several hours before use. Sodium hydride was obtained as a 50% dispersion in oil, the oil was removed by washing with pentane before use and the quantities of sodium hydride quoted refer to the weight of reagent after the removal of oil.

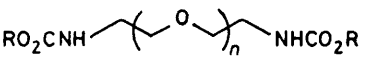
NN′-*Bisethoxycarbonyl*-1,5-*diamino*-3-*oxapentane* (4a).—Hydrazine hydrate (99%, 11.0 ml, 0.277 mol) was added to a hot, stirred suspension of the bis(phthalimido)diamine (3a) (40.0 g, 0.11 mol) in 95% ethanol (100 ml). The solution was heated under reflux for 40 min; a voluminous white precipitate formed, and the mixture was then acidified to pH 1 with hydrochloric acid (6N) and heating was continued for a further 45 min. The reaction mixture was cooled and filtered and the filtrate, together with ethanol washings of the precipitate, was evaporated to a volume of *ca.* 30 ml. After allowing the solution to stand at room temperature for 0.5 h precipitated solid was removed and the filtrate diluted with water (20 ml) to give a solution of the diamine hydrochloride.

Aqueous sodium hydroxide (13.4 g, 0.33 mol in 25 ml H_2O) was added to the cooled, stirred solution of the hydrochloride followed by ether (20 ml); half of a solution of ethyl chloroformate (32 ml, 0.33 mol) in ether (20 ml) was added dropwise over 15 min. The remainder of the ethyl chloroformate was added dropwise and simultaneously with a solution of sodium hydroxide (13.4 g, 0.33 mol in 25 ml H_2O) over a further 15 min. The reaction mixture was stirred at 0 °C for 0.5 h and at room temperature for 1 h, the ether layer was separated, the aqueous phase was extracted with ether, and the combined ethereal solutions were dried and evaporated to give the *bis*(*carbamate*) (4a) (26.8 g, 98%) as an orange oil which could be used for the preparation of the cyclophane derivative (5a) without



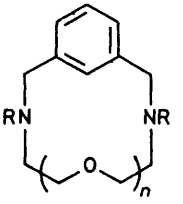
(3)

(3); a *n* = 1
b *n* = 2
c *n* = 3

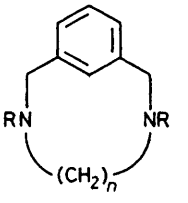


(4)

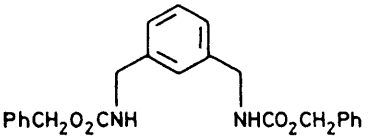
(4) a *n* = 1, R = Et
b *n* = 2, R = Et
c *n* = 3, R = Et
d *n* = 2, R = CH_2Ph
e *n* = 1, R = CH_2Ph



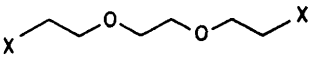
(5) R = CO_2Et
(6) R = Me
(11) R = CO_2CH_2Ph
(12) R = H
a, *n* = 1; b, *n* = 2; c, *n* = 3



(7) R = CO_2Et
(8) R = Me
(9) R = CO_2CH_2Ph
(10) R = H
a, *n* = 5; b, *n* = 8; c, *n* = 6



(13)



(14) a, X = Br
b, X = $OSO_2C_6H_4Me$

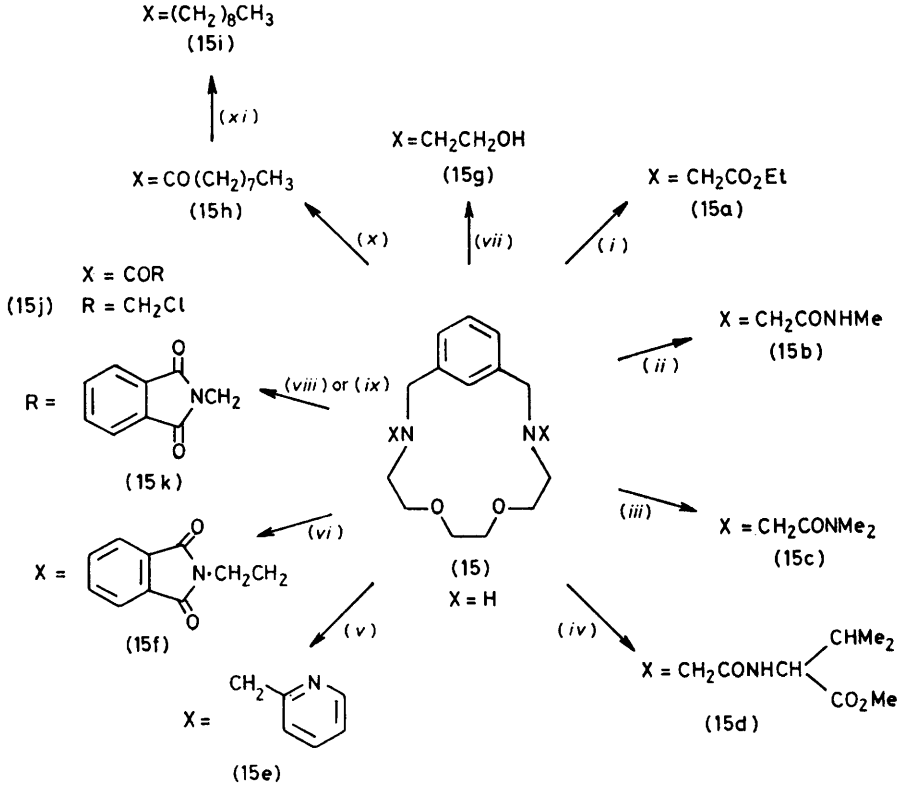
further purification. A sample was purified by short-path distillation at 165—170 °C (0.03 torr) (Found: C, 48.7; H, 8.2; N, 11.0. $C_{10}H_{20}N_2O_5$ requires C, 48.4; H, 8.1; N, 11.3%); $\nu_{max.}$ 3 320 and 1 710 cm^{-1}; $\delta(CDCl_3)$ 5.3 (br s, 2 NH), 4.15 (q, *J* 7 Hz, 2 CH_2CH_3), 3.75—3.20 (m, 2 NCH_2-CH_2O), and 1.25 (t, *J* 7 Hz, 2 CH_2CH_3).

NN′-*Bisethoxycarbonyl*-1,8-*diamino*-3,6-*dioxaoctane* (4b).—The bis(phthalimido)diamine (3b) (33.2 g, 0.081 5 mol) was reacted in a similar manner with hydrazine hydrate (99%, 8.8 ml, 0.18 mol) followed by ethyl chloroformate (20.0 ml, 0.245 mol) giving the *bis*(*carbamate*) (4b) (24.4 g, 100%) as a pale yellow oil. A sample was purified by short-path distillation at 190 °C (0.03 torr) (Found: C, 49.55; H, 8.3; N, 9.45. $C_{12}H_{24}N_2O_6$ requires C, 49.3; H, 8.3; N, 9.6%); $\nu_{max.}$ 3 330 and 1 705 cm^{-1}; $\delta(CDCl_3)$ 5.44 (br s, 2 NH), 4.05 (q, *J* 7 Hz, 2 CH_2CH_3), 3.55 (s, OCH_2CH_2O), 3.6—3.2 (m, 2 OCH_2CH_2N), and 1.16 (t, *J* 7 Hz, 2 CH_2CH_3).

NN′-*Bisethoxycarbonyl*-1,11-*diamino*-3,6,9-*trioxaundecane* (4c).—The bis(phthalimido)diamine (3c) (37.0 g, 0.081 5 mol) was reacted in a similar manner with hydrazine hydrate (99%, 8.8 ml, 0.18 mol) followed by ethyl chloroformate (20.0 ml, 0.245 mol) giving the *bis*(*carbamate*) (4c) (32.9 g, 100%) as a pale yellow oil. A sample was purified by short path distillation at 190 °C (0.04 torr) (Found: C, 49.9; H, 8.3; N, 8.5. $C_{14}H_{28}N_2O_7$ requires C, 50.0; H, 8.4; N, 8.3%); $\nu_{max.}$ 3 340 and 1 715 cm^{-1}; $\delta(CDCl_3)$ 5.50 (br s, 2 NH), 4.15 (q, *J* 7 Hz, 2 CH_2CH_3), 3.8—3.2 (m, 2 OCH_2CH_2O + 2 OCH_2CH_2N), and 1.25 (t, *J* 7 Hz, 2 CH_2CH_3).

NN′-*Bisbenzyloxycarbonyl*-1,8-*diamino*-3,6-*dioxaoctane* (4d).—Hydrazinolysis of the bis(phthalimido)diamine (3b) (48.6 g, 0.119 mol) was carried out as before using hydrazine hydrate (99%, 11.4 ml, 0.25 mol) giving an aqueous solution of the diamine hydrochloride. This solution was cooled (0 °C) and aqueous sodium hydroxide added (10.4 g, 0.262 mol in 20 ml H_2O), followed by dropwise addition of benzyl chloroformate (44.5 g, 0.262 mol) to the stirred reaction mixture over 10 min. A further portion of benzyl chloroformate (44.5 g, 0.262 mol) and aqueous sodium hydroxide (10.4 g, 0.262 mol in 20 ml H_2O) were added simultaneously and dropwise over a further 10 min and stirring was continued at room temperature for 2 h. The reaction mixture was extracted with chloroform and evaporation of the dried extract gave the *bis*(*carbamate*) (4d) (49.8 g, 100%) as a yellow oil. A sample was purified by short-path distillation at 250 °C (0.03 torr) (Found: C, 63.4; H, 6.6; N, 7.0. $C_{22}H_{28}N_2O_6$ requires C, 63.45; H, 6.8; N, 6.7%); $\nu_{max.}$ 3 330 and 1 710 cm^{-1}; $\delta(CDCl_3)$ 7.5—7.2 (m, 2 Ph), 5.35 (br s, 2 NH), 5.15 and 5.1 (s, 2 $ArCH_2$), and 3.7—3.2 (m, OCH_2-CH_2O + 2 OCH_2CH_2N).

NN′-*Bisbenzyloxycarbonyl*-1,5-*diamino*-3-*oxapentane* (4e).—The bis(phthalimido)diamine (3a) (31.2 g, 0.086 mol) reacted as before with hydrazine hydrate (99%, 9.0 ml, 0.185 mol) giving an aqueous solution of the diamine hydrochloride. This solution reacted with benzyl chloroformate (29.8 g, 0.175 mol) as above giving the *bis*(*carbamate*) (4e) (20.3 g, 63%) as a colourless solid by filtration of the reaction mixture. A sample recrystallised from methylene chloride–cyclohexane had m.p. 64—66 °C (Found: C, 64.2; H, 6.5; N, 7.7. $C_{20}H_{24}N_2O_5$ requires C, 64.5; H, 6.5; N, 7.5%); $\nu_{max.}$ 3 440 and 1 710 cm^{-1};



SCHEME 1 Reagents: (*i*) $BrCH_2CO_2Et$; (*ii*) $ClCH_2CONHMe$; (*iii*) $ClCH_2CONMe_2$; (*iv*) *N*-chloroacetyl-L-valine methyl ester; (*v*) 2-(chloromethyl)pyridine; (*vi*) *N*-(2-bromoethyl)phthalimide; (*vii*) ethylene oxide; (*viii*) $ClCH_2COCl$; (*ix*) *N*-phthaloylglycyl chloride; (*x*) $CH_3[CH_2]_7COCl$; (*xi*) $LiAlH_4$

δ($CDCl_3$) 7.4—7.2 (m, 2 Ph), 5.4 (br s, 2 NH), 5.1 (s, 2 $ArCH_2$), and 3.6—3.2 (m, 2 OCH_2CH_2N).

NN′-Bisbenzylocycarbonyl-αα′-diamino-m-*xylene* (13). — A stirred, cooled (0 °C) solution of αα′-diamino-*m*-xylene [5] (6.8 g, 0.05 mol) in water (30 ml) was treated with benzyl chloroformate (9.4 g, 0.055 mol) over a period of 5 min. Additional benzyl chloroformate (9.4 g, 0.055 mol) and aqueous sodium hydroxide (5.2 g, 0.13 mol in 20 ml H_2O) were added dropwise and simultaneously over a further 5 min and stirring was continued for 0.5 h at 0 °C and 2 h at room temperature. The precipitated white solid was removed by filtration, washed with water, and dried giving the *bis*(*carbamate*) (13) (20.2 g, 100%), m.p. 136—137 °C after crystallisation from methylene chloride–cyclohexane (Found: C, 71.0; H, 6.0; N, 7.0. $C_{24}H_{24}N_2O_4$ requires C, 71.3; H, 6.0; N, 6.9%); $\nu_{max.}$ 3 440 and 1 715 cm^{-1}; δ($CDCl_3$) 7.4—7.0 (m, 14 aryl-H), 5.1 (br s, 2 NH), 5.05 (s, 2 CH_2Ph), and 4.25 (d, *J* 6 Hz, 2 $ArCH_2N$).

NN′-Bisethoxycarbonyl-2,8-diaza-5-oxa[9]*metacyclophane* (5a).—Sodium hydride (1.3 g, 0.054 mol) was added in portions during 45 min to a stirred solution of the bis(carbamate) (4a) (6.2 g, 0.025 mol) in dry dimethyl sulphoxide (50 ml) (N_2 atmosphere) and the resulting green solution was set aside at room temperature for 2 h. This solution and a solution of αα′-dibromo-*m*-xylene (6.6 g, 0.025 mol) in dimethyl sulphoxide (50 ml) were added dropwise and simultaneously to vigorously stirred dimethyl sulphoxide (100 ml) over 50 min (N_2 atmosphere). Stirring was continued for 1 h and the orange solution set aside at room temperature overnight before dilution with water (100 ml) and hydrochloric acid (100 ml, 2N). The mixture was extracted with chloroform (3 × 75 ml) and the combined extracts were washed with water (3 × 100 ml), dried, filtered, and evaporated to give an orange oil (9.4 g). Column chromatography [silica, chloroform–ethyl acetate (40 : 60)] afforded the [9]*metacyclophane* (5a) (4.8 g, 54%) as a colourless oil. A sample was purified by short-path distillation at 195 °C (0.03 torr) (Found: *M*, 350.184 5. $C_{18}H_{26}N_2O_5$ requires *M*, 350.184 2); $\nu_{max.}$ 1 695 cm^{-1}; δ($CDCl_3$) 7.60 (br s, 15-H), 7.4—7.1 (m, 11-H, 12-H, 13-H), 4.55 (s, 2 $ArCH_2$), 4.20 (q, *J* 7 Hz, 2 CH_2CH_3), 3.6—3.0 (m, 2 OCH_2CH_2N), and 1.3 (t, *J* 7 Hz, 2 CH_2CH_3).

NN′-Bisethoxycarbonyl-2,11-diaza-5,8-dioxa[12]*metacyclophane* (5b).—A solution of the bis(carbamate) (4b) (7.2 g, 0.025 mol) in dimethyl sulphoxide (50 ml) reacted successively with sodium hydride (1.25 g, 0.52 mol) and αα′-dibromo-*m*-xylene (6.5 g, 0.025 mol) in dimethyl sulphoxide (50 ml) under the previously described reaction conditions giving the crude product (12.5 g) as an orange oil. Column chromatography [silica, chloroform–ethyl acetate (40 : 60)] gave the [12]*metacyclophane* (5b) (4.0 g, 41%) as a colourless oil. A sample was purified by short-path distillation at 200 °C (0.01 torr) (Found: C, 60.9; H, 7.7; N, 7.1. $C_{20}H_{30}N_2O_6$ requires C, 60.9; H, 7.7; N, 7.1%); $\nu_{max.}$ 1 685 cm^{-1}; δ($CDCl_3$) 7.50 (br s, 18-H), 7.4—7.1 (m, 14-H, 15-H, 16-H), 4.55 (s, 2 $ArCH_2$), 4.20 (q, *J* 7 Hz, 2 OCH_2CH_3), 3.7—3.2 (m, OCH_2CH_2O + 2 OCH_2CH_2N), and 1.25 (t, *J* 7 Hz, 2 OCH_2CH_3).

NN′-Bisethoxycarbonyl-2,14-diaza-5,8,11-trioxa[15]*metacyclophane* (5c).—A solution of the bis(carbamate) (4c) (2.2 g, 0.006 5 mol) in dimethyl sulphoxide (50 ml) reacted successively with sodium hydride (0.35 g, 0.015 mol) and αα′-dibromo-*m*-xylene (1.7 g, 0.006 5 mol) in dimethyl sulphoxide (50 ml) under the previously described reaction conditions giving the crude product (3.7 g) as an orange oil. Column chromatography [silica, chloroform–ethyl acetate (40 : 60)] gave the [15]*metacyclophane* (5c) (820 mg, 29%) as a colourless oil. A sample was purified by short-path distillation at 240 °C (0.04 torr) (Found: C, 60.0; H, 8.0; N, 6.3. $C_{22}H_{34}N_2O_7$ requires C, 60.3; H, 7.8; N, 6.4%); $\nu_{max.}$ 1 690 cm^{-1}; δ($CDCl_3$) 7.69 (br s, 21-H), 7.3—7.0 (m, 17-H, 18-H, 19-H), 4.64 (s, 2 $ArCH_2$), 4.17 (q, *J* 7 Hz, 2 OCH_2CH_3), 3.7—3.2 (m, 2 OCH_2CH_2O + 2 OCH_2CH_2N), and 1.25 (t, *J* 7 Hz, 2 OCH_2CH_3).

NN′-Bisethoxycarbonyl-2,8-diaza[9]*metacyclophane* (7a).—A solution of *NN′*-bisethoxycarbonyl-1,5-diaminopentane [6] (40.0 g, 0.016 mol) in dimethyl sulphoxide (50 ml) reacted successively with sodium hydride (0.82 g, 0.034 mol) and αα′-dibromo-*m*-xylene (4.3 g, 0.016 mol) in dimethyl sulphoxide (50 ml) under the reaction conditions described previously giving the crude product (6.0 g) as an orange oil. Column chromatography [silica, chloroform–ethyl acetate (80 : 20)] gave the [9]*metacyclophane* (7a) (2.16 g, 38%) as a colourless oil. A sample was purified by short-path distillation at 180 °C (0.03 torr) (Found: C, 65.3; H, 8.1; N, 7.9. $C_{19}H_{28}N_2O_4$ requires C, 65.5; H, 8.1; N, 8.0%); $\nu_{max.}$ 1 685 cm^{-1}; δ($CDCl_3$) 7.40 (br s, 15-H), 7.4—7.1 (m, 11-H, 12-H, 13-H), 4.55 (s, 2 $ArCH_2$), 4.20 (q, *J* 7 Hz, 2 OCH_2CH_3), 3.3—2.9 (m, 2 NCH_2), 1.30 (t, *J* 7 Hz, 2 OCH_2CH_3), and 1.4—0.9 [m, $NCH_2(CH_2)_3CH_2N$].

NN′-Bisethoxycarbonyl-2,11-diaza[12]*metacyclophane* (7b).—A solution of *NN′*-bisethoxycarbonyl-1,8-diaminooctane [7] (7.4 g, 0.026 mol) in dimethyl sulphoxide (100 ml) reacted successively with sodium hydride (1.35 g, 0.056 mol) and αα′-dibromo-*m*-xylene (6.8 g, 0.026 mol) in dimethyl sulphoxide (100 ml) under the reaction conditions described previously giving the crude product (10.2 g) as an orange oil. Column chromatography [silica, chloroform–ethyl acetate (80 : 20)] gave the [12]*metacyclophane* (7b) (1.92 g, 19%) as a colourless oil. A sample was purified by short-path distillation at 220 °C (0.05 torr) (Found: C, 67.5; H, 8.5; N, 7.0. $C_{22}H_{34}N_2O_4$ requires C, 67.7; H, 8.8; N, 7.2%); $\nu_{max.}$ 1 680 cm^{-1}; δ($CDCl_3$) 7.4—7.2 (m, 14-H, 15-H, 16-H, 18-H), 4.50 (s, 2 $ArCH_2$), 4.20 (q, *J* 7 Hz, 2 OCH_2CH_3), 3.5—3.0 (m, 2 NCH_2), 1.30 (t, *J* 7 Hz, 2 OCH_2CH_3), and 1.4—0.8 (m, $NCH_2[CH_2]_6CH_2N$).

NN′-Bisbenzyloxycarbonyl-2,9-diaza[10]*metacyclophane* (9c).—A solution of *NN′*-bisbenzyloxycarbonyl-1,6-diaminohexane (8.5 g, 0.022 mol) in dimethyl sulphoxide (50 ml) reacted successively with sodium hydride (1.2 g, 0.05 mol) and αα′-dibromo-*m*-xylene (5.8 g, 0.022 mol) in dimethyl sulphoxide (50 ml) under the reaction conditions described previously giving the crude product (10.2 g) as an orange oil. Column chromatography [silica, light petroleum (b.p. 60—80 °C)–ethyl acetate (70 : 30)] gave the [10]-*metacyclophane* (9c) (2.06 g, 19%) as a colourless oil. A sample was purified by short-path distillation at 270 °C (0.03 torr) (Found: C, 73.8; H, 7.3; N, 5.5. $C_{30}H_{34}N_2O_4$ requires C, 74.05; H, 7.0; N, 5.8%); $\nu_{max.}$ 1 680 cm^{-1}; δ($CDCl_3$) 7.5—7.0 (m, 14 aryl-H), 5.15 (br s, 2 $PhCH_2O$), 4.45 (br s, 2 $ArCH_2N$), 3.3—3.1 (m, 2 NCH_2), and 1.2—0.6 (m, $NCH_2[CH_2]_4CH_2N$).

NN′-Bisbenzyloxycarbonyl-2,11-diaza-5,8-dioxa[12]*metacyclophane* (11b).—Three methods were used. (*A*) A solution of *NN′*-bisbenzyloxycarbonyl-1,8-diamino-3,6-dioxa-octane (4d) (5.7 g, 0.013 7 mol) in dimethyl sulphoxide (50 ml) reacted successively with sodium hydride (0.7 g, 0.029 mol) and αα′-dibromo-*m*-xylene (3.6 g, 0.013 7 mol) in dimethyl sulphoxide (50 ml) under the reaction conditions described previously giving the crude product (8.1 g) as an

orange oil. Column chromatography [silica, chloroform–ethyl acetate (80 : 20)] gave the [12]*metacyclophane* (11b) (2.21 g, 31%) as a colourless oil. A sample was purified by short-path distillation at 300 °C (0.02 torr) (Found: C, 69.7; H, 7.0; N, 5.4. $C_{30}H_{34}N_2O_6$ requires C, 69.5; H, 6.6; N, 5.4%); $\nu_{max.}$ 1 690 cm^{-1}; δ($CDCl_3$) 7.5—7.0 (m, 14 aryl-H), 5.16 (s, 2 PhCH_2O), 4.55 (s, 2 ArCH_2N), and 3.7—3.2 (m, OCH_2CH_2O + 2 OCH_2CH_2N).

(*B*) A solution of *NN'*-bisbenzyloxycarbonyl-αα'-diamino-*m*-xylene (13) (8.1 g, 0.02 mol) in dimethyl sulphoxide (75 ml) reacted successively with sodium hydride (1.05 g, 0.044 mol) and 1,8-dibromo-3,6-dioxaoctane (14a) (5.55 g, 0.02 mol) in dimethyl sulphoxide (75 ml) under the reaction conditions described previously, giving the crude product (9.3 g) as an orange oil. Purification, as above, gave the [12]metacyclophane (11b) (3.4 g, 32%).

(*C*) This procedure was identical with that of method (*B*) except that the bis-*p*-toluenesulphonate of 1,8-dihydroxy-3,6-dioxa-octane (14b) (1 mol equiv.) was used in place of the dibromo-compound. The metacyclophane (11b) was purified as above (30% yield).

NN'-*Dimethyl*-2,8-*diaza*-5-*oxa*[9]*metacyclophane* (6a).—Lithium aluminium hydride (800 mg, 21 mmol) was added in portions to a stirred solution of the bisethoxycarbonylmetacyclophane (5a) (942 mg, 2.69 mmol) in ether (15 ml) and the resulting mixture was stirred at room temperature for 2 h. Excess of hydride was destroyed by the cautious addition of water and the resulting suspension was filtered. The residual alumina was washed with ethyl acetate and the combined filtrate and washings were evaporated to dryness giving the [9]*metacyclophane* (6a) (513 mg, 81%) as a pale yellow oil. A sample was purified by short-path distillation at 120 °C (0.02 torr) (Found: C, 71.5; H, 9.3; N, 11.7. $C_{14}H_{22}N_2O$ requires C, 71.75; H, 9.5; N, 11.95%); δ($CDCl_3$) 8.2—7.8 (m, 11-H, 12-H, 13-H, 15-H), 3.60 (s, 2 $ArCH_2N$), 2.99 (t, *J* 5 Hz, 2 OCH_2), 2.46 (s, 2 NCH_3), and 2.37 (t, *J* 5 Hz, 2 NCH_2).

NN'-*Dimethyl*-2,11-*diaza*-5,8-*dioxa*[12]*metacyclophane* (6b).—A solution of the bisethoxycarbonylmetacyclophane (5b) (779 mg, 1.98 mmol) in ether (15 ml) and lithium aluminium hydride (600 mg, 15.8 mmol) gave the required [12]metacyclophane (6b) (512 mg, 93%) as a pale yellow oil. A sample was purified by short-path distillation at 140 °C (0.01 torr) (Found: C, 68.9; H, 9.55; N, 10.3. $C_{16}H_{26}N_2O_2$ requires C, 69.0; H, 9.4; N, 10.1%); δ(CD_2Cl_2) 7.84 (br s, 18-H), 7.12—6.9 (m, 14-H, 15-H, 16-H), 3.63 (s, 2 $ArCH_2N$), 3.54 (s, OCH_2CH_2O), 3.51 (t, *J* 5 Hz, 2 OCH_2), 2.51 (t, *J* 5 Hz, 2 NCH_2), and 2.33 (s, 2 NCH_3).

NN'-*Dimethyl*-2,14-*diaza*-5,8,11-*trioxa*[15]*metacyclophane* (6c).—A solution of the bisethoxycarbonylmetacyclophane (5c) (234 mg, 0.53 mmol) in ether (20 ml) and lithium aluminium hydride (152 mg, 4.0 mmol) gave the required [15]*metacyclophane* (6c) (132 mg, 77%) as a pale yellow oil. A sample was purified by short-path distillation at 180 °C (0.05 torr) (Found: C, 66.8; H, 9.6; N, 8.7. $C_{18}H_{30}N_2O_3$ requires C, 67.05; H, 9.4; N, 8.7%); δ($CDCl_3$) 7.59 (br s, 21-H), 7.3—7.0 (m, 17-H, 18-H, 19-H), 3.75—3.5 (m, 2 $ArCH_2N$ + 6 OCH_2), 2.56 (t, *J* 5 Hz, 2 NCH_2), and 2.29 (s, 2 NCH_3).

NN'-*Dimethyl*-2,8-*diaza*[9]*metacyclophane* (8a).—A solution of the bisethoxycarbonylmetacyclophane (7a) (613 mg, 1.76 mmol) in ether (20 ml) and lithium aluminium hydride (600 mg, 15.8 mmol) gave the required [9]*metacyclophane* (8a) (341 mg, 83%) as a pale yellow oil. A sample was purified by short-path distillation at 140 °C (0.03 torr) (Found: C, 77.7; H, 10.7; N, 12.2. $C_{15}H_{24}N_2$ requires C, 77.5; H, 10.4; N, 12.05%); δ($CDCl_3$) 8.02 (br s, 15-H), 7.3—6.9 (m, 11-H, 12-H, 13-H), 3.57 (s, 2 $ArCH_2N$), 2.42 (s, 2 NCH_3), 2.20 (t, *J* 5 Hz, 2 NCH_2), 8.41 (quintet, *J* 6 Hz, 5-CH_2), and 0.94 (quintet, *J* *ca.* 6 Hz, 4-CH_2 and 6-CH_2).

NN'-*Dimethyl*-2,11-*diaza*[12]*metacyclophane* (8b).—A solution of the bisethoxycarbonylmetacyclophane (7b) (584 mg, 1.5 mmol) in ether (20 ml) and lithium aluminium hydride (450 mg, 12 mmol) gave the required [12]*metacyclophane* (8b) (369 mg, 90%) as a colourless oil. A sample was purified by short-path distillation at 130 °C (0.03 torr) (Found: C, 78.5; H, 10.85; N, 10.2. $C_{18}H_{30}N_2$ requires C, 78.8; H, 11.0; N, 10.2%); δ (CD_2Cl_2, 0 °C) 7.43 (br s, 18-H), 7.3—7.0 (m, 14-H, 15-H, 16-H), 3.42 (s, 2 $ArCH_2N$), 2.31 (s, 2 NCH_3), 2.18 (t, *J* 7 Hz, 2 NCH_2), and 1.6—0.9 (m, $NCH_2[CH_2]_6CH_2N$).

2,11-*Diaza*-5,8-*dioxa*[12]*metacyclophane* (12b).—A solution of the bisbenzyloxcarbonyl[12]metacyclophane (11b) (184 mg) in 45% hydrogen bromide in acetic acid (3.0 ml) was heated on a steam-bath for 3 min, evaporated to dryness, and the residual gum partitioned between water and chloroform. The aqueous phase was separated, basified (aqueous NaOH), and extracted with chloroform. This chloroform extract was dried and evaporated giving the [12]*metacyclophane* (12b) (89 mg, 100%) as a colourless oil. A sample was purified by short-path distillation at 180 °C (0.03 torr) (Found: C, 67.3; H, 9.0; N, 11.5. $C_{14}H_{22}N_2O_2$ requires C, 67.2; H, 8.9; N, 11.2%); $\nu_{max.}$ 3 200 cm^{-1}; δ($CDCl_3$) 7.59 (br s 18-H), 7.4—7.0 (m, 14-H, 15-H, 16-H), 3.86 (s, 2 $ArCH_2N$), 3.63 (s, OCH_2CH_2O), 3.62 (t, *J* 5 Hz, 2 OCH_2), 2.83 (t, *J* 5 Hz, 2 NCH_2), and 2.39 (s,2 NH).

NN'-Bis-(2-*hydroxyethyl*)-2,11-*diaza*-5,8-*dioxa*[12]*metacyclophane* (15g).—Ethylene oxide (0.3 ml, 70 mmol) and water (1 drop) were added to a solution of the [12]metacyclophane (12b) (100 mg, 0.4 mmol) in ethanol (2 ml) and the resulting solution stirred overnight at room temperature. Evaporation gave the diol (15g) (130 mg, 96%) as a colourless oil which was purified by column chromatography [basic alumina, ether–ethanol (12 : 1)] or by short-path distillation at 200 °C (0.04 torr) (Found: C, 64.0; H, 8.9; N, 8.0. $C_{18}H_{30}N_2O_4$ requires C, 63.9; H, 8.9; N, 8.3%); $\nu_{max.}$ 3 420 cm^{-1}; δ(CD_2Cl_2) 8.01 (br s, 18-H, 7.3—6.9 (m, 14-H, 15-H, 16-H), 3.66 (s, 2 $ArCH_2N$), 3.60 (s, OCH_2-CH_2O), 3.53 (t, *J* 5 Hz, 2 OCH_2), 3.37 (t, *J* 5 Hz, 2 CH_2OH), 3.5 (br s, 2 OH), 2.70 (t, *J* 5 Hz, 2 NCH_2), and 2.55 (t, *J* 5 Hz, 2 NCH_2). The *diacetate* was obtained (82% yield) by treatment with acetic anhydride–pyridine (Found: *M*, 422.239 9. $C_{22}H_{34}N_2O_6$ requires *M*, 422.241 7); $\nu_{max.}$ 1 735 cm^{-1}; δ($CDCl_3$) 7.78 (br s, 18-H), 7.2—6.9 (m, 14-H, 15-H, 16-H), 4.19 (t, *J* 6 Hz, 2 CH_2OAc), 3.69 (s, 2 $ArCH_2N$), 3.52 (s, OCH_2CH_2O), 3.47 (t, *J* 6 Hz, 2 OCH_2), 2.83 (t, *J* 6 Hz, 2 NCH_2), 2.68 (t, *J* 6 Hz, 2 NCH_2), and 2.01 (s, 2 $OCOCH_3$).

NN'-*Dinonyl*-2,11-*diaza*-5,8-*dioxa*[12]*metacyclophane* (15i).—A stirred solution of the [12]metacyclophane (12b) (314 mg, 1.26 mmol) in methylene chloride (2 ml) was treated with triethylamine (0.35 ml, 2.52 mmol) and a solution of nonanoyl chloride (445 mg, 2.53 mmol) in methylene chloride (2 ml). Stirring was continued at room temperature for 5 h; the solution was then washed with water, dried, and evaporated giving the crude bis(amide) (15h) (617 mg, 92%) as a red oil. Purification by column chromatography [silica, chloroform–ethyl acetate (80 : 20)] gave the amide as a colourless oil (343 mg) [$\nu_{max.}$ 1 640 cm^{-1}; *m/e* 530 (M^+)]. A solution of the bis(amide)

(84.2 mg, 0.16 mmol) in ether (5 ml) was reduced with lithium aluminium hydride (40 mg, 1.05 mmol) during 2 h at room temperature. Excess of hydride was destroyed by dropwise addition of water, the mixture was filtered, and the residual alumina washed with ethyl acetate. The combined filtrate and washings were evaporated giving the NN′-*dinonyl*[12]*metacyclophane* (15i) as a colourless oil (67 mg, 84%) (Found: *M*, 502.448 0, $C_{32}H_{58}N_2O_2$ requires *M*, 502.449 8); δ(CD_2Cl_2) 7.74 (br s, 18-H), 7.2—6.9 (m, 14-H, 15-H, 16-H), 3.6—3.3 (m, 2 ArCH_2N + 4 OCH_2), and 2.6—0.7 (m, 2 NCH_2 + 2 N[CH_2]$_8CH_3$).

NN′-*Bischloroacetyl*-2,11-*diaza*-5,8-*dioxa*[12]*metacyclophane* (15j).—A solution of the [12]metacyclophane (12b) (117 mg, 0.47 mmol) in ether (15 ml) reacted with triethylamine (0.19 ml, 1.4 mmol) and chloroacetyl chloride (0.11 ml, 1.4 mmol) giving the crude bis(amide) (15j) (230 mg). Purification by t.l.c. (silica, ethyl acetate) gave the pure *amide* (15j) as a colourless oil (112 mg, 59%). A sample was further purified by short-path distillation at 300 °C (0.02 torr) (Found: C, 53.9; H, 6.2; N, 6.9; Cl, 17.75. $C_{18}H_{24}N_2Cl_2O_4$ requires C, 53.6; H, 6.0; N, 6.95; Cl, 17.58%); $\nu_{max.}$ 1 650 cm^{-1}; δ($C_6D_5NO_2$ at 100 °C) 7.44 (s, 18-H), 7.04 (s, 14-H, 15-H, 16-H), 4.48 (s, 2 ArCH_2N), 4.09 (s, OCH_2CH_2O), 3.46 (t, *J* 5 Hz, 2 OCH_2), 3.25 (t, *J* 5 Hz, 2 NCH_2), and 3.14 (s, 2 $COCH_2Cl$).

NN′-*Bis*-(N-*phthaloylglycyl*)-2,11-*diaza*-5,8-*dioxa*[12]*metacyclophane* (15k).—A solution of the [12]metacyclophane (12b) (134 mg, 0.54 mmol) in ether (20 ml) was treated with triethylamine (0.23 ml, 1.7 mmol) and *N*-phthaloylglycyl chloride [8] in ether (10 ml). The resulting mixture was stirred overnight at room temperature, evaporated to dryness, and partitioned between water and chloroform. The chloroform layer was washed (aqueous $NaHCO_3$), dried, and evaporated giving a white crystalline solid (364 mg). Purification by t.l.c. (silica, ethyl acetate) gave the pure [12]metacyclophane derivative (15k), m.p. 220—221 °C (192 mg, 57%) (Found: C, 65.3; H, 5.3; N, 8.9. $C_{34}H_{32}N_4O_8$ requires C, 65.4; H, 5.2; N, 9.0%); $\nu_{max.}$ 1 775, 1 720; and 1 655 cm^{-1}; δ($C_6D_5NO_2$ at 100 °C), 7.88 (s, 18-H), 7.7—6.9 (m, 11 aryl-H), 4.54 (br s, 2 $ArCH_2$-N + 2 $COCH_2N$), 3.7 — 3.1 (m, 4 OCH_2 + 2 NCH_2).

Diethyl 2,11-*Diaza*-5,8-*dioxa*[12]*metacyclophane*-NN′-*bis-acetate* (15a).—A solution of the [12]metacyclophane (12b) (140 mg, 0.56 mmol) and ethyl bromoacetate (0.13 ml, 1.16 mmol) in acetonitrile (15 ml) containing anhydrous potassium carbonate (250 mg, 1.8 mmol) was stirred at room temperature for 1 h. The solution was evaporated to dryness and the residue partitioned between chloroform and water. The organic layer was washed (aqueous $NaHCO_3$), dried, and evaporated giving the *diester* (15a) (201 mg, 85%). A sample was purified by column chromatography (silica, ether) and short-path distillation at 220 °C (0.02 torr) (Found: C, 62.5; H, 8.2; N, 6.8. $C_{22}H_{34}N_2O_6$ requires C, 62.5; H, 8.1; N, 6.6%); $\nu_{max.}$ 1 725 cm^{-1}; δ($CDCl_3$) 7.93 (br s, 18-H), 7.2—6.9 (m, 14-H, 15-H, 16-H), 4.16 (q, *J* 7 Hz, 2 OCH_2CH_3), 3.88 (s, 2 NCH_2CO), 3.58 (s, 2 ArCH_2N), 3.46 (s, OCH_2CH_2O), 3.54 (t, *J* 5 Hz, 2 OCH_2), 2.92 (t, *J* 5 Hz, 2 NCH_2), and 1.26 (t, *J* 7 Hz, 2 OCH_2CH_3).

NN′-*Bis*-(2-*phthalimidoethyl*)-2,11-*diaza*-5,8-*dioxa*[12]*metacyclophane* (15f).—A solution of the [12]metacyclophane (12b) (104 mg, 0.415 mmol) and *N*-(2-bromoethyl)phthalimide [9] (446 mg, 1.76 mmol) in acetonitrile (20 ml) containing anhydrous potassium carbonate (330 mg, 2.39 mmol) was stirred and heated under reflux for 3 d. The solution was evaporated to dryness and the residual gum partitioned between water and chloroform. The organic phase was dried and evaporated giving an orange oil (469 mg) which was purified by t.l.c. to yield the *bis*(*phthalimidoethyl*)-*cyclophane* (15f) (171 mg, 69%) as a pale yellow gum (Found: [*M* — 1]$^+$, 595.251 5. $C_{34}H_{36}N_4O_6$ requires [*M* — 1]$^+$, 595.255 7); $\nu_{max.}$ 1 770 and 1 705 cm^{-1}; δ($CDCl_3$) 7.9—7.6 (8 aryl-H, 2 phthaloyl groups), 7.53 (br s, 18-H), 7.2—6.9 (m, 14-H, 15-H, 16-H), 3.81 (t, *J* 7 Hz, 2 CH_2N-phthaloyl), 3.59 (s, 2 ArCH_2N), 3.30 (t, *J* 5.5 Hz, 2 OCH_2), 3.18 (s, OCH_2CH_2O), 2.82 (t, *J* 7 Hz, 2 NCH_2), and 2.52 (t, *J* 5.5 Hz, 2 NCH_2).

NN′-*Bis*-(N-*methylacetamido*)-2,11-*diaza*-5,8-*dioxa*[12]*metacyclophane* (15b).—A solution of the [12]metacyclophane (12b) (274 mg, 1.1 mmol) and *N*-methyl-2-chloroacetamide [10] (355 mg, 3.3 mmol) in acetonitrile (3 ml) containing anhydrous potassium carbonate (700 mg, 5.1 mmol) was stirred and heated under reflux for 1.25 h. The solution was evaporated and the residual oil partitioned between aqueous hydrochloric acid and chloroform. The aqueous phase was basified (aqueous NaOH) and extracted with chloroform. The chloroform extract was dried and evaporated giving the *diamide* (15b) (417 mg, 97%) as a white crystalline solid, m.p. 124—128 °C (Found: C, 61.0; H, 8.3; N, 14.5. $C_{20}H_{32}N_4O_4$ requires C, 61.2; H, 8.2; N, 14.3%); $\nu_{max.}$ 3 320 and 1 655 cm^{-1}; δ($CDCl_3$) 7.94 (br s, 18-H), 7.2—6.8 (m, 14-H, 15-H, 16-H), 3.69 (s, 2 $ArCH_2N$ + OCH_2CH_2O), 3.62 (t, *J* 5 Hz, 2 OCH_2), 3.14 (s, 2 NCH_2-CO), 2.84 (t, *J* 5 Hz, NCH_2), and 2.71 (d, *J* 5 Hz, 2 NCH_3).

NN′-*Bis*-(NN-*dimethylacetamido*)-2,11-*diaza*-5,8-*dioxa*[12]*metacyclophane* (15c).—A solution of the [12]metacyclophane (12b) (210 mg, 0.84 mmol) and *NN*-dimethyl-2-chloroacetamide [11] (205 mg, 1.68 mmol) in acetonitrile (4 ml) containing anhydrous potassium carbonate (400 mg, 2.9 mmol) was stirred and heated under reflux for 1 h. The product, obtained as in the previous experiment, was a pale yellow oil (343 mg) which was purified by column chromatography (basic alumina, ether) giving the *diamide* (15c) (204 mg, 58%) as a colourless oil (Found: *M*, 420.273 2. $C_{22}H_{36}N_4O_4$ requires *M*, 420.273 6); $\nu_{max.}$ 1 640 cm^{-1}; δ($CDCl_3$) 7.98 (br s, 18-H), 7.3—7.0 (s, 14-H), 15-H, 16-H), 3.77 (s, 2 ArCH_2N), 3.58 (s, OCH_2CH_2O), 3.40 (s, 2 NCH_2CO), 3.57 (t, *J* 5 Hz, 2 OCH_2), 3.00 (s, 2 NCH_3), 2.89 (s, 2 NCH_3), and 2.80 (t, *J* 5 Hz, 2 CH_2N).

NN′-*Bis*-(2-N-*acetyl*-L-*valine methyl ester*)-2,11-*diaza*-5,8-*dioxa*[12]*metacyclophane* (15d).—A solution of the [12]-metacyclophane (12b) (92 mg, 0.37 mmol) and *N*-chloroacetyl-L-valine methyl ester [12] (230 mg, 1.1 mmol) in acetonitrile (2 ml) containing anhydrous potassium carbonate (600 mg, 4.4 mmol) was stirred and heated under reflux for 45 min. The *product* (15d) (176 mg, 80%), obtained as in the previous experiments, was a white crystalline solid, m.p. 76—77 °C, $[\alpha]_D^{25}$ 0° ($CHCl_3$) (Found: C, 60.5; H, 8.4; N, 9.45. $C_{30}H_{48}N_4O_8$ requires C, 60.8; H, 8.2; N, 9.45%); $\nu_{max.}$, 3 310, 1 740, and 1 665 cm^{-1}; δ($CDCl_3$), 8.10 (br s, 18-H), 7.97 (br s, 2 NH), 7.19—6.90 (m, 14-H, 15-H, 16-H), 4.44 (dd, 2 NHC*H*), 3.78 (t, *J* 5 Hz, 2 OCH_2), 3.71 (s, 2 OCH_3), 3.63 (s, OCH_2CH_2O + 2 ArCH_2N), 3.18 (s, 2 NCH_2CO), 2.80 (t, *J* 5 Hz, 2 NCH_2), 2.10 (m, 2 C*H*Me_2), and 0.85 [d, *J* 7 Hz, CH(CH_3)$_2$].

NN′-*Bis*-(2-*pyridylmethyl*)-2,11-*diaza*-5,8-*dioxa*[12]*metacyclophane* (15e).—A solution of the [12]metacyclophane (12b) (175 mg, 0.7 mmol) and freshly prepared [13] 2-chloromethylpyridine (180 mg, 1.4 mmol) in acetonitrile (5 ml) containing anhydrous potassium carbonate (300 mg, 2.1 mmol) was stirred at room temperature overnight and

TABLE 1

N.m.r. spectra of complexes of the [9]metacyclophane (6a) with primary alkylammonium salts in CD_2Cl_2

Guest	Temperature (°C)	Chemical shifts of host [a] (p.p.m.) 15-H	$ArCH_2N$	OCH_2 [b]	NCH_2 [b]	NMe	Chemical shifts, of guest (p.p.m.)
	35	8.24	3.60	2.99	2.37	2.46	
	−80		4.00 (A), 3.20 (B) [c]				
$PhCH_2\overset{+}{N}H_3NCS^-$	20	7.76	3.64	2.82	2.46	2.38	4.09
	−60		4.04 (A), 3.12 (B) [c]				
(*R*)-$PhCHMe\overset{+}{N}H_3NCS^-$	35	7.90	3.64	2.89	2.47	2.43	5.34 (q, *J* 7 Hz), 1.64 (d, *J* 7 Hz)
	−60		4.04 (A1), 3.12 (B1) [c] 3.93 (A2), 3.12 (B2) [c]			2.28 (Me1), 2.19 (Me2),	
(*R,S*)-$PhCHMe\overset{+}{N}H_3NCS^-$	35	7.74	3.63	2.84	2.46	2.37	5.35 (q, *J* 7 Hz), 1.65 (d, *J* 7 Hz)
	−60 [a]		3.99 (A12), 3.12 (B12) [c]			2.21 (Me12)	

[a] Chemical-shift data at low temperatures are restricted to signals showing definable temperature dependence. The labels A, B, *etc.* refer to Scheme 2. [b] Observed as triplets, *J ca.* 5 Hz, at 35 °C. [c] J_{AB} *ca.* 15 Hz.

TABLE 2

N.m.r. spectra of complexes of the [12]metacyclophane (6b) with primary alkylammonium salts in CD_2Cl_2

Guest	Temperature (°C)	Chemical shifts of host (p.p.m.) [a] 18-H	OCH_2-CH_2O	$ArCH_2N$ [b]	OCH_2 [c]	NCH_2 [c]	NMe	Chemical shifts of guest (p.p.m)
	35 [d]	7.82	3.54	3.54	3.51	2.51	2.33	
H^+NCS^-	35	8.06	3.72	4.04	3.77	2.98	2.65	
	−80	7.97	*ca.* 3.8	*ca.* 4.0	*ca.* 3.8	*ca.* 3.08	2.62	
$NH_4^+NCS^-$	35	7.55	3.62	3.56	3.62	2.68	2.33	
	−100		*ca.* 3.71	*ca.* 3.7(A), *ca.* 3.0(B),	*ca.* 3.71	2.64	2.18	
$Me\overset{+}{N}H_3NCS^-$	35	7.37	3.69	3.48	3.66	2.72	2.31	1.93
	−90		3.82	*ca.* 3.8(A), 2.97(B)	*ca.* 3.8, *ca.* 3.55	*ca.* 2.72	2.27	1.49
$MeCH_2\overset{+}{N}H_3NCS^-$	35	7.39	3.62	3.49	3.63	2.68	2.34	2.66 (q, *J* 7 Hz), 1.16 (t, *J* 7 Hz)
	−90		3.78	*ca.* 3.6(A), 3.00(B)	3.78	2.71	2.25	2.5(br), 1.08(br)
$Me_2CH\overset{+}{N}H_3NCS^-$	35	7.56	3.54	3.54	3.59	2.61	2.35	3.21 (septet, *J* 6 Hz) 1.18 (d, *J* 6 Hz)
	−95		*ca.* 3.8	*ca.* 3.9(A), 3.16(B)	*ca.* 3.8	2.76	2.33	1.18(br)
$Me_3C\overset{+}{N}H_3NCS^-$	35	7.74	3.58	3.58	3.59	2.64	2.40	1.32
	−90					*ca.* 2.9(br) *ca.* 2.5(br)	2.35	1.18
$MeCH_2CH_2\overset{+}{N}H_3NCS^-$	35	7.44	3.59	3.50(AB)	3.61	2.66	2.35	
	−90		*ca.* 3.8	*ca.* 3.8(A), 3.03(B)	*ca.* 3.8	2.70	2.25	
$Me_2CHCH_2\overset{+}{N}H_3NCS^-$	35	7.53	3.53	3.53(AB)	3.58	2.63	2.38	2.46 (t, *J* 7 Hz), 1.86(m), 0.94 (d, *J* 6 Hz)
	−90		*ca.* 3.7	*ca.* 3.7(A), 3.14(B)	3.7	2.69	*ca.* 2.3	2.3(br), 1.8(br), 0.92(br)
$Me_3CCH_2\overset{+}{N}H_3CNS^-$	35 [d]	7.70	3.47	3.56(AB)	3.55	2.62	2.43	2.57, 0.99
$PhCH_2\overset{+}{N}H_3NCS^-$	35	7.52	3.62	3.48(AB)	3.57	2.57	2.11	3.78
	−80			*ca.* 3.9(A), 2.93(B)		2.60	1.82	
(*R,S*)-$PhCHMe\overset{+}{N}H_3NCS^-$	35	7.57	3.56	3.44(AB12)	3.53	2.55	2.07(Me12)	4.06 (q, *J* 7 Hz), 1.52 (d, *J* 7 Hz)
	−80		*ca.* 3.7	*ca.* 3.8(A1), 2.90(B1)	*ca.* 3.7	2.69(br.)	2.06(Me1)	1.48(br)
				ca. 3.8(A2), 2.96(B2)		2.42(br)	1.54(Me2)	
$Ph_2CH\overset{+}{N}H_3NCS^-$	35	7.82	3.63	3.63(AB)	3.53	2.59	2.07	5.11
	−80			3.80(A), 3.09(B)		2.7(br), 2.06(br)	1.59	4.85(br)

[a] The labels A, B, *etc.* refer to Scheme 2. There is some ambiguity in the assignments of singlet signals to OCH_2CH_2O and $ArCH_2N$. [b] J_{AB} *ca.* 13 Hz for $ArCH_2N$ for resolved AB systems at low temperatures. [c] Observed as triplets, *J ca.* 5 Hz, at 35 °C. Separated signals at low temperatures are unresolved multiplets. [d] Small changes in chemical shift and line-broadening only at low temperatures down to −100 °C.

heated under reflux for 1.5 h. The mixture was evaporated to dryness and the residue extracted with chloroform. Evaporation of the chloroform extract gave the crude product as an orange oil (327 mg) which was purified by t.l.c. (basic alumina, ether) giving the required *cyclophane* (15e) as a yellow oil (167 mg, 55%) (Found: *M*, 432.253 0. $C_{26}H_{32}N_4O_2$ requires *M*, 432.252 5); δ($CDCl_3$) 8.48 (d, *J* 5 Hz, 2 × pyridyl 2-H), 8.10 (br s, 18-H), 7.8—6.9 (m, 3 aryl-H + 6 pyridyl-H), 3.88 (s ,2 CH_2N), 3.57 (s, OCH_2CH_2O), 3.70 (s, 2 pyridyl-CH_2N), 3.62 (t, *J* 5 Hz, 2 OCH_2), and 2.76 (t, *J* 5 Hz, 2 OCH_2).

RESULTS AND DISCUSSION

The application of n.m.r. spectroscopy for determining the equilibrium constant for the association of host and guest molecules in chloroform solution has been described.[14] This ' two phase ' method was found to be unsuitable for the diazametacyclophanes (6) because the macrocycles were found to be significantly soluble in the aqueous phase, presumably as their monothiocyanate salts, in the presence of a guest amine thiocyanate. It therefore becomes necessary to use a single-phase technique [2] to examine the relative strengths of guest–host binding in complexes of the macrocycles (6).

The addition of 1 equiv. of a guest primary alkylammonium thiocyanate to a solution of a host metacyclophane (6) in either $CDCl_3$ or CD_2Cl_2 resulted in large chemical-shift changes for some of the host proton signals (Tables 1—4). This, together with the increased solubility of the thiocyanate salt in the organic solvent, provided useful qualitative evidence for complex formation. It was soon found [2] that the n.m.r. spectra of many such solutions showed temperature dependence that could be associated in a quantitative way with complex formation. These effects are illustrated in

TABLE 3

N.m.r. spectra of complexes of the [12]metacyclophane (6b) with polyfunctional primary alkylammonium salts in C_2DCl_2

Guest	Temperature (°C)	Chemical shifts of host (p.p.m.) [a] 18-H	OCH_2-CH_2O	$ArCH_2N$	OCH_2 [b]	NCH [b]	NMe	Chemical shifts of guest (p.p.m.)
(*R*,*S*)-PhCH$\overset{+}{N}H_3CO_2$Me-SCN$^-$	35	7.93	3.66	3.66	3.67	2.83	2.47	4.59, 3.84
	−98			*ca.* 3.8(A12), *ca.* 2.9(B12) [c]			*ca.* 2.0(Me1), *ca.* 1.5(Me2) [c]	
L-Me_2CHCHN$\overset{+}{H}_3CO_2$Me-SCN$^-$	35 [d]	7.88	3.67	3.62	3.67	2.82	2.51	3.82, 3.38 (d, *J* 5 Hz), 1.98(m), 0.94 (d, *J* 7 Hz), 0.88 (d, *J* 7 Hz)
$HOCH_2CH_2\overset{+}{N}H_3SCN^-$	35	7.52	3.62	3.52	3.64	2.67	2.36	2.72 (t, *J* 5 Hz), *ca.* 3.62 (t, *J* 5 Hz)
	−90			*ca.* 3.7(A), *ca.* 3.0(B) [c]				
$H_3\overset{+}{N}(CH_2)_8\overset{+}{N}H_3SCN^-$ (0.5 mol)	35 [e]	7.53	3.59	3.50	3.60	2.64	2.37	*ca.* 2.65 (t, *J* 7 Hz), *ca.* 1.9(m), 1.30(m)
$H_3\overset{+}{N}(CH_2)_2\overset{+}{N}H_3SCN^-$ (0.5 mol)	35 [f]	7.68	3.60	3.53	3.60	2.59	2.37	2.78

[a] As footnote *a*, Table 2. Data at low temperatures are restricted to signals showing definable temperature dependence. [b] Triplets, J_{AB} *ca.* 5 Hz. [c] Signals at low temperatures were very broad, chemical shifts are therefore approximate. [d] As footnote *d*, Table 2. [e] Saturated solution of guest, spectrum run in CD_2Cl_2 but not examined at low temperatures. [f] Saturated solution of guest, spectrum run in $CDCl_3$ and not examined at low temperatures.

TABLE 4

N.m.r. spectra of complexes of the [15]metacyclophane (6c) with primary alkylammonium salts in CD_2Cl_2

Guest	Temperature (°C)	Chemical shifts of host (p.p.m.) [a] 21-H	$ArCH_2N$	OCH_2 [b]	NCH_2 [b]	NMe	Chemical shifts of guest (p.p.m.)
	35	7.59	3.71	3.57	2.56	2.29	
$PhCH_2\overset{+}{N}H_3NCS^-$	35		3.52	3.61	2.64	2.00	3.98
	−85 [c]		*ca.* 3.7(A), 3.00(B)				
(*R*,*S*)-PhCHMe$\overset{+}{N}H_3NCS^-$	35		3.51	3.63	2.62	2.02	4.31 (q, *J* 7 Hz), 1.52 (d, *J* 7 Hz)
	−85 [c]		*ca.* 3.7 (A1 + A2), *ca.* 2.85 (B1 + B2)			1.92(Me1), 1.64(Me2)	

[a] As footnote *a*, Table 3. [b] As footnote *b*, Table 3. [c] Spectra at low temperatures poorly resolved and chemical shifts uncertain.

Benzylammonium Thiocyanate Complex of NN′-*Dimethyl*-2,11-*diaza*-5,8-*dioxa*[12]*metacyclophane* (6b).—A solution of the metacyclophane (6b) (21.8 mg, 0.078 5 mmol) and benzylammonium thiocyanate (13.0 mg, 0.078 5 mmol) in CD_2Cl_2 evaporated to give the *complex* (15 mg, 43%) as a white crystalline solid, m.p. 115—117 °C, recrystallised from cyclohexane–ethanol or chloroform–trichlorofluoromethane (Found: C, 64.6; H, 8.2; N, 12.3; S, 7.1. $C_{24}H_{36}N_4O_2S$ requires C, 64.8; H, 8.2; N, 12.6; S, 7.2%); δ($CDCl_3$), 7.67 (br s, 18-H), 7.3—7.1 (m, 8 aryl-H), 5.90 (br s, $\overset{+}{N}H_3$) 3.77 (s, $CH_2\overset{+}{N}H_3$), 3.57 (s, 2 $ArCH_2N$), 3.65 (s, OCH_2CH_2O), 3.62 (t, *J* 5 Hz, OCH_2), 2.65 (t, *J* 5 Hz, NCH_2), and 2.21 (s, 2 NCH_3).

Figures 1 and 2 for the complexes formed by the metacyclophane (6b) with benzylammonium thiocyanate

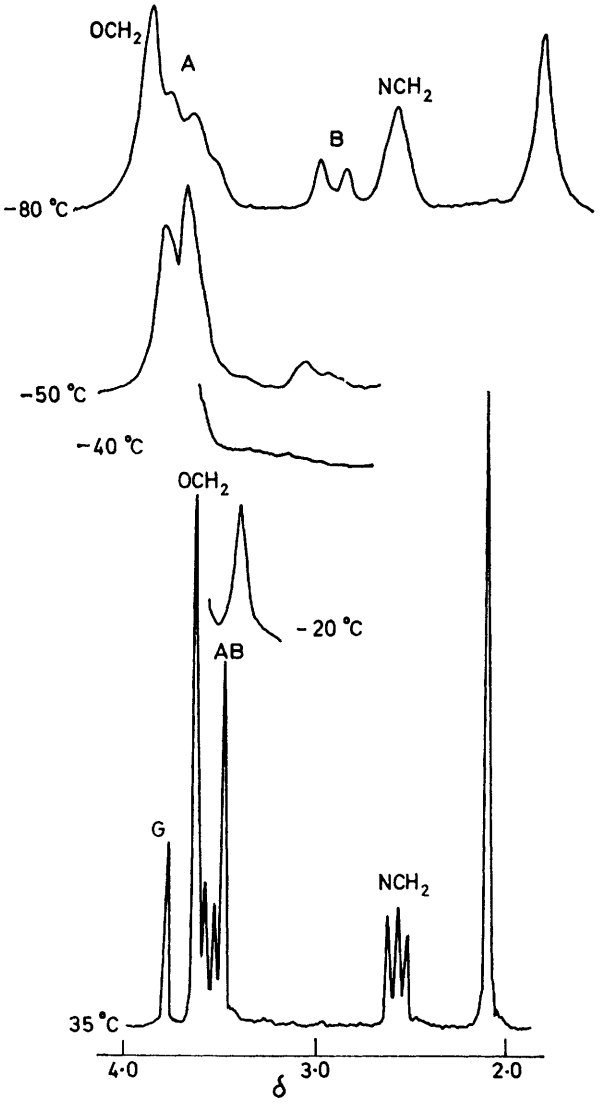


FIGURE 1 Hydrogen-1 n.m.r. spectrum (100 MHz) of host NCH_2, OCH_2, and NMe protons of the complex of (6b) with benzylammonium thiocyanate in CD_2Cl_2 (host : guest ratio 1 : 1). The signals marked AB and A and B are assignable to the $ArCH_2N$ protons and the signal marked G to the guest $PhCH_2N$ protons

and (*R*,*S*)-phenylethylammonium thiocyanate respectively. The significance of temperature dependence of this type will be discussed in the section that covers complex formation by the host (6b).

Formation of Complexes by the Metacyclophane (6a) *and its Conformational Behaviour*.—The n.m.r. spectrum of the [9]metacyclophane (6a) at 35 °C indicates that the ring system undergoes rapid conformational inversion, but at low temperatures the spectrum is consistent with slow inversion, on the n.m.r. time scale, of a non-planar conformation and in particular the benzylic methylene protons are observable as a well defined AB system. The minimum-energy conformation of the diaza[9]-metacyclophane system is not immediately obvious from an examination of molecular models and a number of conformational possibilities were therefore examined by molecular-mechanics calculations [15] using the methods that have been outlined elsewhere [16] and the force field that is summarised in ref. 16 and Table 5. The additional force constants for ethers (Table 5) were derived from the literature,[17] and, since we were seeking qualitative rather than quantitative significance in our results, interactions involving lone-pair electrons or dipole moments associated with heteroatoms were ignored. As in earlier work [16] the Hill equation was chosen to estimate non-bonded interactions since that approach had reproduced, fairly well, energy barriers for conformational changes and minimum-energy conformations in related systems.[16,18]

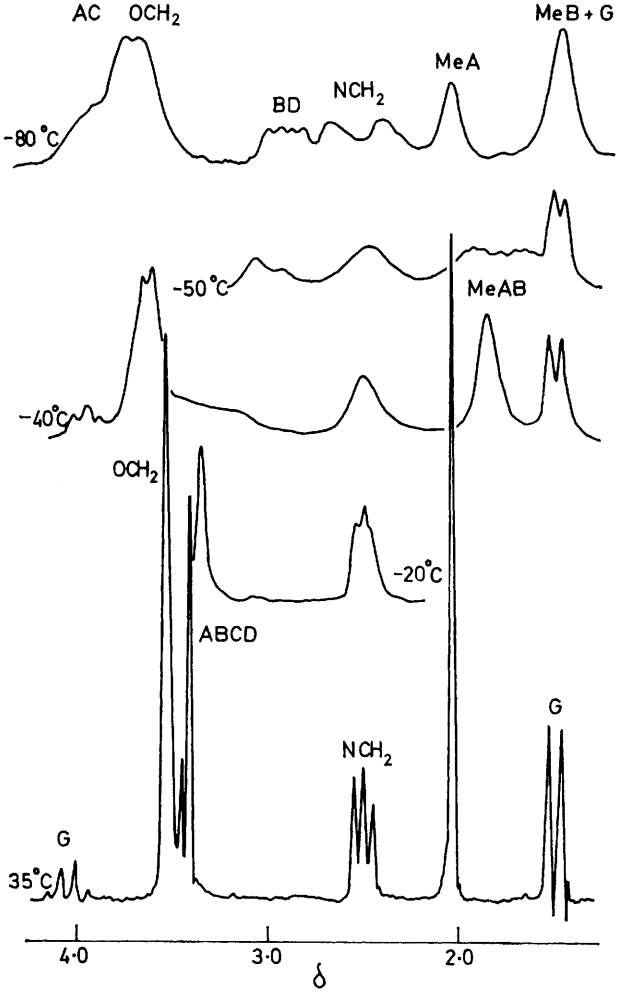


FIGURE 2 Hydrogen-1 n.m.r. spectrum (100 MHz) of host NCH_2, OCH_2, and NMe protons of the complex of (6b) with (*R*,*S*)-phenylethylammonium thiocyanate in CD_2Cl_2 (host : guest ratio 1 : 1). The signals marked ABCD and A, B, C, and D are assignable to the $ArCH_2N$ protons and the signals marked G to the guest $ArCHCH_3\overset{+}{N}$ protons

The minimum-energy ground-state conformation for the metacyclophane (6a) found by these procedures is

shown in (16), and for the inversion (16a) ⇌ (16b) the point on the inversion pathway shown in (17) was found

TABLE 5

Additional force-field parameters (*cf.* ref 17) used for strain-energy calculations

(*a*) Bond stretching $E_R = 0.5\ k_R\ (r - r_o)^2$

C–O bond k_R, 732 kcal Å^{-2} mol^{-1} r_o 1.41 Å

(*b*) Angle deformation $E_\theta = 0.5 k_\theta(\theta - \theta_o)^2$

Angle	k_θ/kcal rad^{-2} mol^{-1}	θ_o/rad
C–O–C	138	1.946 04
C–C–O	124	1.946 04
H–C–O	95	1.902 41

(*c*) Torsion $E_\phi = 0.5\ k_\phi\ (A + \cos n\phi)$

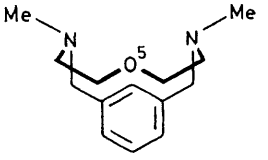
C–O bond k_ϕ, 2.7 kcal mol^{-1} A, 1 n, 3

(*d*) Non-bonded interactions: E_{NBI} [a] $= A \exp(-r/0.0736B) - C(B/r)^6$

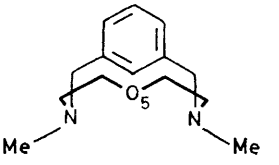
Interaction	A	B [b]	C
O,C	91 900	3.1	0.249
O,H	57 100	2.6	0.155
O,N	86 900	2.9	0.236
O,O	96 000	2.8	0.261

[a] E_{NBI} in kcal mol^{-1}, r in Å. [b] Corresponding to a van der Waals radius of 1.4 Å for O.

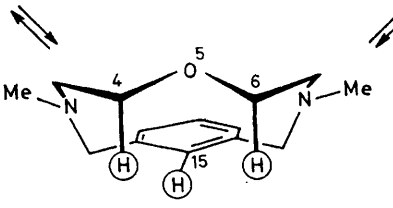
to be the probable transition state. The inversion process was not, however, examined in sufficient detail



(16a)



(16b)



(17)

to definitely exclude other points from representing the transition state. The strain energy in (17) arises primarily from the non-bonding interactions between the encircled hydrogen atoms, and the conformation is defined by the coplanarity of the C(15)–H bond and the indicated hydrogen substituents at C-4 and C-6.

The difference (11.9 kcal mol^{-1}) between the calculated strain energies of the two conformations (16) and (17) can be equated with the enthalpy of activation for the inversion process (16a) ⇌ (16b). Since it is reasonable to assume that the entropy of activation for this process is approximately zero this calculated energy difference can be compared directly with the free energy of activation ($\Delta G^\ddagger$ 11.0 ± 0.3 kcal mol^{-1}) derived from the data for the coalescence of the AB system from the benzylic methylene group of (6a), obtained from the n.m.r. spectrum of (6a) at low temperatures. The good agreement between the calculated and experimental values may be fortuitous, in view of the approximations made in the calculations, but it supports our view that the minimum energy conformation of the [9]metacyclophane system is as shown in (16).

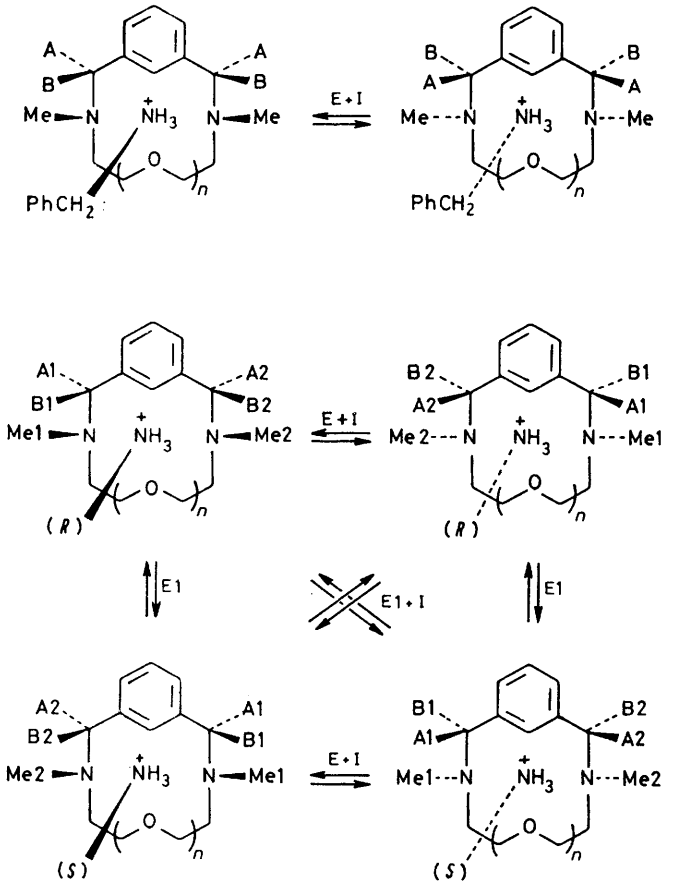
The analogous [9] metacyclophane (8a), in which the bridge oxygen atom is replaced by a methylene group, was also examined in a similar way and the minimum energy conformation and transition state for ring inversion were found to be analogous to (16) and (17) [O-5 replaced by C(5)H_2]. In this case the measured energy barrier for conformational inversion ($\Delta G^\ddagger$ 10.8 ± 0.3 kcal mol^{-1}) is almost the same as that for the cyclophane (6a) but the calculations predict an enthalpy of activation (strain energy difference 13.6 kcal mol^{-1}) that does not agree so well with the measured value. This discrepancy indicates the limitations of the force field used in the calculations and possibly an inadequate procedure for finding the transition states.

The conformation (16) of the metacyclophane (6a) is not unsuitable for hydrogen bonding from a guest ammonium cation to the two nitrogen atoms of the macrocycle but, at best, only two hydrogen bonds can be formed and the limited number of heteroatoms in the macrocycle limits the extent to which a complex can be stabilised by favourable electrostatic interactions. On the basis of chemical-shift changes (Table 1) cyclophane (6a) forms a complex with both benzylammonium thiocyanate and phenylethylammonium thiocyanate. In both cases the temperature dependence of the n.m.r. spectrum (Tables 1 and 5) could only be rationalised on the basis of slow inversion of the ring system but fast dissociation and recombination of the complex.

In general a host molecule, such as (6a), in a complex adopts a conformation that is suitable for optimising the various attractive interactions, such as hydrogen bonding and electrostatic attraction,* between the two components of the complex involving attachment of the

* The distinction between hydrogen bonds and electrostatic interactions is made here for convenience; on theoretical grounds all non-covalent interactions important for complex formation may be regarded as electrostatic in nature (ref. 19) other than hydrophobic interactions.

guest to a particular face of the macrocycle. If the complex dissociates and the host and guest components recombine with the guest molecule attached to the other face of the macrocycle the host molecule must undergo conformational inversion to provide the same optimum conformation for complex formation. This process is therefore labelled E + I in Scheme 2, where E refers to the exchange process and I to the necessary inversion of the host macrocycle.[12] Either step may be rate-determining or the two processes may occur simultaneously. The second type of exchange process shown in Scheme 2, labelled E1, involves exchange of guest molecules of different chirality and it may take place at a single face of the host molecule (E1) or involve face to face exchange and inversion of the host macrocycle (E1 + I). The effects of these various processes upon the sites occupied by the individual protons of the benzylic methylene groups and by the *N*-methyl groups of the host macrocycle are included in Scheme 2. Depending upon the relative rates of the exchange (E and E1) and inversion (I) processes different types of spectral behaviour may be observed.



SCHEME 2 Guest–host exchange processes for complexes of the diazametacyclophanes (6a–c)

Thus the n.m.r. spectrum of the benzylammonium thiocyanate complex of (6a) shows temperature dependence that is very similar to that shown by the free host molecule and although this is associated, for the complexed species, with the process E + I it does not define which process determines the overall rate. The n.m.r. spectrum of the complex of (6a) with (*R*)-phenylethylammonium thiocyanate shows similar behaviour and the averaged sites for the benzylic methylene protons give rise to a singlet signal at 35 °C, although as indicated in Scheme 2 the process E + I actually only averages the pairs of sites A1, B2 and A2, B1. However, at low temperatures the expected separate doublet signals associated with the sites A1 and A2 are observable together with two separated *N*-methyl signals assignable to the sites Me1 and Me2. The n.m.r. spectrum of the analogous complex prepared using (*R,S*)-phenylethylammonium thiocyanate does not show this doubling of signals at low temperatures because the additional exchange process E1 remains fast on the n.m.r. time scale at all temperatures down to −90 °C, resulting in averaging of the pairs of sites A1, A2 and B1, and B2 and Me1, Me2. From the observed line widths at −90 °C it is possible to estimate [20] the maximum free-energy barrier for the exchange process E1 ($\Delta G^{\ddagger} \leqslant 9.4$ kcal mol^{-1}). The estimated maximum value for this barrier is significantly less than that associated with the processes E + I and E1 + I ($\Delta G^{\ddagger}$ *ca.* 11.0 kcal mol^{-1}) which is essentially identical with the barrier for ring inversion ($\Delta G^{\ddagger}$ 11.0 kcal mol^{-1}) of the free host macrocycle.

This result suggests that weak complex formation has little effect upon ring inversion barriers and presumably in the case of the metacyclophane (6a) the inversion process does not significantly change the binding energy between the two components of the complex at the transition state [*cf.* (17)]. This is not surprising in view of the calculations, outlined above, of the minimum energy (16) and transition state (17) conformations of the host macrocycle, since examination of conformations, (16) and (17) suggest similar possibilities in both cases for binding to a guest ammonium cation. Thus detachment and re-attachment of the guest cation can occur at lower energy points on the inversion pathway with little or no effect on the activation energy for the process E + I.

Formation of Complexes by the Metacyclophane (6b).—The n.m.r. spectra of both the [12]metacyclophane (6b) and its monothiocyanate salt are essentially unchanged over the temperatures range +35 to −100 °C, other than by line-broadening at low temperatures. This result indicates that the barrier for the conformational inversion of this ring system is low ($\Delta G^{\ddagger} < 9$ kcal mol^{-1}). The spectrum of the complex of host (6b) with benzylammonium thiocyanate, prepared either from the addition of one equivalent of the guest thiocyanate to the host diamine or of one equivalent of the guest, as the free amine, to the monothiocyanate salt of the host, showed pronounced temperature dependence (Figure 1). Thus the benzylic methylene group of the host gave a singlet signal at 35 °C which separated into an AB system at low temperatures. This effect may be understood in the terms of the process E + I (Scheme 2) but in this case,

since the process I is fast, the energy barrier for the site exchange process ($\Delta G^{\ddagger}$ 10.8 kcal mol^{-1}) must be associated with the free-energy barrier for dissociation of the complex together with a possible additional increment associated with the inversion process.

TABLE 6

Temperature dependence of n.m.r. spectra of complexes of metacyclophanes (6) and associated energy barriers ($\Delta G^{\ddagger}$) in CD_2Cl_2

Host	Guest	Temperature dependence [a]	$\Delta G^{\ddagger}$ [b]/kcal mol^{-1}	Process
(6a)		A + B→AB	11.0	I
(6a)	$PhCH_2\overset{+}{N}H_3NCS^-$	A + B→AB	11.0	I
(6a)	(*R*)-$PhCHMe\overset{+}{N}H_3NCS^-$	A1 + B1 + A2 + B2→A1B2 + A2B1	11.0	I
		Me1 + Me2→Me12	11.0	I
(6a)	(*R*,*S*)-$PhCHMe\overset{+}{N}H_3NCS^-$	A12 + B12→AB12	11.0	I
		Me1 + Me_2→Me12	⩽9.4 [c]	E
(6b)	$\overset{+}{N}H_4NCS^-$	A + B→AB	8.7	E + I
(6b)	$Me\overset{+}{N}H_3NCS^-$	A + B→AB	10.1	E + I
(6b)	$MeCH_2\overset{+}{N}H_3NCS^-$	A + B→AB	10.7	E + I
(6b)	$Me_2CH\overset{+}{N}H_3NCS^-$	A + B→AB	10.1	E + I
(6b)	$Me_3C\overset{+}{N}H_3NCS^-$	A + B→AB	9.3	E + I
(6b)	$MeCH_2CH_2\overset{+}{N}H_3NCS^-$	A + B→AB	10.2	E + I
(6b)	$Me_2CHCH_2\overset{+}{N}H_3NCS^-$	A + B→AB	9.7	E + I
(6b)	$Me_3CCH_2\overset{+}{N}H_3NCS^-$	A + B→AB	⩽9.0 [d]	E + I
(6b)	$PhCH_2\overset{+}{N}H_3NCS^-$	A + B→AB	10.8	E + I
(6b)	(*R*,*S*)-$PhCHMe\overset{+}{N}H_3NCS^-$	A1 + A2 + B1 + B2→AB12	10.9	E + I, E, E1 [e]
		Me1 + Me2→Me12	10.6	E
(6b)	$Ph_2CH\overset{+}{N}H_3NCS^-$	A + B→AB	11.1	E + I
(6b)	$HOCH_2CH_2\overset{+}{N}H_3NCS^-$	A + B→AB	8.8	E + I
(6b)	(*R*,*S*)-$PhCH\overset{+}{N}H_3CO_2MeNCS^-$	A1 + A2 + B1 + B2→AB12	9.3	E + I, E, E1 [e]
		Me1 + Me2→Me12	8.6	E
(6b)	(L)-$Me_2CH\overset{+}{N}H_3CO_2MeNCS^-$		⩽9.0	E + I, E1 [e]
(6c)	$PhCH_2\overset{+}{N}H_3NCS^-$	A + B→AB	9.8	E + I
(6c)	(*R*,*S*)-$PhCHMe\overset{+}{N}H_3NCS^-$	A1 + A2 + B1 + B2→AB12	9.8	E + I, E, E1
		Me1 + Me2→Me12	9.7	E

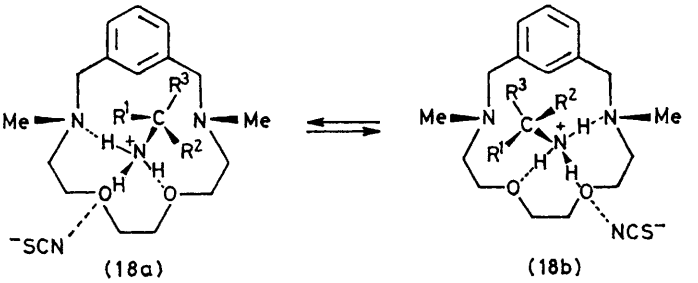
[a] For details of chemical shifts see Tables 1—4. The symbols A, B *etc.* refer to these Tables and to Scheme 2. [b] Value of $\Delta G^{\ddagger}$ based upon approximations for exchange rates at coalescence temperature (accurate to ±0.5 kcal mol^{-1}). [c] Based upon maximum exchange broadening at −90 °C. [d] Based upon failure to observe signal separation at −100 °C. [e] Precise process cannot be established on basis of limited data, value stated for energy barrier refers to slowest process.

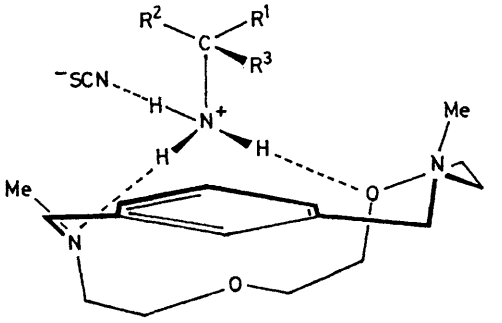
The complex of metacyclophane (6b) with (*R*,*S*)-phenylethylammonium thiocyanate showed similar spectral behaviour, but in this case additional signal separation at low temperatures could be associated with the four sites A1, A2, B1, and B2 for the benzylic protons and the two sites Me1 and Me2 for the methyl protons of the host molecule (Scheme 2). These signals are in fact exchanged in different pairs by the processes E + I, E1 + I and E1 as indicated in the Scheme but no significant differences could be detected in the energy barriers ($\Delta G^{\ddagger}$ 10.9 ± 0.3 and $\Delta G^{\ddagger}$ 10.6 ± 0.3 kcal mol^{-1}) associated with the different types of process (Table 6 and *cf.* Part 3 of this series).

The energy barriers for all these detectable processes are associated primarily with dissociation of the complex, together possibly with a small increment that is associated with the required conformational changes of the host macrocycle. This latter contribution is likely to remain constant in a series of complexes of the same macrocycle or of closely related macrocycles, and the relative magnitudes of the energy barriers for the process E + I for a series of complexes are therefore directly related to the free energy of complex formation (*cf.* ref. 21). Thus in the series of complexes of the host (6b) with primary alkylammonium thiocyanates, $R\overset{+}{N}H_3NCS^-$, for which data is summarised in Tables 2 and 5, the following trends are observable. (*a*) In the series R = H, Me, CH_2Me, $CHMe_2$, and CMe_3 the energy barrier for the process E + I first increases with increased size of the group R and then decreases. The decrease is obviously interpretable in the terms of increased steric repulsion between host and guest components as the group R becomes sterically more demanding. The initial increase in the energy barrier, and by implication the strength of guest–host binding, in the series R = H < Me < Et suggests that increased shielding of the positively charged nitrogen centre by the group R also assists complex formation. (*b*) The effect of β-substituents in the group R in the series R = CH_2CH_3, CH_2CH_2Me, CH_2CHMe_2, and CH_2CMe_3 is clearly explained by an examination of molecular models. Although one or two β-alkyl substituents can be accommodated with relatively small non-bonded interactions, the third methyl sub-

stituent of the neopentyl group interacts strongly with the macrocycle and there is a marked decrease in the stability of the complex. (*c*) The complex of the host (6b) with benzylammonium thiocyanate was crystalline and an *X*-ray analysis of the crystal structure showed [22] that the complex had the structure shown in outline in (19, R^1 = Ph, R^2 = R^3 = H). The results commented upon in (*a*) and (*b*) above are consistent with similar structures (19) ≡ (18) in solution for all primary alkylammonium thiocyanate complexes of (6b). In particular the groups R^1 and R^2 in (18) can be relatively large, but the group R^3 is in a sterically crowded position, hence the drop in complex stability for R = CMe_3 (R^1 = R^2 = R^3 = Me). Additionally the chemical shifts of the *N*-methyl groups in complexes in which one or more of the groups R^1, R^2, or R^3 of (18) is a phenyl group show significant shifts to high field as compared with the spectrum of the free host (R = CH_2Ph 0.22, R = CHMePh 0.26, and R = $CHPh_2$ 0.26 p.p.m.). These shifts, which increase as the temperature is lowered, indicate that one of the *N*-methyl groups of the host lies in the shielding zone of the aromatic substituent of the guest cation. This effect is particularly marked for the *N*-methyl signals observable for the complexes with (*R*)- or (*R*,*S*)-phenylethylammonium thiocyanate (one *N*-Me signal at 1.54 p.p.m. at −80 °C but the other at 2.06 p.p.m.) and benzhydrylammonium thiocyanate (both *N*-Me signals at 1.59 p.p.m. at −80 °C). These results are consistent with the occupation of the positions assigned to the larger groups R^1 and R^2 in (18) by the phenyl or methyl substituents. In the case of the complex with benzylammonium thiocyanate, although the crystal structure indicates a single 'frozen' structure, (18a) or (18b), it is clear from the n.m.r. results that the interconversion (18a) ⇌ (18b) takes place rapidly on the n.m.r. time scale down to the lowest temperatures at which measurements were made (*cf.* Part 1),[1] and at −80 °C both NMe groups give signals at the averaged chemical shift, 1.82 p.p.m.

The metacyclophane (6b) also formed complexes with a number of primary alkylammonium salts $R\overset{+}{N}H_3\ X^-$ in which the group R contained an additional functional group, but in all the cases examined the energy barrier for the process E + I was significantly reduced by this group. Examples of this type are listed in Tables 3 and 6. The reasons for this effect of the additional functional group do not appear to be steric in origin, but in the cases examined the group was one which could participate in hydrogen bonding. The effect upon the barrier to the process E + I, and presumably the weaker binding between guest and host components, therefore

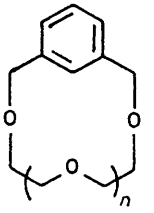




appears to originate in competitive inter- or intramolecular hydrogen bonding involving this functional group and the $\overset{+}{N}H_3$ group of the guest cation. Nevertheless the chemical-shift changes observed on adding the guest compound to a solution of the host (6b) indicate that complex formation does occur, and the increased solubility of the guest salt provides additional evidence for this.

Formation of Complexes by Metacyclophane (6c).—The n.m.r. spectrum of the diaza[15]metacyclophane (6c) showed significant changes in chemical shift on the addition of one equivalent of a guest primary alkylammonium thiocyanate (Table 4). The temperature dependence of the n.m.r. spectra of these complexes of (6c) was rather similar to that observed for the complexes of the [12]metacyclophane (6b) but in the case of (6c) the free-energy barriers for the process E + I were somewhat lower than for the analogous complexes of the cyclophane (6b) (Table 6). This is rather surprising in view of the known relative abilities of 18-crown-6 and 15-

crown-5 systems to form complexes with primary alkylammonium thiocyanates.[14,23,24] Thus, on the basis of partition experiments between $CDCl_3$ and water, the values of K_α for the formation of complexes between benzylammonium thiocyanate and the crown ether analogues (20a and b) are 1.6×10^2 and 3.6×10^4 dm^3 mol^{-1} respectively, and similar effects were observed [23] for other related pairs of 15-crown-4 and 18-crown-5 systems. The examination of monoaza-15-crown-5 and -18-crown-6 analogues using n.m.r. line-shape methods also showed that the 18-membered host bonds more strongly to a guest ammonium salts.[1] We have no explanation to offer for the apparently anomalous behaviour of the diazametacyclophane systems (6b) and (6c). Thus examination of the n.m.r. spectra of the



(20)

a, $n = 2$
b, $n = 3$

complexes of (6c) at 100 MHz did not reveal signals corresponding to different stereoisomers of the complexes, as found for the monoaza-18-crown-6-system described in Part 1 of this series.[1] A more detailed examination of the n.m.r. spectra of the complexes of diaza-18-crown-6 analogues will be reported in a future publication.

Formation of Complexes by Metacyclophanes (15).—The parent metacyclophane (12b) did not form strong complexes with benzylammonium thiocyanate. Thus, although the addition of the guest salt to a solution of the host (12b) resulted in significant upfield shifts of some of the n.m.r. signals, the absence of temperature dependence of this spectrum on cooling the solution of the complex to −90 °C shows that the strength of complex formation is relatively weak. This result may reflect the lower proton affinity of a secondary amine,[25] but it may also result from the less effective screening of unfavourable interactions between the lipophilic solvent and the lipophobic charged centres within the complex by the hydrogen substituents of (12b) as compared with the methyl substituents of (6b). The effect is analogous to that observed for a guest ammonium cation as compared with a primary alkylammonium cation.

TABLE 7

N.m.r. spectra of complexes of the [15]metacyclophane derivatives (15g) and (15) and associated energy barriers ($\Delta G^\ddagger$) in CD_2Cl_2

Host	Side chain	Guest	Temperature (°C)	Chemical shifts of host (p.p.m.) [a] 18-H	OCH_2-CH_2O	$ArCH_2N$	OCH_2 [b] (ring)	NCH_2 [b] (ring)	OCH_2 (side chain)	NCH_2 (side chain)	Chemical shifts of guest (p.p.m.)	Energy barriers (process) (kcal mol^{-1}, ±0.5)
(15g)	CH_2CH_2OH		35	8.01	3.61	3.66	3.37	2.54	3.53	2.70		
(15g)	CH_2CH_2OH	H^+NCS^-	35	7.96	3.66	3.81	3.65	2.95	3.56	2.79		No changes in spectrum down to −80 °C
(15g)	CH_2CH_2OH	$PhCH_2\overset{+}{N}H_3NCS^-$	35 −60	7.45	3.04	3.48 3.76(A) 3.04(B)	3.31	2.50	3.77	2.50	4.98	From $ArCH_2N$ $\Delta G^\ddagger$ *ca.* 11.9 (E + I)
(15g)	CH_2CH_2OH	$HOCH_2CH_2\overset{+}{N}H_3NCS^-$	35 −60	7.46	3.15 *ca.* 3.3 *ca.* 2.8	3.54	3.79	2.69	3.45	2.73	3.72(m), 2.98(m)	From OCH_2CH_2O $\Delta G^\ddagger$ *ca.* 10.8 (E + I)
(15g)	CH_2CH_2OH	$PhCH\overset{+}{N}H_3CO_2MeNCS^-$	35	7.81	3.36	3.77 *ca.* 3.9(A) 2.96(B)	3.60	2.71	3.53	2.75	4.80	From $ArCH_2N$ $\Delta G^\ddagger$ *ca.* 10.8 (E + I)
(15g)	CH_2CH_2OH	$Me_2CHCH_2CO_2MeN\overset{+}{H}_3$-$PF_6^-$	35	7.88	3.52	3.86	3.60	2.80	3.56	2.95	3.70(d), *ca.* 2.1(m), 0.93(d)	[c]
(15e)	$CH_2C_5H_4N$		35	8.06	3.55	3.83	3.58	2.71		3.66		
(15e)	$CH_2C_5H_4N$	$PhCH_2\overset{+}{N}H_3NCS^-$	35 −70		3.52	3.57 2.90(A) [d] *ca.* 3.8(B) [d]	3.61	2.67		3.43 3.04 [d] 3.60 [d]		From $ArCH_2N$ and NCH_2 $\Delta G^\ddagger$ 11.7 (E + I)

[a] Low temperature spectra were poorly resolved in most cases and chemical shifts at low temperatures are approximate. The descriptions A, B refer to Scheme 2. [b] Observed as triplets, J *ca.* 5 Hz. [c] Signals broadened below −50 °C but signal separation into AB systems, *etc.*, was not resolved. [d] AB systems were observed in the low temperature spectrum for both $ArCH_2N$ and $PyCH_2N$; the assignment is arbitrary.

The *NN'*-bis-(2-hydroxyethyl)metacyclophane (15g) was found to form relatively strong complexes with a variety of guest compounds (Table 7) and both large chemical shift changes and temperature dependence of the n.m.r. spectra of these complexes could be observed. The apparently stronger binding to ethanolamine thiocyanate by the host (15g) as compared with the host (6b) is of interest and may be a consequence of secondary binding interactions between the hydroxy substituents in the side chains and the hydroxy group of the guest cation. However, benzylammonium thiocyanate is also more strongly bound by the host (15g) and evidently the change of side chain from methyl to 2-hydroxyethyl has some effect on the primary binding interaction associated with the macrocycle and the $\overset{+}{N}H_3$ group of the guest.

The benzylammonium thiocyanate complex of the pyridine derivative (15e) also gave a reasonably well resolved n.m.r. spectrum at low temperatures and both the $ArCH_2N$ protons and side chain NCH_2-pyridyl protons gave temperature-dependent signals (Table 7). From the calculated energy barrier for the process E + I this host also forms complexes with the benzylammonium cation in which the binding energy is slightly enhanced by the side chains.

The diamides (15b), (15c), and (15d) also formed

complexes with benzylammonium thiocyanate and other guest molecules. The n.m.r. spectra were not well resolved at 100 MHz, particularly at low temperatures, and the results are therefore not reported in Table 6. The observable, poorly resolved, temperature dependence of the spectra suggest that energy barriers in the range 10—12 kcal mol^{-1} are involved.

The formation of complexes by these crown ether derivatives having additional functional groups in the side chain is encouraging in view of the need for such groups for catalysis and for the provision of secondary bonding sites.

[8/705 *Received*, 14*th April*, 1978]

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