Conformational Behaviour of Medium-sized Rings. Part 13.[1] 5,18-Dihydro- and 5,11,12,18-Tetrahydrotribenzo[*b,f,j*][1,4]diazacyclododecine-6,17-diones

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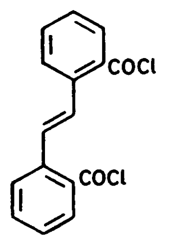
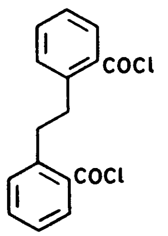
The unsaturated (3) and saturated (6) bislactams have been prepared from condensations of *o*-phenylenediamine with the bisacyl chlorides (1) and (2) derived from *trans*-stilbene-2,2'-dicarboxylic acid and bibenzyl-2,2'-dicarboxylic acid, respectively. Dynamic ^1H n.m.r. spectroscopy demonstrates that the 5,18-dibenzyl derivative (5) of (3) and the 5,18-dimethyl- (7) and 5,18-dibenzyl- (8) derivatives of (6) adopt enantiomeric non-planar conformations with averaged C_2 symmetry in solution. In the case of the two 5,18-dibenzyl derivatives (5) and (8), ring inversion is shown to be slow ($\Delta G^\ddagger$ = 20.4 and 21.1 kcal mol^{-1}, respectively) on the ^1H n.m.r. time scale at room temperature and probably involves propeller-like conformations (9a) $\rightleftharpoons$ (9b) as the enantiomeric ground-state conformations. Both the 5,18-dimethyl- (7) and -dibenzyl (8) derivatives of the saturated bislactam (6) form 1 : 1 inclusion compounds, (7) with *o*-xylene and (8) with ethanol.

THE ability which a few trisalicylides (*e.g.* tri-*o*-thymotide[2-5]), trithiosalicylides (*e.g.* tri-6-methylthiosalicylide[6,7]), and trianthranilides (*e.g.* *N,N'*-dimethyl-,[8,9] *N,N'*-dibenzyl-,[8,9] and *N,N',N''*-tribenzyl-[8,9] trianthranilides, and *N,N'*-dimethyl-*N''*-benzyltri-3-methyltrianthranilide[1,10]) have for forming inclusion compounds and/or undergoing spontaneous resolution encouraged us to search for topologically related molecules which might exhibit one or more of these properties. In the first instance, we considered replacing one of the amide linkages in the trianthranilide constitution by an olefinic or bismethylene bridge but came to the conclusion that a synthesis of analogues of this kind would not be a straightforward undertaking. However, it occurred to us that the constitutionally isomeric bislactams should be readily accessible from condensations of *o*-phenylenediamine with the bisacyl chlorides (1) and (2) derived from *trans*-stilbene-2,2'-dicarboxylic acid[11] and bibenzyl-2,2'-dicarboxylic acid,[12] respectively. Indeed, the 12-membered ring bislactams (3) and (6) were obtained in good yield by this simple approach. Reaction of *o*-phenylenediamine with the bisacyl chloride (1) of *trans*-stilbene-2,2'-dicarboxylic acid in benzene solution at room temperature gave the unsaturated bislactam (3); employing the same conditions, the saturated bislactam (6) was prepared from the bisacyl chloride (2) of bibenzyl-2,2'-dicarboxylic acid. *N*-Methylation of (3) and (6) affords the 5,18-dimethyl derivatives (4) and (7), respectively. *N*-Benzylation of (3) and (6) affords the 5,18-dibenzyl derivatives (5) and (8), respectively.



(1)



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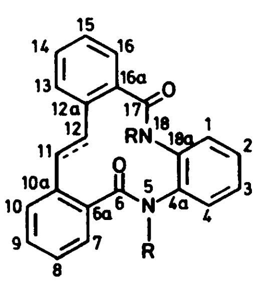


	- - - - -	R
(3)	CH=CH	H
(4)	CH=CH	Me
(5)	CH=CH	CH_2Ph
(6)	CH_2–CH_2	H
(7)	CH_2–CH_2	Me
(8)	CH_2–CH_2	CH_2Ph

In this paper, we discuss the conformational behaviour of these 12-membered ring bislactams in solution in relation to our knowledge[13,14] of the structures adopted by the two 5,18-dimethyl derivatives (4) and (7) in the solid state. This investigation has been the subject of two preliminary communications.[13,14]

EXPERIMENTAL

The general methods have been discussed in Parts 3[15] and 6.[16]

5,18-Dihydrotribenzo[b,f,j][1,4]*diazacyclododecine*-6,17-*dione* (3).—A solution of *o*-phenylenediamine (175 mg) in dry benzene (50 ml) was added to a solution of stilbene-2,2'-dicarboxylic acid dichloride (1) [m.p. 158—159 °C (lit.,[11] 159 °C)] in dry benzene (100 ml) and the reaction mixture was stirred at room temperature for 3 h. Additional *o*-phenylenediamine (100 mg) was added and stirring was continued overnight. The solid which precipitated was filtered off and recrystallised from methanol to yield 5,18-*dihydrotribenzo*[b,f,j][1,4]*diazacyclododecine*-6,17-*dione* (3) (220 mg, 39%), m.p. 270—271 °C [Found: *M* (mass spec.), 340. $C_{22}H_{16}N_2O_2$ requires *M*, 340], $\nu_{max.}$ (Nujol) 3 300 (NH) and 1 660 cm^{-1} (CO).

5,18-Dimethyl-5,18-*dihydrotribenzo*[b,f,j][1,4]*diazacyclododecine*-6,17-*dione* (4).—The unsaturated bislactam (3) (150 mg) was stirred with sodium hydride (150 mg) and methyl iodide (1 ml) in dry dimethyl sulphoxide (20 ml) at room temperature for 2 h. The excess of sodium hydride was destroyed by addition of water whereupon the 5,18-*dimethyl derivative* (4) precipitated (152 mg, 94%), m.p. 246—247 °C [Found: C, 78.2; H, 5.6; N, 7.3%; *M* (mass spec.), 368. $C_{24}H_{20}N_2O_2$ requires C, 78.2; H, 5.5; N, 7.6%; *M*, 368], $\nu_{max.}$ (Nujol) 1 640 cm^{-1} (CO); $\tau(CDCl_3)$ 2.50—2.82 (12 H, m, ArH), 2.90 (2 H, s, olefinic protons), and 6.85 (6 H, s, 2 × NMe).

This derivative recrystallises [13] from methanol as well-formed parallelopipeds which are suitable for *X*-ray crystallography. The structure of (4) in the solid state [13] is shown in Figure 1.

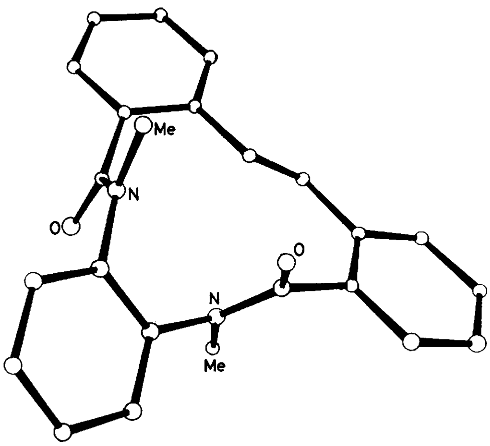


FIGURE 1 The structure of the 5,18-dimethyl derivative (4) of the unsaturated bislactam (3) in the solid state [13]

5,18-*Dibenzyl*-5,18-*dihydrotribenzo*[b,f,j][1,4]*diazacyclododecine*-6,17-*dione* (5).—Benzyl bromide (1.5 ml) was added to a solution of the unsaturated bislactam (3) (90 mg) in dry dimethyl sulphoxide (10 ml) containing sodium hydride (90 mg) and the reaction mixture was stirred at room temperature for 4 h. The excess of sodium hydride was destroyed by addition of water and the reaction mixture was extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and the solvent was evaporated off to afford an oil which crystallised from ether–light petroleum (b.p. 60—80 °C) as needles of the 5,18-*dibenzyl derivative* (5) (73 mg, 53%), m.p. 203—205 °C [Found: *M* (mass spec.), 520.2154. $C_{36}H_{28}N_2O_2$ requires *M*, 520.2151], $\nu_{max.}$ (Nujol) 1 640 cm^{-1} (CO); $\tau(CDCl_3)$ 2.40—3.60 (24 H, m, aromatic and olefinic protons) and 5.30 and 5.47 (4 H, AB system, J_{AB} 14.8 Hz, 2 × benzylic CH_2).

Bibenzyl-2,2'-dicarbonyl Dichloride (2).—Bibenzyl-2,2'-dicarboxylic acid [m.p. 235—237 °C (lit.,[12] 231 °C)] (130 mg) was refluxed with thionyl chloride (1.5 ml) for 4 h. During the first 0.5 h all the acid dissolved but refluxing was continued for a further 3.5 h to ensure that the reaction was complete. The excess of thionyl chloride was distilled off under reduced pressure and the residue was recrystallised from benzene to give *bibenzyl*-2,2'-*dicarbonyl dichloride* (2) (110 mg, 74%), m.p. 164—167 °C (Found: C, 62.5; H, 3.9; Cl, 22.9. $C_{16}H_{12}Cl_2O_2$ requires C, 62.6; H, 3.94; Cl, 23.1%).

5,11,12,18-*Tetrahydrotribenzo*[b,f,j][1,4]*diazacyclododecine*-6,17-*dione* (6).—A solution of *o*-phenylenediamine (0.56 g) in dry benzene (100 ml) was added to a solution of the bisacyl chloride (2) (1.6 g) in dry benzene (400 ml) and the reaction mixture was stirred at room temperature for 3 h. Additional *o*-phenylenediamine (0.3 g) was added and stirring was continued overnight. The solid which precipitated was filtered off and recrystallised from methanol to give 5,11,12,18-*tetrahydrotribenzo*[b,f,j][1,4]*diazacyclododecine*-6,17-*dione* (6) (1.1 g, 62%), m.p. >300 °C [Found: C, 77.4; H, 5.5; N, 8.3%; *M* (mass spec.), 342.1357. $C_{22}H_{18}N_2O_2$ requires C, 77.2; H, 5.30; N, 8.2%; *M*, 342.1368], $\nu_{max.}$ (Nujol) 3 200 (NH) and 1 640 cm^{-1} (CO).

5,18-*Dimethyl*-5,11,12,18-*tetrahydrotribenzo*[b,f,j][1,4]-*diazacyclododecine*-6,17-*dione* (7).—The saturated bislactam (6) (150 mg) was stirred with sodium hydride (150 mg) and methyl iodide (1 ml) in dry dimethyl sulphoxide (20 ml) at room temperature for 3 h. In order to destroy excess of sodium hydride, water was added, whereupon the 5,18-*dimethyl derivative* (7) precipitated (146 mg, 90%), m.p. 273 °C [Found: C, 78.0; H, 6.2; N, 7.4%; *M* (mass spec.), 370. $C_{24}H_{22}N_2O_2$ requires C, 77.8; H, 6.0; N, 7.6%; *M*, 370], $\nu_{max.}$ (Nujol) 1 650 cm^{-1} (CO); $\tau(CDCl_3)$ 2.62—2.73 (12 H, m, ArH), 6.78 (6 H, s, 2 × NMe), and 6.95—7.22 (4H, AA'BB' system, CH_2CH_2); $\delta(CDCl_3$; $SiMe_4$ as standard) 171.2 (carbonyl carbons), 139.7, 137.4, 136.6, 130.0, 129.4, 128.8, and 126.8 (aromatic carbons), 38.6 (*N*-methyl carbons), and 36.5 (methylene carbons).

On recrystallisation from xylene (mixed isomers) this derivative forms [14] a 1 : 1 inclusion compound with *o*-xylene in the form of single crystals which are amenable to *X*-ray crystallography. The structure of (7) in the solid state [14] is shown in Figure 2.

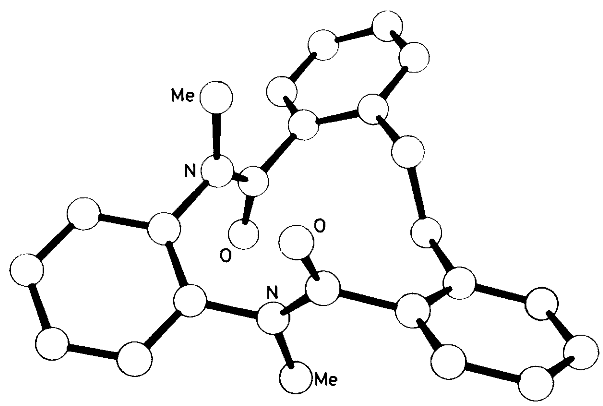


FIGURE 2 The structure of the 5,18-dimethyl derivative (7) of the saturated bislactam (6) in the solid state [14]

5,18-*Dibenzyl*-5,11,12,18-*tetrahydrotribenzo*[b,f,j][1,4]-*diazacyclododecine*-6,17-*dione* (8).—A solution of the saturated bislactam (6) (200 mg) in dry dimethyl sulphoxide (15 ml) containing sodium hydride (200 mg) was stirred with benzyl bromide (1.5 ml) at room temperature for 4 h. Excess of sodium hydride was destroyed with water and the reaction mixture was extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and the solvent was evaporated off to afford an oil which crystallised from ether–light petroleum (b.p. 60—80 °C) to give needles of the 5,18-*dibenzyl derivative* (8) (200 mg, 66%), m.p. 149—150 °C [Found: C, 82.7; H, 6.0; N, 5.4%; *M* (mass spec.), 522. $C_{36}H_{30}N_2O_2$ requires C, 82.7; H, 5.8; N, 5.4%; *M*, 522], $\nu_{max.}$ (Nujol) 1 630 cm^{-1} (CO); $\tau(CDCl_3)$ 2.22—3.44 (22 H, m, ArH), 5.07 and 5.23 (4 H, AB system, J_{AB} 14.7 Hz, 2 × benzylic CH_2), and 6.48—7.24 (4 H, AA'BB' system, CH_2CH_2).

An interesting property of this derivative is its striking ability to form a 1 : 1 inclusion compound with ethanol. This was first noted when (8) was dissolved in chloroform containing 2% of ethanol (present as a stabilizer), the solvent removed under reduced pressure at room temperature, and the residue recrystallised from ether–light petroleum (b.p. 60—80 °C) to give a crystalline sample which was shown by ^{1}H n.m.r. spectroscopy ($CDCl_3$) to contain a molar proportion of ethanol. This ethanol can be removed from the crystals *in vacuo* (<1.0 mmHg) at +90 °C within 4 h.

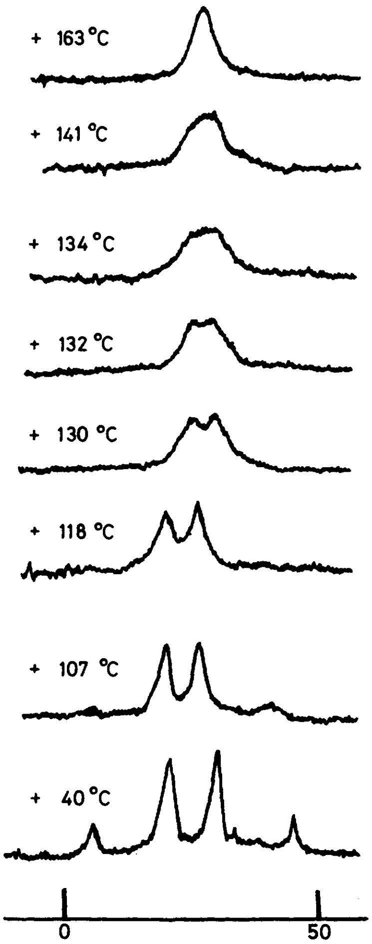


FIGURE 3 The temperature dependence of the AB system for the benzylic-methylene protons in the 5,18-dibenzyl derivative (5) of the unsaturated bislactam (3)

Determination of Rates of Conformational Change by ^{1}H *N.m.r. Spectroscopy*.—For compounds (5) and (8) site-exchange rate constants, k_c, were calculated at the coalescence temperature, T_c, by using the approximate relationship (1), which is suitable for exchange of nuclei between two sites A and B with equal populations and chemical shifts, ν_A and ν_B, respectively, and a mutual coupling constant, J_{AB}. The temperature dependences of the AB systems for

$$k_c = \pi[(\nu_A - \nu_B)^2 + 6\ J_{AB}^2]^{\frac{1}{2}}/2^{\frac{1}{2}} \qquad \text{(i)}$$

the benzylic-methylene protons in compounds (5) and (8) are illustrated in Figures 3 and 4, respectively.

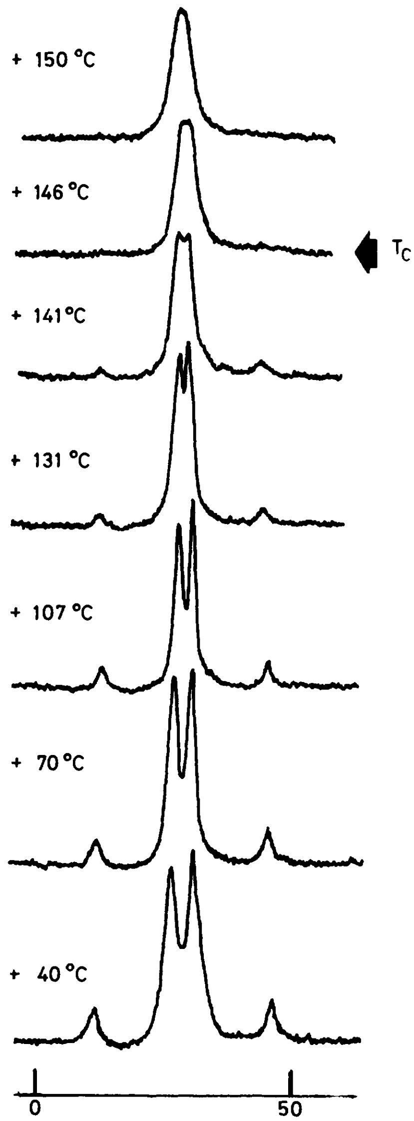
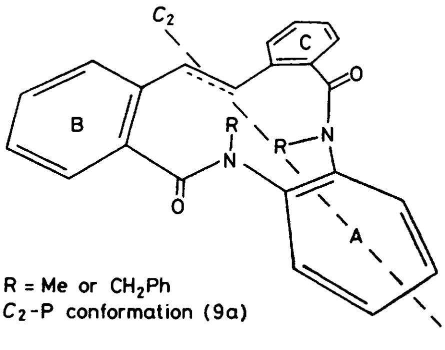


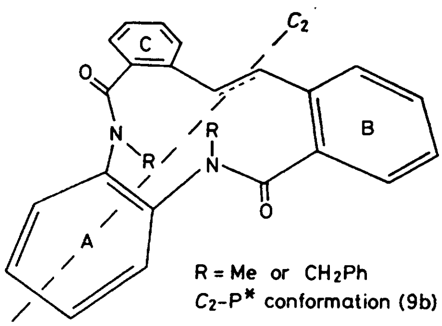
FIGURE 4 The temperature dependence of the AB system for the benzylic-methylene protons in the 5,18-dibenzyl derivative (8) of the saturated bislactam (6)

RESULTS AND DISCUSSION

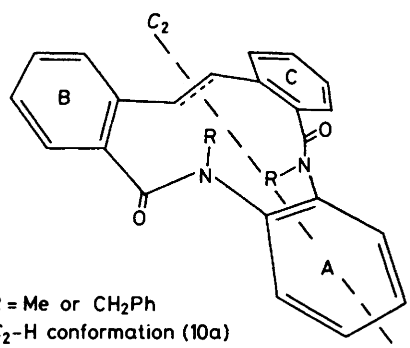
The temperature dependences of the ^{1}H n.m.r. spectra of the two 5,18-dimethyl derivatives (4) and (7) were investigated. When the unsaturated bislactam (4) was examined at +20 °C in deuteriochloroform–carbon disulphide (1 : 1), singlets were observed at τ 2.90 and 6.85 for the olefinic and *N*-methyl protons, respectively. No change occurred on cooling the solution down to −90 °C. When the saturated bislactam (7) was examined at +20 °C in deuteriochloroform–carbon disulphide (1 : 2), a singlet was observed at τ 6.78 for the *N*-methyl protons and the bismethylene protons appeared as an AA'BB' system between τ 6.95 and 7.22. On cooling the solution down to −80 °C, the singlet broadened very slightly while the AA'BB' system only exhibited changes in its line shape as a result of a progressive increase in the chemical-shift separation between the A and B protons as the temperature was lowered. The temperature dependence of the ^{1}H n.m.r. spectrum of (7) was also



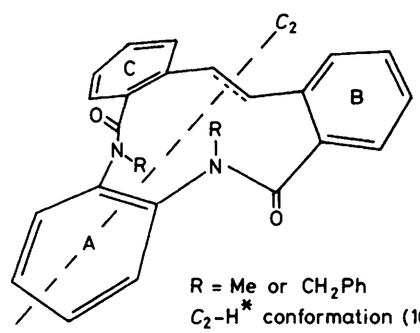
R = Me or CH_2Ph
C_2-P conformation (9a)



R = Me or CH_2Ph
C_2-P* conformation (9b)

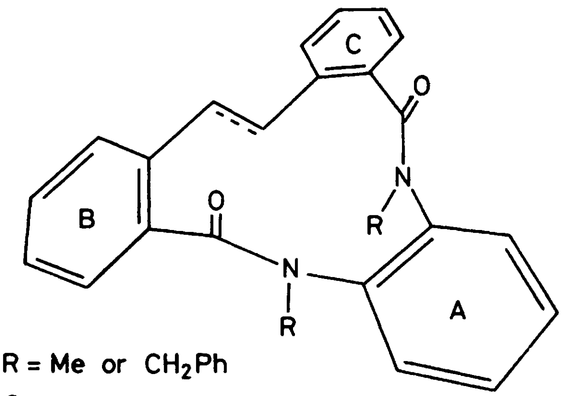


R = Me or CH_2Ph
C_2-H conformation (10a)

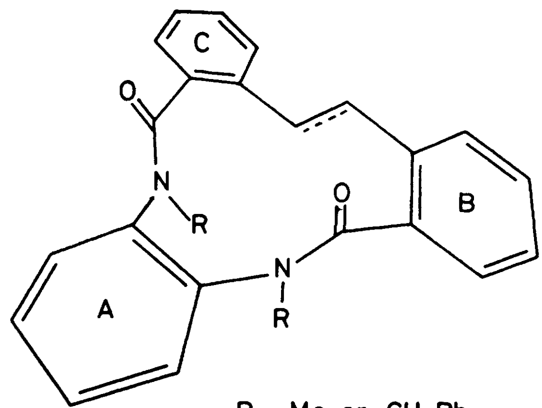


R = Me or CH_2Ph
C_2-H* conformation (10b)

examined above room temperature in nitrobenzene. This experiment revealed that the AA′BB′ system for the bismethylene protons coalesces to a singlet at +140 °C. These observations suggest that a slow ring inversion process is occurring in solution between enantiomeric conformations with C_2 symmetry. There are two possible diastereoisomeric C_2 conformations to consider for compounds (4) and (7) which retain two *trans*-amide linkages and either a *trans*-olefinic bond or an antiperiplanar bismethylene linkage. They are the C_2-propeller (C_2-P) conformation (9a) in which the C ⩵ C bond is aligned approximately parallel to ring A, and the C_2-helix (C_2-H) conformation (10a) in which the C ⩵ C bond is aligned approximately orthogonal to ring A. Both conformations have their enantiomeric



R = Me or CH_2Ph
C_1- H conformation (11a)



R = Me or CH_2Ph
C_2- H* conformation (11b)

counter-parts and these are designated C_2-P* (9b) and C_2-H* (10b), respectively. *X*-Ray crystallography [13,14] has shown that both the 5,18-dimethyl derivatives (4) and (7) exist as propeller-like conformations (9a and b) in the solid state (see Figures 1 and 2, respectively) although in the case of the unsaturated bislactam (4), the conjugational demands for planarity imposed upon the *trans*-stilbenoid portion of the molecule severely distort [13] the propeller conformation and destroy its molecular C_2 axis. By contrast, the saturated bislactam (7) adopts propeller-like conformations (9a and b) with almost perfect C_2 symmetry in the solid state.[14] It seems reasonable, therefore, to conclude that the slow ring inversion observed in solution for (7) is associated with a C_2-P $\rightleftharpoons$ C_2-P* (9a $\rightleftharpoons$ 9b) process. Since the 5,18-dimethyl derivative (7) does not contain a suitable n.m.r. probe to investigate the barrier to ring inversion, we prepared the 5,18-dibenzyl derivative (8) and examined (see Figure 4) the temperature dependence of its ^{1}H n.m.r. spectrum in hexadeuteriodimethyl sulphoxide. The AB system observed for the prochiral benzylic methylene protons at +40 °C coalesced to a singlet at +146 °C. The rate constant of 88 s^{-1} calculated at this coalescence temperature corresponds to a $\Delta G^\ddagger$ value of 21.1 kcal mol^{-1} for the ring-inversion process. The ^{1}H n.m.r. spectrum of the 5,18-dibenzyl derivative (5) of the unsaturated bislactam (3) also exhibits an AB system (τ_A 5.30, τ_B 5.47, and J_{AB} 14.8 Hz) for its prochiral benzylic-methylene protons in deuteriochloroform at room temperature. When the temperature dependence was examined (see Figure 3) in hexadeuteriodimethyl sulphoxide, the AB system coalesced to give a singlet at +134 °C. The rate constant of 95 s^{-1} calculated at this coalescence temperature corresponds to a $\Delta G^\ddagger$ value of 20.4 kcal mol^{-1} for the ring inversion. Again a process involving ring inversion between enantiomeric propeller-like conformations is the most likely one in view of the distorted propeller conformation (Figure 1) adopted by the 5,18-dimethyl derivative (4) in the solid state.[13] The conformational itinerary for the C_2-P $\rightleftharpoons$ C_2-P* ring inversion process (9a $\rightleftharpoons$ 9b) is given in Figure 5. In addition to involving the C_2-helical conformations C_2-H (10a) and C_2-H* (10b) as intermediates the asymmetrical helical conformations C_1-H (11a) and C_1-H* (11b) must also be implicated as intermediates. These C_1-helical conformations (11a and b) participate with two-fold degeneracy in the conformational itinerary. Although reorientations of the olefinic bond and the bis-methylene linkage probably occur by means of a pedalling motion,[16] reorientation of a *trans*-

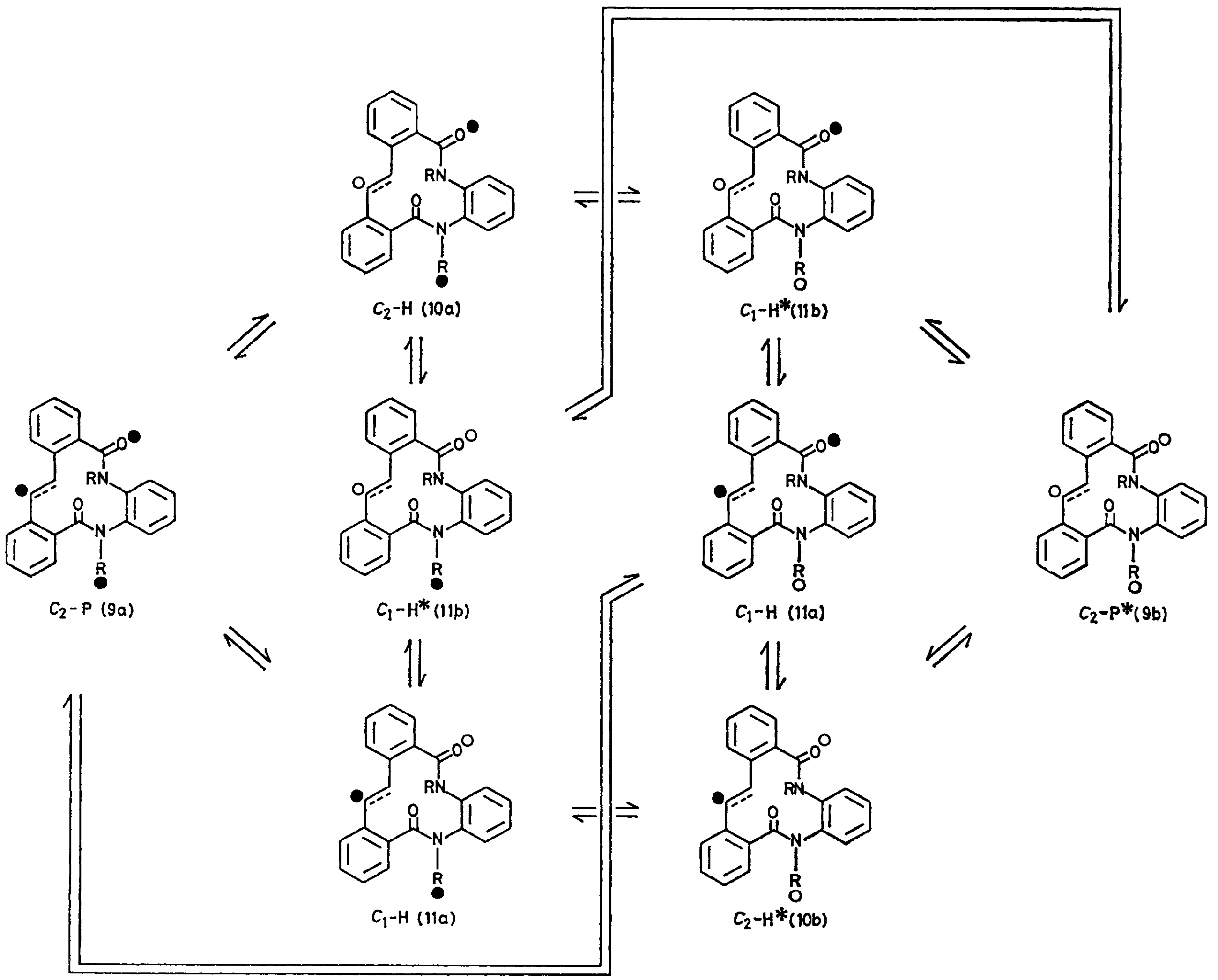


FIGURE 5 Conformational itinerary involving the C_2-P (9a), C_2-P* (9b), C_2-H (10a), C_2-H* (10b), C_1-H (11a), and C_1-H* (11b) conformations of compounds (4), (5), (7), and (8). For (4), ---- = CH=CH and R = Me; for (5), ---- = CH=CH and R = CH_2Ph; for (7), ---- = CH_2–CH_2 and R = Me; for (8), ---- = CH_2–CH_2 and R = CH_2Ph: ● ≡ a group or atom oriented above the mean plane of the ring and ○ ≡ a group or atom oriented below the mean plane of the ring

amide linkage must involve a further intermediate where the linkage assumes the *cis*-geometry temporarily. Thus, it is not surprising that the magnitudes of the barriers (20.4 and 21.1 kcal mol^{-1}, respectively) to C_2-P $\rightleftharpoons$ C_2-P* (9a $\rightleftharpoons$ 9b) inversion in compounds (5) and (8) are of the same order as those found[9] for *N,N'*-disubstituted trianthranilide derivatives where a similar mechanism for ring inversion has been proposed.[9]

Finally, it should be noted that both derivatives of the saturated bislactam (6) form inclusion compounds. The 5,18-dimethyl derivative (7) crystallises[14] from a mixture of *o*-, *m*-, and *p*-xylene as a 1 : 1 inclusion compound with *o*-xylene. The 5,18-dibenzyl derivative (8) has the remarkable ability to form a 1 : 1 inclusion compound with ethanol which can survive recrystallisation from aprotic solvents.

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REFERENCES

1 Part 12, S. J. Edge, W. D. Ollis, J. S. Stephanatou, and J. F. Stoddart, preceding paper.

2 H. M. Powell, *Nature*, 1952, **170**, 155; D. Lawton and H. M. Powell, *J. Chem. Soc.*, 1958, 2339.

3 D. J. Williams and D. Lawton, *Tetrahedron Lett.*, 1975, 111.

4 R. Arad-Yellin, S. Brunie, B. S. Green, M. Knossow, and G. Tsoucaris, *J. Am. Chem. Soc.*, 1979, **101**, 7529; R. Arad-Yellin, B. S. Green, M. Knossow, and G. Tsoucaris, *Tetrahedron Lett.*, 1980, **21**, 387.

5 R. Gerdil and J. Allemand, *Tetrahedron Lett.*, 1979, 3499; *Helv. Chim. Acta*, 1980, **63**, 1750.

6 G. B. Guise, W. D. Ollis, J. A. Peacock, J. S. Stephanatou, and J. F. Stoddart, *Tetrahedron Lett.*, 1980, **21**, 4203; Part 10, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1637.

7 E. Gil, A. Quick, and D. J. Williams, *Tetrahedron Lett.*, 1980, **21**, 4207.

8 W. D. Ollis, J. A. Price, J. S. Stephanatou, and J. F. Stoddart, *Angew. Chem. Int. Ed. Engl.*, 1975, **14**, 169; W. D. Ollis, J. S. Stephanatou, J. F. Stoddart, and A. G. Ferrige, *Angew. Chem. Int. Ed. Engl.*, 1976, **15**, 223.

9 Part 11, A. Hoorfar, W. D. Ollis, J. A. Price, J. S. Stephanatou, and J. F. Stoddart, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1649.

10 S. J. Edge, W. D. Ollis, J. S. Stephanatou, and J. F. Stoddart, D. J. Williams and K. A. Woode, *Tetrahedron Lett.*, 1981, **22**, 2229.

11 P. Ruggli and R. E. Meyer, *Helv. Chim. Acta*, 1922, **5**, 28.

12 R. C. Fuson, *J. Am. Chem. Soc.*, 1926, **48**, 830.

13 W. D. Ollis, J. S. Stephanatou, J. F. Stoddart, A. Quick, D. Rogers, and D. J. Williams, *Angew. Chem. Int. Ed. Engl,*. 1976, **15**, 757.

14 W. D. Ollis, J. S. Stephanatou, J. F. Stoddart, G. Unal, and D. J. Williams, *Tetrahedron Lett.*, 1981, **22**, 2225.

15 Part 3, W. D. Ollis and J. F. Stoddart, *J. Chem. Soc., Perkin Trans. 1*, 1976, 926.

16 Part 6, D. J. Brickwood, W. D. Ollis, J. S. Stephanatou, and J. F. Stoddart, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1398.