Conformational Behaviour of Medium-sized Rings. Part 15.[1] 1,9,17-Triaza[2.2.2]metacyclophane-2,10,18-trione Derivatives

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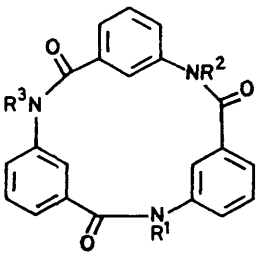
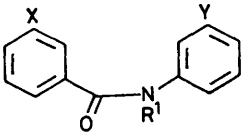
The stepwise synthesis of 1,9-dimethyl-1,9,17-triaza[2.2.2]metacyclophane-2,10,18-trione (1) from methyl *m*-aminobenzoate and *m*-nitrobenzoyl chloride is reported. The temperature dependences (i) of the ^{1}H-decoupled ^{13}C n.m.r. spectrum of the 1,9,17-trimethyl derivative (2) and (ii) of the ^{1}H n.m.r. spectrum of the 1,9-dimethyl-17-benzyl derivative (3) are interpreted in terms of equilibration between diastereoisomeric crown and saddle conformations in solution. The 1,9-dimethyl derivative (1) is believed to exist predominantly in the saddle conformation in solution.

THE success of a stepwise approach to the synthesis of trianthranilide derivatives[2] with 12-membered rings starting from *o*-aminobenzoic (anthranilic) acid and *o*-nitrobenzoyl chloride raised the possibility that the isomeric *meta* analogues with 15-membered rings might be attainable from *m*-aminobenzoic acid and *m*-nitrobenzoyl chloride as starting materials. In this paper, we describe the stepwise synthesis of the 1,9-dimethyl- (1), 1,9,17-trimethyl- (2), and 1,9-dimethyl-17-benzyl- (3) triaza[2.2.2]metacyclophane-2,10,18-triones and discuss the conformational behaviour of their 15-membered rings in solution. The results have already been summarised, together with an *X*-ray crystal structure of the 1,9,17-trimethyl derivative (2) in a preliminary communication.[3]

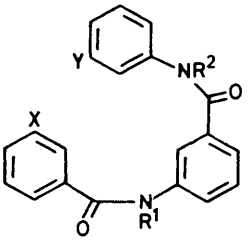


	R^1	R^2	R^3
(1)	Me	Me	H
(2)	Me	Me	Me
(3)	Me	Me	CH_2Ph

The acyclic amino-acid precursor (13) to the 1,9-dimethyl derivative (1) was obtained from methyl *m*-aminobenzoic acid[4] and *m*-nitrobenzoyl chloride[5] by two slightly different routes in which the initial and final steps are common to each route. In the initial common steps, *m*-nitrobenzoylation of methyl *m*-aminobenzoic acid gave the amide (4) which was *N*-methylated to yield, after aqueous work-up, a mixture of the methyl ester (5) and the acid (6). The acid (6) was converted into its acid chloride (8) and condensed with another equivalent of methyl *m*-aminobenzoate to give the bisamide (10). This compound was also prepared by a carbodi-imide-promoted condensation of the acid (6) with methyl *m*-aminobenzoate. Reduction of the aromatic nitro-group in the methyl ester (5) afforded the amine which was condensed with *m*-nitrobenzoyl chloride to yield a constitutionally isomeric bisamide (9). This isomer (9) was also obtained by a carbodi-imide-promoted condensation of *m*-nitrobenzoic acid with the amine (7). Methylation of both (9) and (10) afforded the same *N*,*N*′-dimethyl derivative (11) which, upon saponification of the methyl ester group, yielded the acid (12). Reduction of the aromatic nitro-group in (12)



	R^1	X	Y
(4)	H	NO_2	CO_2Me
(5)	Me	NO_2	CO_2Me
(6)	Me	NO_2	CO_2H
(7)	Me	NH_2	CO_2Me
(8)	Me	NO_2	COCl



	R^1	R^2	X	Y
(9)	H	Me	NO_2	CO_2Me
(10)	Me	H	NO_2	CO_2Me
(11)	Me	Me	NO_2	CO_2Me
(12)	Me	Me	NO_2	CO_2H
(13)	Me	Me	NH_2	CO_2H

gave the acyclic amino-acid derivative (13) which underwent cyclisation, on treatment with *N*,*N*′-dicyclohexylcarbodi-imide in dichloromethane, to afford the desired 1,9-dimethyltriaza[2.2.2]metacyclophane-2,10,18-trione (1) in 26% yield. Methylation of (1) gave the 1,9,17-trimethyl derivative (2); benzylation of (1) gave the 1,9-dimethyl-17-benzyl derivative (2).

EXPERIMENTAL

The general methods have been discussed in Parts 3[6] and 6.[7]

m-*Nitrobenzoyl Chloride*.[4]—*m*-Nitrobenzoic acid (200 g)

was heated under reflux with freshly distilled thionyl chloride (300 ml) until the evolution of gases ceased. Excess of thionyl chloride was distilled off and the residue was distilled twice under reduced pressure (b.p. 153 °C at 12 mmHg) to give *m*-nitrobenzoyl chloride which solidified on cooling, m.p. 33 °C (lit.,[4] m.p. 33 °C).

Methyl m-*Aminobenzoate*.[5]—Hydrogen chloride gas was passed into dry methanol (350 ml) until saturation was achieved. *m*-Aminobenzoic acid (50 g) was added to this solution and the reaction mixture was heated under reflux for 3 h. The hot solution was added to excess of water (1 l) and then neutralised with aqueous sodium carbonate. The oil that separated was extracted with ether. The ethereal layer was washed several times, dried, and concentrated to afford a residual oil. This oil was distilled under reduced pressure to give methyl *m*-aminobenzoate (43 g, 78%), b.p. 120 °C at 0.65 mmHg (lit.,[5] b.p. 152—153 °C at 11 mmHg). It solidified on cooling.

Methyl 3-(3-*Nitrobenzamido*)*benzoate* (4).—A solution of *m*-nitrobenzoyl chloride (23.3 g) in ether (200 ml) was added dropwise at room temperature to a stirred mixture of methyl *m*-aminobenzoate (19.0 g) in ether (300 ml) and sodium hydroxide (5.2 g) in water (100 ml). Stirring was continued for 0.5 h and the solid that separated was filtered off, washed several times with water, and finally with ether. Crystallisation from ethanol gave *methyl* 3-(3-*nitrobenzamido*)*benzoate* (4) (36.5 g, 96%), m.p. 164—167 °C [Found: C, 60.0; H, 4.2; N, 9.3%; *M* (mass spec.), 300. $C_{15}H_{12}N_2O_5$ requires C, 60.0; H, 4.0; N, 9.3%; *M*, 300], τ($CDCl_3$) 1.20—2.75 (9 H, m, ArH and NH) and 6.11 (3 H, s, OMe).

Methyl 3-(N-*Methyl*-3-*nitrobenzamido*)*benzoate* (5) *and* 3-(3-*Nitro*-N-*methylbenzamido*)*benzoic Acid* (6).—A mixture of methyl 3-(3-nitrobenzamido)benzoate (4) (3 g) sodium hydride (600 mg), and methyl iodide (1.5 ml) in dimethyl sulphoxide (20 ml) was stirred overnight at room temperature. Water was carefully added to the reaction mixture to decompose the excess of sodium hydride. After extraction of this aqueous solution several times with chloroform, the organic layer was separated, washed, dried, and concentrated to afford an oily residue. This was subjected to chromatography on silica gel with chloroform–light petroleum (b.p. 40—60 °C) (1 : 1) as eluant. Recrystallisation of the crude product from ethanol gave *methyl* 3-(N-*methyl*-3-*nitrobenzamido*)*benzoate* (5), m.p. 82—83 °C [Found: C, 60.9; H, 4.7; N, 8.8%; *M* (mass spec.), 314. $C_{16}H_{14}N_2O_5$ requires C, 61.1; H, 4.45; N, 8.9%; *M*, 314], τ($CDCl_3$) 1.76—2.82 (8 H, m, ArH), 6.10 (3 H, s, CO_2Me), and 6.44 (3 H, s, NMe). The aqueous layer from the chloroform extraction was acidified and the precipitated crude acid was filtered off and dissolved in dilute aqueous sodium hydroxide. After reacidification, the acid was extracted with chloroform and crystallised ultimately from ethanol to give 3-(N-*methyl*-3-*nitrobenzamido*)*benzoic acid* (6), m.p. 184—185 °C [Found: C, 59.7; H, 4.3; N, 9.6%; *M* (mass spec.), 300. $C_{15}H_{12}N_2O_5$ requires C, 60.0; H, 4.0; N, 9.3%; *M*, 300].

Methyl 3-(3-*Amino*-N-*methylbenzamido*)*benzoate* (7).—Methyl 3-(*N*-methyl-3-nitrobenzamido)benzoate (5) (8 g) was dissolved in ethyl acetate (80 ml) and platinum oxide (200 mg) was added. The reaction mixture was stirred in the presence of an atmosphere of hydrogen at room temperature. After 3 h the uptake of hydrogen was complete. The catalyst was filtered off and the filtrate was concentrated to afford a solid residue which was crystallised from ethanol to give an almost quantitative yield of *methyl* 3-(3-*amino*-N-*methylbenzamido*)*benzoate* (7), m.p. 118—119 °C [Found: C, 67.6; H, 5.6; N, 9.8%; *M* (mass spec.), 284. $C_{16}H_{16}N_2O_3$ requires C, 67.6; H, 5.6; N, 9.8%; *M*, 284], τ($CDCl_3$) 2.00—3.60 (8 H, m, ArH), 6.10 (3 H, s, CO_2Me), and 6.51 (3 H, s, NMe).

Methyl 3-[N-*Methyl*-3-(3-*nitrobenzamido*)*benzamido*]*benzoate* (9).—(a) A solution of *m*-nitrobenzoyl chloride (2.9 g) in ether (25 ml) was added dropwise to a stirred suspension of methyl 3-(3-amino-*N*-methylbenzamido)benzoate (7) (4.0 g) in a mixture of dioxan (15 ml), ether (15 ml), and a solution of sodium hydroxide (800 mg) in water (20 ml). After the addition was complete the stirring was continued at room temperature until a white precipitate was formed. The solid was filtered off and the filtrate was extracted with ether. The ethereal layer was separated and concentrated to a residue which was added to the original solid. The combined crude product was crystallised from ethanol to give methyl 3-[*N*-methyl-3-(3-nitrobenzamido)benzamido]-benzoate (9) (5.5 g, 90%). Some crystals had m.p. 135—138 °C while others had m.p. 155—165 °C. The crystals were not separated and the ^1H n.m.r. spectral data indicated the presence of only one compound in solution: τ($CDCl_3$) 0.42 (1 H, s, NH), 1.20—3.24 (12 H, m, ArH), 6.10 (3 H, s, CO_2Me), and 6.57 (3 H, s, NMe).

(b) A solution of *N*,*N*′-dicyclohexylcarbodi-imide (2 g) in dry dichloromethane (20 ml) was added dropwise to a stirred solution of *m*-nitrobenzoic acid (3.3 g) in dry ethyl acetate at room temperature. The stirring was continued for a period of 0.5 h and then a solution of methyl 3-(3-amino-*N*-methylbenzamido)benzoate (7) (4 g) in dry dichloromethane (50 ml) was added dropwise. After this addition was complete, the reaction mixture was stirred for a further 3 h. The precipitated *N*,*N*′-dicyclohexylurea was then filtered off and the filtrate was concentrated to afford a residue which was dissolved in dichloromethane. Washing with water was followed by successive washings with dilute hydrochloric acid, a dilute solution of sodium hydrogen carbonate, and a saturated solution of sodium chloride. The organic layer was separated, dried, and concentrated to give a crude product. This was crystallised from ethanol to yield methyl 3-[*N*-methyl-3-(3-nitrobenzamido)benzamido]benzoate (9) (8 g, 66%) with properties and spectral characteristics identical with those of the compound obtained by method (a).

Methyl 3-[(N-*Methyl*-3-*nitrobenzamido*)-3-*benzamido*]*benzoate* (10).—(a) 3-(3-Nitro-*N*-methylbenzamido)benzoic acid (6) (2.5 g) and thionyl chloride (5 ml) were heated under reflux for 3 h. Excess of thionyl chloride was distilled off and the acid chloride (8), which solidified with time, was used in the following reaction without further purification. A suspension of the acid chloride (8) (3.2 g) was added dropwise with stirring at room temperature to a mixture of methyl *m*-aminobenzoate (1.5 g) dissolved in ether (15 ml) and a solution of sodium hydroxide (400 mg) in water (5 ml). The stirring was continued for 5 h. The solid that separated was filtered off and recrystallised from ethanol to give *methyl* 3-[(N-*methyl*-3-*nitrobenzamido*)-3-*benzamido*]*benzoate* (10). The recrystallisation afforded two different crystalline forms: plates with m.p. 146—148 °C and needles with m.p. 167—169 °C which could be separated by hand-picking. Both crystalline forms gave the same mass spectral [Found: *M* (mass spec.), 433. $C_{23}H_{19}N_3O_6$ requires *M*, 433] and ^1H n.m.r. data: τ($CDCl_3$) 1.64 (1 H, s, NH), 1.88—2.92 (12 H, m, ArH), 6.13 (3 H, s, CO_2Me), and 6.50 (3 H, s, NMe).

(b) A solution of *N,N'*-dicyclohexylcarbodi-imide (2.1 g) in dry dichloromethane (25 ml) was added dropwise to a stirred solution of 3-(3-nitro-*N*-methylbenzamido)benzoic acid (6) (3.0 g) in dry ethyl acetate (50 ml) at room temperature. The stirring was continued for a period of 0.5 h and then a solution of methyl *m*-aminobenzoate (1.6 g) in dry dichloromethane (10 ml) was added dropwise to the reaction mixture. After the addition was complete, the reaction mixture was stirred for a further 3 h. The precipitated *N,N'*-dicyclohexylurea was filtered off and the filtrate was concentrated to give a solid. The crude residue was dissolved in dichloromethane and washed successively with water, dilute hydrochloric acid, a dilute solution of sodium hydrogen carbonate, and a saturated solution of sodium chloride. The organic layer was separated, dried, and concentrated to afford the crude product which was crystallised from ethanol to give *methyl* 3-[(N-*methyl*-3-*nitrobenzamido*)-3-*benzamido*]*benzoate* (10) (2.6 g, 60%) (Found: C, 63.6; H, 4.63; N, 9.63%. $C_{23}H_{19}N_3O_6$ requires C, 63.7; H, 4.39; N, 9.69%). This compound was identical with that prepared previously by method (a).

Methyl 3-[N-*Methyl*-3-(N-*methyl*-3-*nitrobenzamido*)*benzamido*]*benzoate* (11) *and* 3-[N-*Methyl*-3-(N-*methyl*-3-*nitrobenzamido*)*benzamido*]*benzoic Acid* (12).—(a) Methyl iodide (2 ml) was added to a stirred solution of methyl 3-[*N*-methyl-3-(3-nitrobenzamido)benzamido]benzoate (9) (4.5 g) in dimethyl sulphoxide (20 ml) containing sodium hydride (360 mg). Stirring was continued at room temperature overnight. Water was carefully added to destroy excess of sodium hydride. Extraction of the aqueous solution with chloroform gave an organic layer which was separated, washed several times with water, dried, and concentrated to a residue. This solid crystallised from ethanol to give *methyl* 3-[N-*methyl*-3-(N-*methyl*-3-*nitrobenzamido*)*benzamido*]*benzoate* (11), m.p. 109—111 °C [Found: C, 64.5; H, 4.7; N, 9.3%; *M* (mass spec.), 447. $C_{24}H_{21}N_3O_6$ requires C, 64.4; H, 4.7; N, 9.4%; *M*, 447], τ($CDCl_3$) 1.82—2.22 (12 H, m, ArH), 6.10 (3 H, s, CO_2Me), and 6.56 and 6.68 (6 H, 2 × s, 2 × NMe). Acidification of the aqueous layer from the chloroform extraction gave a white solid which was filtered off and washed several times with water before being redissolved in dilute aqueous sodium hydroxide. Re-acidification with dilute hydrochloric acid gave the crude material which was crystallised from aqueous ethanol to afford 3-[N-*methyl*-3-(N-*methyl*-3-*nitrobenzamido*)-*benzamido*]*benzoic acid* (12), m.p. 197—199 °C [Found: C, 64.4; H, 4.8; N, 9.9%; *M* (mass spec.), 433. $C_{23}H_{19}N_3O_6$ requires C, 63.7; H, 4.4; N, 9.7%; *M*, 433], τ($CDCl_3$–CD_3OD), 1.80—3.30 (12 H, m, ArH), and 6.56 and 6.69 (6 H, 2 × s, 2 × NMe).

(b) Sodium hydride (300 mg) was added to a solution of methyl 3-[(*N*-methyl-3-nitrobenzamido)-3-benzamido]benzoate (10) (1.0 g) and methyl iodide (1 ml) in dry dimethyl sulphoxide (15 ml). The reaction mixture was stirred at room temperature overnight. Water was carefully added to destroy excess of sodium hydride and the reaction mixture was then poured into ice–water (150 ml). The aqueous solution was extracted with chloroform. The chloroform layer was separated, dried, and concentrated to give a solid, which upon recrystallisation from ethanol afforded methyl 3-[*N*-methyl-3-(*N*-methyl-3-nitrobenzamido)benzamido]-benzoate (11), m.p. 109—111 °C. This compound was identical with that prepared previously by method (a).

(c) A solution of methyl 3-[*N*-methyl-3-(*N*-methyl-3-nitrobenzamido)benzamido]benzoate (11) (1.1 g) in dimethyl sulphoxide (3 ml), to which potassium hydroxide (600 mg) in water (5 ml) had been added, was stirred at room temperature for 2 h. More water (20 ml) was added to the reaction mixture and the aqueous solution was washed with chloroform and then acidified with dilute hydrochloric acid to give a white solid which was filtered off and crystallised from ethanol to give 3-[*N*-methyl-3-(*N*-methyl-3-nitrobenzamido)benzamido]benzoic acid (12) (600 mg, 56%), m.p. 194—196 °C. Recrystallisation from water gave crystals with m.p. 197—199 °C identical with those already characterised under method (a).

3-[N-*Methyl*-3-(N-*methyl*-3-*aminobenzamido*)*benzamido*]-*benzoic Acid* (13).—3-[*N*-Methyl-3-(*N*-methyl-3-nitrobenzamido)benzamido]benzoic acid (12) (2.0 g) was dissolved in ethanol (150 ml) and platinum oxide (80 mg) was added. The reaction mixture was stirred in the presence of an atmosphere of hydrogen at room temperature. During a period of 5 h, the expected amount of hydrogen was consumed. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue crystallised from ethanol giving 3-[N-*methyl*-3-(N-*methyl*-3-*aminobenzamido*)*benzamido*]*benzoic acid* (13) (1.7 g, 85%), m.p. 192—195 °C [Found: C, 68.7; H, 5.5; N, 10.4%; *M* (mass spec.), 403. $C_{23}H_{21}N_3O_4$ requires C, 68.5; H, 5.2; N, 10.4%; *M*, 403], τ($CDCl_3$) 1.80—3.30 (12 H, m, ArH) and 6.55 and 6.69 (6 H, 2 × s, 2 × NMe).

1,9-*Dimethyl*-1,9,17-*triaza*[2.2.2]*metacyclophane*-2,10,18-*trione* (1).—A solution of 3-[*N*-methyl-3-(*N*-methyl-3-aminobenzamido)benzamido]benzoic acid (13) (2.4 g) in dry dichloromethane (100 ml) was added to a solution of *N,N'*-dicyclohexylcarbodi-imide (1.5 g) in dry dichloromethane (25 ml) and the reaction mixture was stirred overnight at room temperature. The precipitated *N,N'*-dicyclohexylurea was filtered off and the filtrate was washed with cold water, dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and finally with a saturated solution of sodium chloride. The dried solvent was evaporated off and the residue was subjected to preparative t.l.c. on silica gel using ethyl acetate as eluant. The product (1.2 g) was isolated and dissolved in ethyl acetate (2 ml) and left at room temperature. Within 20 min a solid crystallised out of the solution and was filtered off and characterised as 1,9-*dimethyl*-1,9,17-*triaza*[2.2.2]*metacyclophane*-2,10,18-*trione* (1) (600 mg, 26%), m.p. 174—176 °C [Found: *M* (mass spec.), 385.1433. $C_{23}H_{19}N_3O_3$ requires *M*, 385.1426], τ($CDCl_3$) 1.09 (1 H, bs, NH), 2.41—3.38 (11 H, m, ArH), 4.18 (1 H, bs, ArH), 6.47 and 6.72 (6 H, 2 × s, 2 × NMe), δ(CD_2Cl_2; $SiMe_4$ as standard) 169.8, 169.0, and 168.8 (carbonyl carbons), 146.0, 143.8, 137.4, 137.2, 136.7, 131.1, 130.0, 128.1, 127.7, 127.4, 127.0, 126.1, 125.0, 122.7, and 119.5 (aromatic carbons), and 38.3 and 37.7 (*N*-methyl carbons).

1,9,17-*Trimethyl*-1,9,17-*triaza*[2.2.2]*metacyclophane*-2,10,-18-*trione* (2).—A solution of the *N,N'*-dimethyl derivative (1) (300 mg) in tetrahydrofuran (10 ml) was stirred with sodium hydride (100 mg) and methyl iodide (1 ml) at room temperature. After 2 h, water was carefully added to the reaction mixture to destroy excess of sodium hydride. The product was extracted several times with chloroform and the combined chloroform layers were washed with water, dried, and concentrated to leave a solid. This residue was crystallised from ethanol to give 1,9,17-*trimethyl*-1,9,17-*triaza*[2.2.2]*metacyclophane*-2,10,18-*trione* (2) (230 mg, 72%), m.p. >320 °C (Found: C, 72.3; H, 5.5; N, 10.7%; *M* (mass spec.), 399. $C_{24}H_{21}N_3O_3$ requires C, 72.2; H, 5.3; N, 10.5%; *M*, 399), τ($CDCl_3$) 2.76—3.30 (12 H, m, ArH)

and 6.70 (9 H, s, 3 × NMe); δ(CD_2Cl_2; $SiMe_4$ as standard) 170.3 (carbonyl carbons), 144.2, 129.8, 128.9, and 127.2 (aromatic carbons), and 38.2 (*N*-methyl carbons).

1,9-*Dimethyl*-17-*benzyl*-1,9,17-*triaza*[2.2.2]*metacyclophane*-2,10,18-*trione* (3).—Benzyl bromide (55 mg) was added at room temperature to a stirred reaction mixture containing the *N,N'*-dimethyl derivative (1) (100 mg) and sodium hydride (80 mg) in tetrahydrofuran (2 ml). The stirring was continued overnight and water was carefully added to destroy excess of sodium hydride. The tetrahydrofuran was distilled off at reduced pressure and more water (100 ml) was added. The product was extracted several times with chloroform. The combined chloroform layers were washed with water, dried, and concentrated to leave an oily residue which was purified by preparative t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 40—60 °C) (1 : 1) as eluant. Crystallisation of the product from ethanol gave 1,9-*dimethyl*-17-*benzyl*-1,9,17-*triaza*[2.2.2]-*metacyclophane*-2,10,18-*trione* (3) (80 mg, 65%), m.p. 159—165 °C [Found: *M* (mass spec.), 475. $C_{30}H_{25}N_3O_3$ requires *M*, 475], τ($CDCl_3$) 2.62—3.48 (17 H, m, ArH), 5.08 (2 H, bs, benzylic CH_2), and 6.68 and 6.74 (6 H, 2 × s, 2 × NMe).

Determination of Rates of Conformational Change by ^{1}H *N.m.r. Spectroscopy*.—The methods used have been fully described.[6,8,9] The computer programs (coded in FORTRAN IV) used to generate theoretical line shapes are described for the general methods I and II.

Method I. A program (I) for exchange of nuclei between two unequally populated sites, A and B, with no mutual coupling. In the case of compound (2), (a) the carbonyl carbons, (b) one of the quaternary aromatic carbons, and (c) the *N*-methyl carbons all gave rise to two singlets of unequal intensities in their ^{1}H decoupled ^{13}C n.m.r. spectra at low temperatures. Thus, spectral line shapes were simulated using this program. Calculated and observed spectra are shown in Figure 1.

Method II. A program (III) for the case in which nuclei are exchanged between the pairs of sites A1 and B1, A2 and B2, A1 and A2, and B1 and B2 of two AB systems. This program was used to simulate the spectral line shapes associated with the benzylic-methylene protons of compound (3). The exchange rate (k_2) between the sites A2 and B2 was fast compared with exchange rates (k_{12}) and (k_{21}) between sites A1 and A2, and B1 and B2, and the

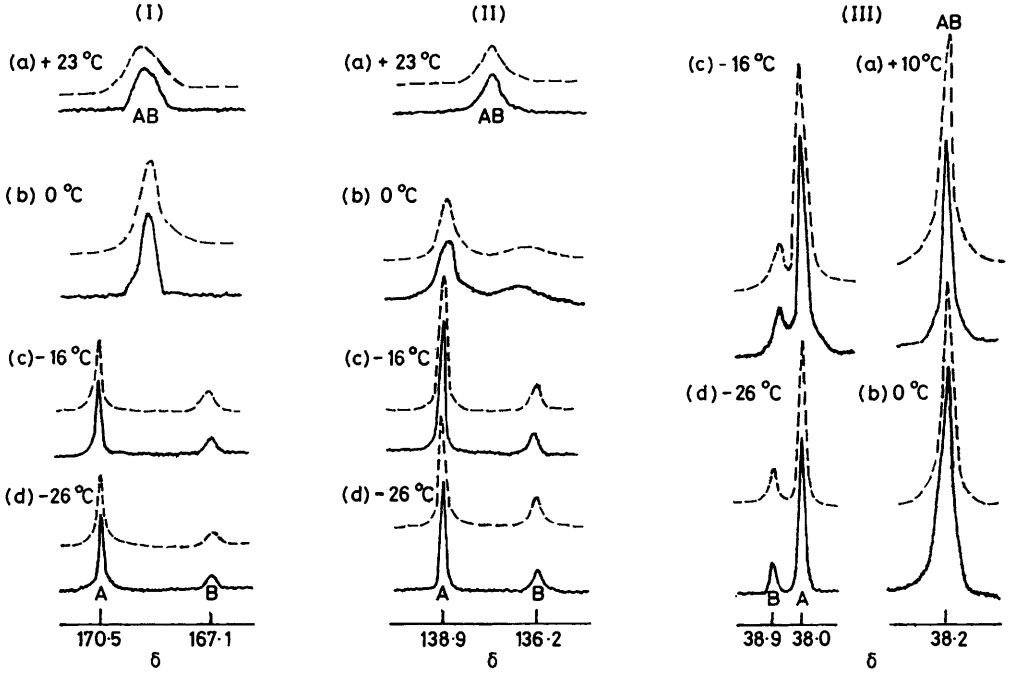


FIGURE 1 Observed (full line) and computed (broken line) spectra of (I) the carbonyl carbons, (II) one of the quaternary aromatic carbons, and (III) the *N*-methyl carbons for compound (2). (I) The carbonyl carbons, (a) at +23 °C, k_{AB} = 129 s^{-1}; (b) at 0 °C, k_{AB} = 18 s^{-1}; (c) at −16 °C, k_{AB} = 1.1 s^{-1}; (d) at −26 °C, k_{AB} = 0.7 s^{-1}. (II) One of the quaternary aromatic carbons, (a) at +23 °C, k_{AB} = 86 s^{-1}; (b) at 0 °C, k_{AB} = 13.5 s^{-1}; (c) at −16 °C, k_{AB} = 1.1 s^{-1}; (d) at −26 °C, k_{AB} = 0.5 s^{-1}. (III) The *N*-methyl carbons, (a) at +10 °C, k_{AB} = 52 s^{-1}; (b) at 0 °C, k_{AB} = 29 s^{-1}; (c) at −16 °C, k_{AB} = 4.4 s^{-1}; (d) at −26 °C, k_{AB} = 0.5 s^{-1}

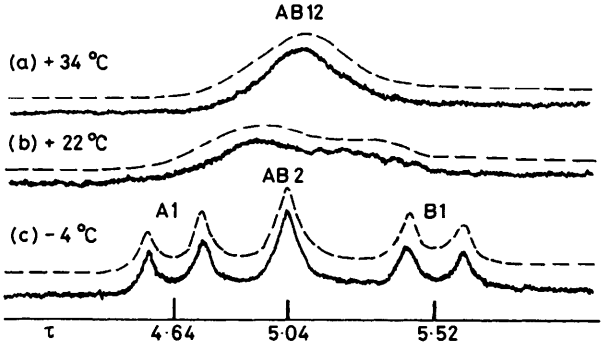


FIGURE 2 Observed (full line) and computed (broken line) spectra of the benzylic-methylene protons of compound (3): (a) At +34 °C, k_1 87 s^{-1}, k_2 100 000 s^{-1}, k_{12} 175 s^{-1}; (b) at +22 °C, k_1 27 s^{-1}, k_2 100 000 s^{-1}, k_{12} 54 s^{-1}; (c) at −4 °C, k_1 2 s^{-1}, k_2 100 000, k_{12} 4 s^{-1}

exchange rate (k_1) between the sites A1 and B1. Thus, protons in sites A2 and B2 give rise to a single line (AB2) at the average site chemical shift, whereas nuclei in sites A1 and B1 give rise to a typical four-line AB system. Calculated and observed spectra are shown in Figure 2.

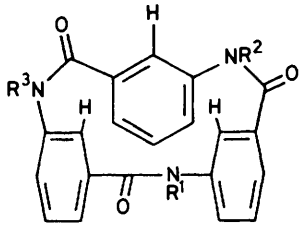
RESULTS AND DISCUSSION

The temperature-dependent ^{1}H n.m.r. spectra of the 1,9,17-trimethyl- (2) and 1,9-dimethyl-17-benzyl- (3) derivatives demonstrate that two diastereoisomeric conformations are populated in solution. In the case of the 1,9,17-trimethyl derivative (2), the singlet observed at τ 6.70 in dideuteriodichloromethane divides at −60 °C into two singlets with approximate relative intensities of 1 : 4 at τ 6.64 and 6.67, respectively. In addition, a broad singlet (τ 3.57) integrating for *ca.* 0.2 H emerges at higher field from the remainder of the spectrum for the aromatic protons. In the case of the 1,9-dimethyl-17-benzyl derivative (3), the benzylic-methylene protons exhibit (i) an AB system (τ_{A1} 4.64, τ_{B1} 5.52, J_{A1B1} = 14.0 Hz, pop. 1 = 0.72) assignable to a relatively rigid conformation and (ii) a singlet (τ_{AB2} 5.04, pop. 2 = 0.28) associated with a relatively flexible conformation in deuteriochloroform–carbon disulphide (1 : 1) at −60 °C. At this temperature, two other spectral features are worthy of note. Firstly, the constitutionally heterotopic *N*-methyl groups afford two high intensity singlets at τ 6.68 and 6.70 and two low intensity singlets at τ 6.57 and 6.73. Secondly, a broad singlet (τ 3.93) integrating for *ca.* 0.3 H emerges at higher field from the remainder of the spectrum for the aromatic protons. Clearly, the high field aromatic signal observed at low temperature in the ^{1}H n.m.r. spectra of both compounds (2) and (3) arises from the flexible conformation.

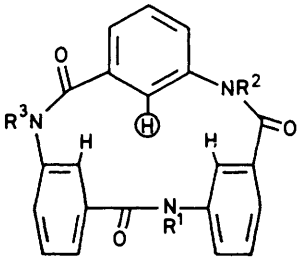
Inspection of molecular models suggests that in both the rigid and flexible conformations all three amide linkages have the *cis* geometry. The rigid conformation has C_3 symmetry † and can be likened to a crown (14) whereas the flexible conformation is asymmetric and can be likened to a saddle (15). These diastereoisomeric conformations are in equilibrium with their enantiomers according to the following scheme:

$$\text{Crown} \rightleftharpoons \text{Saddle} \rightleftharpoons \text{Saddle*} \rightleftharpoons \text{Crown*}$$

In the case of the 1,9-dimethyl-17-benzyl derivative (3), the major diastereoisomer corresponds to the crown (14) and the minor diastereoisomer corresponds to the saddle (15) conformations. The temperature-dependent ^{1}H n.m.r. spectra (Figure 2) reveal two exchange processes which can be associated with (i) slow ring inversion between enantiomeric crown conformations involving the intermediacy of enantiomeric saddle conformations and (ii) slow ring interconversion between crown and saddle conformations. Ring inversion of the saddle conformations appears to be fast on the ^{1}H n.m.r. time scale reflecting the flexible nature of this conformation and its ability to ring invert by torsional changes. The rate constants for the two experimentally detectable exchange processes gave $\Delta G^{\ddagger}$ values of 15.3 and 14.9



Crown conformation (14)



Saddle conformation (15)

kcal mol^{-1} respectively for the Crown ⇌ Crown* inversion and Crown ⟶ Saddle interconversion processes. Examination of space-filling molecular models reveals that the aromatic proton, which is encircled in the formula for the saddle conformation (15), projects into the shielding regions of the other two aromatic rings. The integrated intensity of the signal for this proton provides a measure of the population of the flexible saddle conformation (15) in solution. Thus, in the case of the 1,9,17-trimethyl derivative (2), the saddle conformation (15) corresponds to the minor diastereoisomer in solution as indicated by the relative intensity associated with this ^{1}H n.m.r. probe in the low-temperature spectrum. Although spectral changes were also observed in the *N*-methyl proton region of the spectrum on cooling, the temperature dependences (Figure 2) of the resonances for (a) the carbonyl carbons, (b) one of the quaternary aromatic carbons, and (c) the *N*-methyl carbons in the ^{1}H-decoupled ^{13}C n.m.r. spectra were eminently more suitable for line-shape analysis on account of the better resolution characterising the pairs of signals arising from the diastereoisomeric conformations at low temperatures. Two signals with relative intensities of 4 : 1 were observed for each of the carbon probes at −65 °C and an average value of 14.4 kcal mol^{-1} was obtained for $\Delta G^{\ddagger}_{\text{Crown} \rightarrow \text{Saddle}}$. In the solid state, the 1,9,17-trimethyl derivative (2) adopts a lopsided crown conformation as revealed (Figure 3) by an *X*-ray structure analysis on crystals of (2) obtained from toluene.

† It should be recognised that this description also applies to lopsided ground state conformations with averaged C_3 symmetry on the n.m.r. time scale.

The ^{1}H n.m.r. spectrum of the 1,9-dimethyl derivative (1) in dideuteriodichloromethane exhibits a broad singlet which integrates for *one* proton at τ 4.18. This observation suggests that this derivative (1) exists predominantly in the saddle conformation in solution. This suggestion is supported by the absence of any temperature dependence, other than chemical-shift changes for the amide, aromatic, and *N*-methyl protons, in the ^{1}H n.m.r. spectrum of this derivative (1), when the dideuteriodichloromethane solution is cooled down to −90 °C.

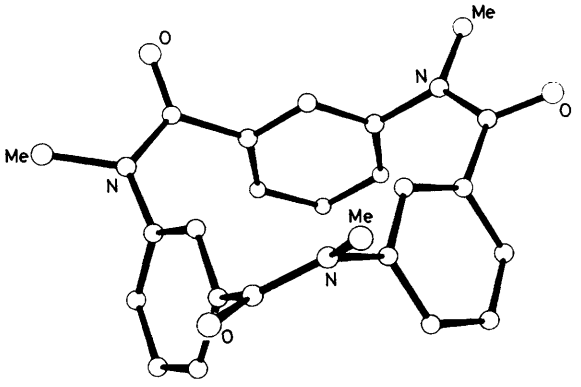


FIGURE 3 The structure of 1,9,17-trimethyl-1,9,17-triaza[2.2.2]-metacyclophane-2,10,18-trione (2) in the solid state[3]

In conclusion it should be noted that the conformational behaviour of the 15-membered rings in compounds (1)—(3) has obviously similarities with that of the 9-membered rings in the cyclotriveratrylene series.[10]

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