Tetrahedron Letters Vol. 21, pp 4215 - 4218
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0040-4039/80/1022-4215$02.00/0

SYNTHESIS AND CONFORMATIONAL BEHAVIOUR OF 1,9,17-TRIAZA[2.2.2]METACYCLOPHANE-2,10,18-TRIONE DERIVATIVES

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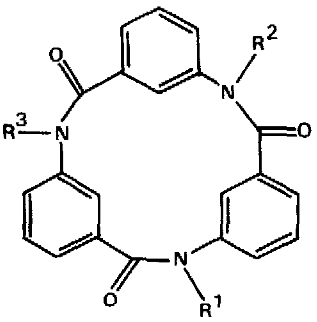
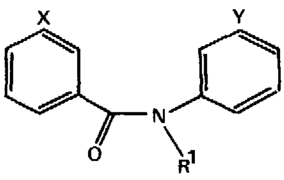
Summary. The 1,9,17-triaza[2.2.2]metacyclophane-2,10,18-trione derivatives (1) – (3) have been synthesised. X-Ray crystallography shows that the 1,9,17-trimethyl derivative (3) adopts a Crown conformation (11) in the solid state. Dynamic n.m.r. spectroscopy indicates that both the 1,9-dimethyl-17-benzyl- (2) and 1,9,17-trimethyl- (3) derivatives exist as interconverting mixtures of Crown (11) and Saddle (12) conformations with the former predominating at equilibrium in solution.

The success of a stepwise approach in achieving a synthesis of trianthranilide[2,3] derivatives from *o*-aminobenzoic (anthranilic) acid and *o*-nitrobenzoyl chloride encouraged us to examine an analogous synthetic strategy for the construction of some isomeric macrocycles starting from *m*-aminobenzoic acid and *m*-nitrobenzoyl chloride. We now describe the synthesis of the 1,9-dimethyl- (1), 1,9-dimethyl-17-benzyl- (2), and 1,9,17-trimethyl- (3) triaza[2.2.2]metacyclophane-2,10,18-triones and the examination of the conformational behaviour of their 15-membered rings in both the solution and the solid states.

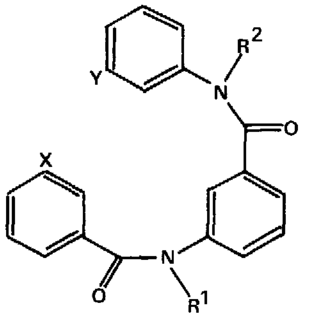
Compound (1) was obtained[4] from methyl-*m*-aminobenzoate and *m*-nitrobenzoyl chloride in eight steps. (i) *m*-nitrobenzoylation (*m*-$NO_2C_6H_4COCl$, NaOH, Et_2O, H_2O) of *m*-$H_2NC_6H_4CO_2Me$ afforded the amide (4), (ii) *N*-methylation (MeI, NaH, Me_2SO) of (4), followed by base (NaOH, H_2O) treatment during the work-up of the methyl ester yielded the acid (5) which (iii) was converted ($SOCl_2$) into its acid chloride (6), (iv) condensation (NaOH, Et_2O, H_2O) of (6) with *m*-$H_2NC_6H_4CO_2Me$ gave the methyl



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



	R^1	X	Y
4	H	NO_2	CO_2Me
5	Me	NO_2	CO_2H
6	Me	NO_2	COCl



	R^1	R^2	X	Y
7	Me	H	NO_2	CO_2Me
8	Me	Me	NO_2	CO_2Me
9	Me	Me	NO_2	CO_2H
10	Me	Me	NH_2	CO_2H

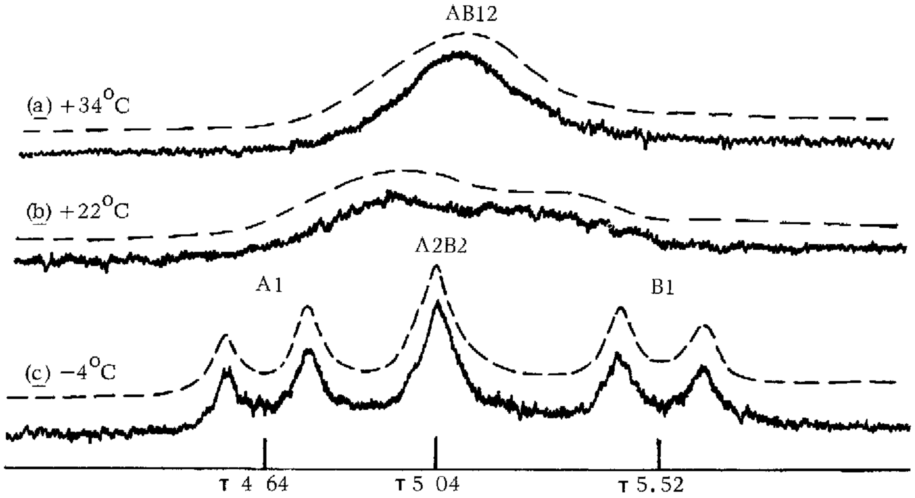
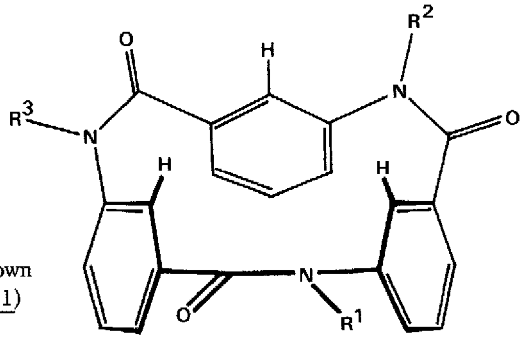
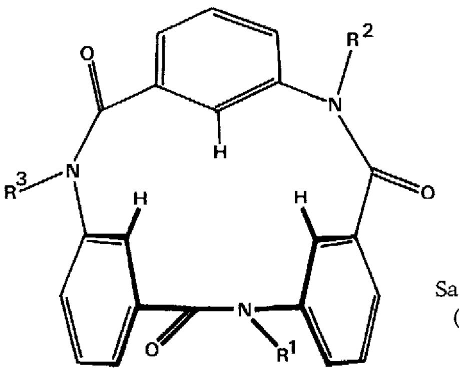


Figure 1 Observed (full line) and computed (broken line) spectra of the benzylic methylene protons of compound (2) (a) at + 34°C, k_1 = 87 s^{-1}, k_2 = 100 000 s^{-1}, k_{12} = 175 s^{-1}, (b) at + 22°C, k_1 = 27 s^{-1}, k_2 = 100 000 s^{-1}, k_{12} = 54 s^{-1}, (c) at - 4°C, k_1 = 2 s^{-1}, k_2 = 100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

ester (7), (v) methylation (MeI, NaH, Me_2SO) of (7) afforded the N,N'-dimethyl derivative (8), (vi) saponification (KOH, Me_2SO, H_2O) of the methyl ester (8) yielded the acid (9), and (vii) reduction (H_2, PtO_2, EtOH) of the aromatic nitro group in (9) gave the acyclic amino acid derivative (10) which (viii) underwent cyclisation on treatment with N,N'-dicyclohexylcarbodiimide in dichloromethane to provide the desired 1,9-dimethyltriaza[2 2.2]metacyclophane-2,10,18-trione (1), m.p 174–176°, in 26% yield Benzylation ($PhCH_2Br$, NaH, THF) of (1) gave the 1,9-dimethyl-17-benzyl derivative (2), m.p. 159–165°, ^1H n.m.r data at 30°C τ ($CDCl_3$–CS_2, 1 1) 2 40–3 80 (17H, m, aromatic protons), 5 06 (2H, broad signal, benzylic methylene protons), and 6.68 and 6.74 (2 x 3H, 2 x s, 2 x NMe). Evidence was obtained for the presence of two diastereoisomeric conformations in solution from the low temperature spectra In particular, the benzylic methylene protons give (i) an AB system (τ_{A1} 4.64, τ_{B1} 5 52, J = 14 0 Hz, pop. 1 = 0 72) assignable to a relatively rigid conformation and (ii) a singlet (τ_{A2B2} 5 04, pop 2 = 0 28) associated with a relatively flexible conformation at -60°C.[5] Examination of molecular models suggests



Crown
(11)



Saddle
(12)

that the rigid conformation has $\underline{C}_3$ symmetry and can be likened to a Crown (11) whereas the flexible conformation is asymmetric and can be likened to a Saddle (12). These diastereoisomeric conformations are in equilibrium with their enantiomers according to the following scheme

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

The ^{1}H n.m.r. spectral line shapes for the benzylic methylene protons were simulated (see Figure 1) at different temperatures using a program[6] suitable for exchanging nuclei between the pairs of sites A1 and B1, A2 and B2, A1 and A2, and B1 and B2. The rate constants for the site exchanges gave $\Delta\underline{G}^{\ddagger}$ values of 15.3 and 14.9 kcal mol^{-1} respectively for the Crown $\rightleftharpoons$ Crown* inversion and Crown $\rightarrow$ Saddle interconversion processes. Methylation (MeI, NaH, THF) of (1) gave the 1,9,17-trimethyl derivative, m.p. > 320°, ^{1}H n.m.r. data at 30°C: τ (CD_2Cl_2) 2.76–3.30 (12H, m, aromatic protons) and 6.80 (9H, s, 3 x NMe). Although spectral changes were observed[7] for this solution on cooling, the temperature dependences (see Figure 2) of the resonances for (a) the carbonyl carbons, (b) one of the quaternary aromatic carbons, and (c) the $\underline{N}$-methyl carbons in the ^{1}H-decoupled ^{13}C n.m.r. spectra were more instructive. At -65°C, two signals with relative intensities of 4 : 1 were observed for each of these carbon probes in keeping with the presence of two unequally populated diastereoisomeric conformations in solution. Line shape analyses of all three ^{13}C signals were carried out using a program[6] suitable for exchange of nuclei between two unequally populated sites A and B with no mutual coupling. An average $\Delta\underline{G}^{\ddagger}$ value of 14.4 kcal mol^{-1} was obtained for the interconversion of the major into the minor isomer. We have tentatively assigned these isomers to the Crown (11) and Saddle (12) conformations respectively because (i) the 1,9-dimethyl-17-benzyl derivative (2) prefers to adopt the Crown (11) conformation in solution and (ii) the 1,9,17-trimethyl derivative (3) crystallises from toluene in a lopsided Crown-like conformation as shown by the results of an X-ray crystal structure analysis. Comparisons (see Figure 3) of the torsional angles associated with the cis-amide linkages shows that the solid state conformation not

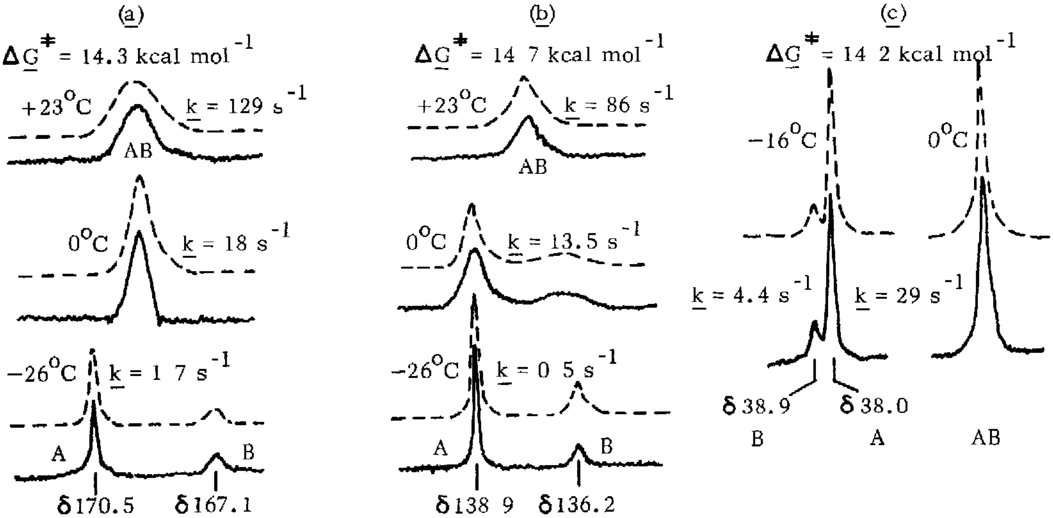


Figure 2. Observed (full line) and computed (broken line) spectra of (a) the carbonyl carbons, (b) one of the quaternary aromatic carbons, and (c) the $\underline{N}$-methyl carbons for compound (3)

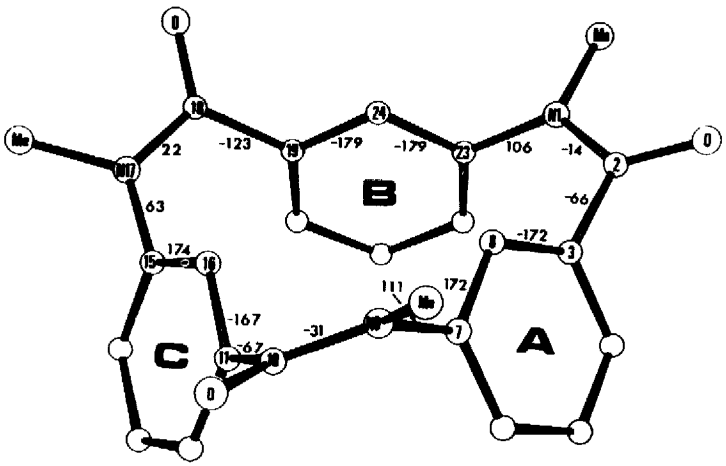


Figure 3. The solid state conformation of the 1, 9, 17-trimethyl derivative (3)

only lacks $\underline{C}_3$ symmetry but also displays[8] significant distortions from coplanarity of the atoms comprising each of the three amide bonds In addition to the significant departures from *synperiplanar* geometry exhibited by the C–CO–NMe–C torsional angles, out-of-plane deformations characterise both the carbonyl carbon and nitrogen atoms [9]

Crystallographic Data Crystals of (3) are triclinic, $\underline{a}$ = 13.546 (1), $\underline{b}$ = 9.216 (1), $\underline{c}$ = 9 469 (1) Å, α = 107.45 (1), β = 109.49 (1), γ = 72 43 (1)°, $\underline{U}$ = 1036 Å^3, space-group $\underline{P}\bar{1}$, $\underline{Z}$ = 2, $\underline{D}_c$ = 1.28 g cm^{-3}. Of the 3097 independent reflections (θ ≤ 60°) measured on a diffractometer using Cu–$\underline{K}_\alpha$ radiation, 138 were classified as unobserved. The structure was solved using the symbolic addition procedure and refined to give an $\underline{R}$ value of 0 042

References and Footnotes

1. Present address Department of Chemistry, University of Ghana, Legon, Ghana.
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3. W. D. Ollis, J S. Stephanatou, J. F. Stoddart, and A. G. Ferrige, *Angew.Chem.Internat.Edn* , 1976, **15**, 223.
4. The compositions of all new compounds were confirmed by elemental analyses. Structural assignments were based upon the results of high resolution mass spectrometry and ^{1}H n.m.r. spectroscopic evidence.
5. At this temperature, the constitutionally heterotopic $\underline{N}$-methyl protons give two high intensity singlets at τ 6.68 and 6.70 and two low intensity singlets at τ 6.57 and 6.73.
6. W. D. Ollis and J. F Stoddart, *J.Chem.Soc Perkin I*, 1976, 926.
7. The singlet (τ 6.80) at 30°C for the $\underline{N}$-methyl protons separated out into two singlets with τ values of 6.74 and 6.77 and relative intensities of 1 4 respectively at -60°C.
8. *Cf* J D. Dunitz and F. K. Winkler, *Acta Cryst* , 1975, **B31**, 251 and references therein.
9. Large out-of-plane deformations occur at the nitrogen atoms in the amide linkages between aromatic rings A and B, and A and C, the out-of-plane bending parameters (X_N) defined in ref. 8 amount to 17° and 19°, respectively

(Received in UK 9 July 1980)