Conformational Behaviour of Medium-sized Rings. Part 4.[1] Heterocyclic Analogues of 7,8,13,14-Tetrahydrobenzo[6,7]cyclonona[1,2,3-*de*]naphthalene and 7,8,15,16-Tetrahydrocyclodeca[1,2,3-*de*:6,7,8-*d'e'*]dinaphthalene

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The temperature dependences of the ^{1}H n.m.r. spectra of 8*H*,15*H*-dinaphtho[1,8-*bc* : 1',8'-*gh*][1,5]dioxecin (4) and of heterocyclic analogues (2a, b, e, and f) of 7,8,13,14-tetrahydrobenzo[6,7]cyclonona[1,2,3-*de*]naphthalene have been interpreted in terms of ring inversion between enantiomeric twist-boat conformations. The temperature dependences of the ^{1}H n.m.r. spectra of the dithionins (2c and d) have been interpreted in terms of interconversions between chair and twist-boat conformations. A comparison of activation parameters shows that when *peri*-annelated naphthalene rings replace *ortho*-annelated benzene rings in ' 6,8,6 ' systems (1), chair-like conformations are destabilised relative to boat-like conformations and the energy barriers to ring inversions involving pseudorotational processes are considerably higher.

THE recognition that 5,6,11,12-tetrahydrodibenzo[*a,e*]cyclo-octene (1; W = X = Y = Z = CH_2)[2-5] and many heterocyclic analogues [2,3,6,7] of this ' 6,8,6 ' system (1) exist in diastereoisomeric conformations in solution has encouraged us to examine the nine- and ten-membered ring systems (2)—(4) in which *ortho*-annelated benzene rings of (1) are replaced partially or wholly by *peri*-annelated naphthalene rings. Although the stereochemistry and transannular reactions of the seven- and eight-membered ring systems, exemplified by the 7,12-dihydropleiadenes (5) and by derivatives (6) of 7*H*,14*H*-cyclo-octa[1,2,3-*de*:5,6,7-*d'e'*]dinaphthalene, have attracted [8] attention in recent years, the conformational behaviour of higher-membered ring homologues such as (2)—(4) had not been discussed in the literature prior to publication of our preliminary communication [9] in 1974.

Base-promoted condensations between 1,8-bisbromomethylnaphthalene (7) and 1,2-dihydroxybenzene (8a), 3,4-dihydroxytoluene (8b), benzene-1,2-dithiol (8c), toluene-3,4-dithiol (8d), *NN'*-dimethyl-*o*-phenylenediamine (8e), and *NN'*-ditosyl-*o*-phenylenediamine (8f) afforded compounds (2a–f). Compounds (3) and (4) were obtained by base-promoted condensations of 1,8-dihydroxynaphthalene (9) with *o*-xylylene dibromide (10) and 1,8-bisbromomethylnaphthalene (7), respectively. In the preparation of the dioxecin (4), *C*-alkylation also occurred, affording a spiro-dienone with either structure (11) or (12). Evidence for structure (11) was forthcoming from the ^{1}H n.m.r. spectrum of the diacetate [*i.e.* either (13) or (14)] obtained on (i) borohydride reduction of the spiro-dienone to give a diol followed by (ii) acetylation of the diol. The absence of (i) vicinal coupling between H_a and H_b, and (ii) allylic coupling between H_a and H_c is excellent evidence for assigning structure (13) to the diacetate and hence structure (11) to the spiro-dienone.

In this paper we discuss the results of our studies on

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[2] Part 1, R. Crossley, A. P. Downing, M. Nógrádi, A. Braga de Oliveira, W. D. Ollis, and I. O. Sutherland, *J.C.S. Perkin I*, 1973, 205.
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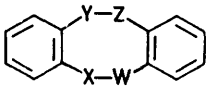
[8] W. C Agosta, *J. Amer. Chem. Soc.*, 1967, **89**, 3505, 3926; C. R. Johnson and D. C. Vegh, *Chem. Comm.*, 1969, 557; P. T. Lansbury, *Accounts Chem. Res.*, 1969, **2**, 210.
[9] D. J. Brickwood, W. D. Ollis, and J. F. Stoddart, *Angew. Chem. Internat. Edn.*, 1974, **13**, 731.

the conformational behaviour of the nine- and ten-membered ring systems (2)—(4) in solution by dynamic ^{1}H n.m.r. spectroscopy.[10]



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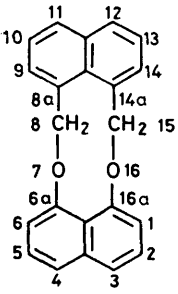

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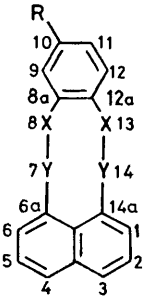
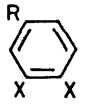
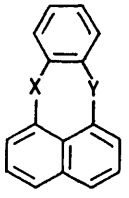


(2) a; R = H, X = O, Y = CH_2
b; R = Me, X = O, Y = CH_2
c; R = H, X = S, Y = CH_2
d; R = Me, X = S, Y = CH_2
e; R = H, X = NMe, Y = CH_2
f; R = H, X = NTs, Y = CH_2

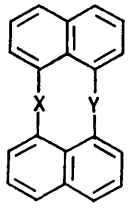
(3) R = H, X = CH_2, Y = O



(8) a; R = H, X = OH
b; R = Me, X = OH
c; R = H, X = SH
d; R = Me, X = SH
e; R = H, X = NHMe
f; R = H, X = NHTs
(10) R = H, X = CH_2Br



(5)



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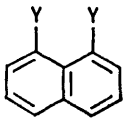


(7) Y = CH_2Br
(9) Y = OH

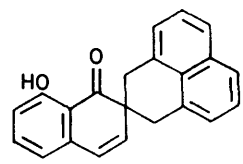
EXPERIMENTAL

The general methods are described in Part 3.[1]

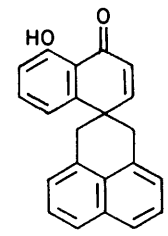
7H,14H-*Benzo*[b]*naphtho*[1,8-fg][1,4]*dioxonin* (2a).—1,8-Bisbromomethylnaphthalene (7) [11] (1.0 g) dissolved in dimethyl sulphoxide (20 ml) was added dropwise under nitrogen to a stirred mixture of 1,2-dihydroxybenzene (8a) (0.35 g) and sodium hydride (0.35 g) in dimethyl sulphoxide (20 ml). The mixture was stirred for 5 h and then poured into water (500 ml). Extraction with chloroform (3 × 100 ml), followed by washing of the combined extracts with water (3 × 100 ml), afforded a crude product after removal of the solvent under diminished pressure. This product was purified by (*a*) preparative t.l.c. on silica gel (chloroform as eluant) and then by (*b*) sublimation at 135° (10 mmHg) to give the dioxonin (2a) (0.1 g, 12%), m.p. 125—127° [Found: *M* (mass spec.), 262.0994. $C_{18}H_{14}O_2$ requires *M*, 262.0994], τ ($CDCl_3$) 2.04—3.12 (10 H, m, aromatic) and 4.59 (4 H, s, 2 × CH_2).

10-*Methyl*-7H,14*H*-*benzo*[b]*naphtho*[1,8-fg][1,4]*dioxonin* (2b).—1,8-Bisbromomethylnaphthalene (7) (5 g) dissolved in dimethyl sulphoxide (60 ml) was added dropwise during 1 h under nitrogen to a stirred mixture of 3,4-dihydroxytoluene (8b) (3 g) and sodium hydride (1 g) in dimethyl sulphoxide (20 ml). The mixture was stirred for 10 h and then poured into water (1 l). Extraction with chloroform (3 × 200 ml), followed by washing of the combined extracts with water (3 × 100 ml), afforded the crude product after removal of the solvent under diminished pressure. This product was subjected to column chromatography on silica gel using chloroform–light petroleum (b.p. 60—80 °C) as eluant to give a crystalline compound. Recrystallisation from chloroform–light petroleum (b.p. 60—80 °C) gave the *dioxonin* (2b) (0.93 g, 21%), m.p. 120—121° [Found: C, 82.5; H, 5.85%; *M* (mass spec.), 276.1144. $C_{19}H_{16}O_2$ requires C, 82.6; H, 5.85%; *M*, 276.1150], τ ($CDCl_3$–CS_2) 2.12—3.36 (9 H, m, aromatic), 4.68 and 4.72 (4 H, 2 × s, 2 × CH_2), and 7.74 (3 H, s, CH_3).

7H,14H-*Benzo*[b]*naphtho*[1,8-fg][1,4]*dithionin* (2c).—1,8-Bisbromomethylnaphthalene (7) (5.0 g) in dimethyl sulphoxide (50 ml) was added dropwise during 1 h under nitrogen to a stirred mixture of benzene-1,2-dithiol (8c) [12] (2.3 g) and sodium hydride (1 g) in dimethyl sulphoxide (50 ml). The mixture was stirred for 16 h and then poured into water (1 l). The organic material was extracted with chloroform (3 × 200 ml) and the extracts were washed with water (3 × 100 ml) and dried ($MgSO_4$). Removal of the solvent under diminished pressure gave an oil which was subjected to column chromatography on silica gel using chloroform–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant to afford the *dithionin* (2c) (0.12 g, 3%), m.p. 195—197 ° [Found: *M* (mass spec.), 294.0935. $C_{18}H_{13}S_2$ requires *M*, 294.0937], τ ($CDCl_3$) 2.44—3.28 (10 H, m, aromatic) and 5.12 (4 H, br s, 2 × CH_2).



(11)



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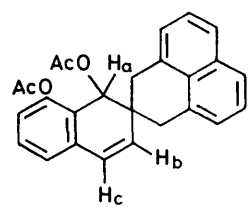

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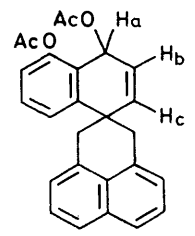


(14)

10-*Methyl*-7H,14H-*benzo*[b]*naphtho*[1,8-fg][1,4]*dithionin*

[10] For reviews see: G. Binsch, *Topics Stereochem.*, 1968, **3**, 97; I. O. Sutherland, *Ann. Reports N.M.R. Spectroscopy*, 1971, **4**, 71.

[11] R. H. Mitchell and F. Sondheimer, *Tetrahedron*, 1968, **24**, 1397.

[12] A. Ferretti, *Org. Synth.*, 1962, **42**, 54.

(2d).—1,8-Bisbromomethylnaphthalene (7) (10 g) in dimethyl sulphoxide (100 ml) was added dropwise during 1 h to a stirred mixture of toluene-3,4-dithiol (8d) (5 g) and sodium hydride (3 g) in dimethyl sulphoxide (40 ml) under a stream of dry nitrogen. The mixture was stirred for 16 h and then poured into water (1.5 l). The organic material was extracted with chloroform (3 × 250 ml) and the extracts were washed with water (3 × 150 ml) and dried ($MgSO_4$). Removal of the solvent under diminished pressure gave an oil which was subjected to column chromatography on silica gel using chloroform–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant to afford a crystalline compound. Recrystallisation from chloroform–light petroleum (b.p. 60—80 °C) gave the *dithionin* (2d) (1.0 g, 10%), m.p. 272—274° (Found: C, 74.2; H, 5.35; S, 20.9%. $C_{19}H_{16}S_2$ requires C, 74.0; H, 5.25; S, 20.8%), τ ($CDCl_3$) 2.38—3.46 (9 H, m, aromatic), 5.08 (4 H, br s, 2 × CH_2), and 8.00 (3 H, s, CH_3).

7,8,13,14-*Tetrahydro*-8,13-*dimethylbenzo*[b]*naphtho*[1,8-fg]-[1,4]*diazonine* (2e).—1,8-Bisbromomethylnaphthalene (7) (2.8 g) in dry tetrahydrofuran (50 ml) was added dropwise during 2 h under a stream of dry nitrogen to a stirred mixture of *NN'*-dimethyl-*o*-phenylenediamine (8e) [13] (1.24 g) and sodium hydride (0.5 g) in dry tetrahydrofuran (50 ml). The mixture was stirred for 16 h and then poured into water (300 ml). The organic material was extracted with chloroform (2 × 200 ml) and the extracts were dried ($MgSO_4$). Removal of the solvent under diminished pressure gave an oil which was purified by preparative t.l.c. on silica gel using chloroform–light petroleum (b.p. 60—80 °C) as eluant to afford the *diazonine* (2e) (80 mg, 3%), m.p. 100—102°, τ ($CDCl_3$) 2.19 and 2.62 (2 H and 4 H, t and d, *J* 5 Hz, naphtho-protons), 3.05 (4 H, s, benzo-protons), 5.46 (4 H, br s, 2 × CH_2), and 7.14 (6 H, s, 2 × CH_3).

7,8,13,14-*Tetrahydro*-8,13-*bis*-p-*tolylsulphonylbenzo*[b]-*naphtho*[1,8-fg][1,4]*diazonine* (2f).—*NN'*-Ditosyl-*o*-phenylenediamine (8f) [14] (1.94 g) was suspended in water (15 ml) and potassium hydroxide (0.56 g) was added. 1,8-Bisbromomethylnaphthalene (7) (1.56 g) in benzene (30 ml) was added with stirring to the aqueous suspension and the mixture was stirred under reflux for 16 h. Benzene was removed under diminished pressure and the suspension was filtered and washed with water. The crude product was recrystallised from chloroform to afford the *diazonine* (2f) (2.34 g, 88%), m.p. >320° (sublimes at 300—302°) (Found: C, 67.3; H, 5.15; N, 4.6; S, 11.5. $C_{32}H_{28}N_2S_2O_4$ requires C, 67.6; H, 4.95; N, 4.9; S, 11.3%), τ ($CDCl_3$) 1.95—2.90 (14 H, m, aromatic naphtho- and tosyl protons), 3.24 (4 H, s, benzo-protons), 4.24 and 5.11 (4 H, two superimposed AB systems, J_{AB} 13.0 Hz, 2 × CH_2), and 7.50 (6 H, s, 2 × CH_3).

8,13-*Dihydrobenzo*[g]*naphtho*[1,8-bc][1,5]*dioxonin* (3).—*o*-Xylylene dibromide (10) (3.14 g) in dimethyl sulphoxide (25 ml) was added dropwise during 0.5 h under a stream of dry nitrogen to a stirred mixture of 1,8-dihydroxynaphthalene (9) (2.0 g) and sodium hydride (1.0 g) in dimethyl sulphoxide (50 ml). The mixture was stirred for 10 h and then it was poured into water (500 ml). The organic material was extracted with chloroform (3 × 100 ml) and the extracts were washed with water (3 × 100 ml) and dried ($MgSO_4$). Removal of the solvent under diminished pressure gave an oil which was subjected to column chromatography on silica gel using chloroform–light petroleum (b.p. 60—80 °C) as eluant to afford the *dioxonin* (3) (0.1 g, 5%), m.p. 125—126°, τ ($CDCl_3$–CS_2) 2.65—3.25 (10 H, m, aromatic) and 5.04 (4 H, s, 2 × CH_2).

8H,15H-*Dinaphtho*[1,8-bc : 1',8'-gh][1,5]*dioxecin* (4).—1,8-Bisbromomethylnaphthalene (7) (5 g) in dimethyl sulphoxide (50 ml) was added dropwise during 1 h under a stream of nitrogen to a stirred mixture of 1,8-dihydroxynaphthalene (9) (2 g) and sodium hydride (0.75 g) in dimethyl sulphoxide (50 ml). The mixture was stirred for 16 h then poured into water (1.5 l). The organic material was extracted with chloroform (3 × 200 ml) and the extracts were washed with water (3 × 100 ml) and dried ($MgSO_4$). Removal of the solvent under diminished pressure gave an oily residue which was subjected to column chromatography on silica gel using chloroform-light petroleum (b.p. 60—80 °C) (1 : 1) as eluant to afford two crystalline constitutionally isomeric products. The isomer eluted second was the *dioxecin* (4) (0.25 g, 5%), m.p. 214—215° (from light petroleum, b.p. 60—80 °C) [Found: C, 84.3; H, 5.25%; *M* (mass spec.), 312.1137. $C_{22}H_{16}O_2$ requires C, 84.6; H, 5.15%; *M*, 312.1150], $\nu_{max.}$ (Nujol) 1260, 1 050, and 825 cm^{-1}, $\lambda_{max.}$ ($CHCl_3$) 198 nm (log ε 4.2), τ ($CDCl_3$–CS_2) 2.04—2.83 (12 H, m, aromatic) and 4.46 (4 H, s, 2 × CH_2). The isomer eluted first was 8-*hydroxyspiro*[*naphthalene*-2(1H),2'(3'H)-1'H-*phenalen*]-1-*one* (11) (0.20 g, 4%), m.p. 178—180 °C)] (from chloroform–light petroleum (b.p. 60—80 °C) [Found: C, 84.8; H, 5.35%; *M* (mass spec.), 312.1137. $C_{22}H_{16}O_2$ requires C, 84.6; H, 5.15%; *M*, 312.1150], $\nu_{max.}$ (Nujol) 1 600, 1 340, and 1 160 cm^{-1}, $\lambda_{max.}$ ($CHCl_3$) 293 (log ε 4.13) and 373 nm (4.01), τ($CDCl_3$) 2.24—3.72 (10 H, m, aromatic and OH), 3.77 and 4.17 (2 H, AB system, J_{AB} 10 Hz, olefinic), and 6.29 and 7.10 (4 H, 2 AB systems, J_{AB} 16 Hz, 2 × CH_2). A portion (20 mg) of this isomer was reduced with sodium borohydride (10 mg) in methanol (5 ml) and tetrahydrofuran (5 ml). After 15 min at room temperature, the mixture was acidified with 5N-hydrochloric acid (0.1 ml) and then diluted with water (20 ml). The organic material was extracted into ether (2 × 20 ml) and dried ($MgSO_4$). Evaporation afforded an oil which was acetylated with acetic anhydride (2 ml) in pyridine (10 ml) to give the *diacetate* (13) (21 mg, 82%), m.p. 184—187° [Found: *M* (mass spec.), 398. $C_{26}H_{22}O_4$ requires *M*, 398], τ ($CDCl_3$) 2.25—3.13 (9 H, m, aromatic), 3.51 and 4.24 (2 H, AB system, J_{AB} 10 Hz, olefinic), 6.01 (1 H, s, >C*H*OAc), 6.52 and 6.64 (2 H, AB system, J_{AB} 16 Hz, CH_2), 6.92 (3 H, s, aromatic OAc), 7.11 and 7.23 (2 H, AB system, J_{AB} 15 Hz, CH_2), and 8.08 (3 H, s, >CHOAc).

Determination of Rates of Conformational Changes by Dynamic ^1H *N.m.r. Spectroscopy*.—The methods used have been described in Parts 1,[2] 2,[15] and 3.[1] The computer programs (coded in Fortran IV) used to generate the theoretical line-shapes are now described for the general methods I—III.

Method I. A program (I) * for exchange of nuclei between two equally populated sites A and B, with no mutual coupling. The aromatic methyl group of compound (2d) gave two singlet signals of unequal intensities at low temperatures and so spectral line shapes were simulated between −33 and −3 °C by using this program. Calculated and observed spectra are shown in Figure 1.

Method II. A program (III) * for exchange of nuclei between the pairs of sites A1 and B1, A2 and B2, A1 and A2, and B1 and B2 in two AB systems. This program was used

* The program numbers (*viz.* I and III) established in Part 3 [1] will be adhered to in this paper; these programs will form the basis of a collection for reference in future Parts of this series.

[13] G. W. H. Cheeseman, *J. Chem. Soc.*, 1955, 3309.
[14] H. Stetter, *Chem. Ber.*, 1953, **86**, 161.
[15] Part 2, R. P. Gellatly, W. D. Ollis, and I. O. Sutherland, *J.C.S. Perkin I*, 1976, 913.

to simulate the ^{1}H n.m.r. spectral line shapes associated with the C-7 and C-14 methylene protons of compound (2c) between −51 and +10 °C. At low temperatures, this compound exhibits (Figure 2 and Table 1) two AB systems (A1B1

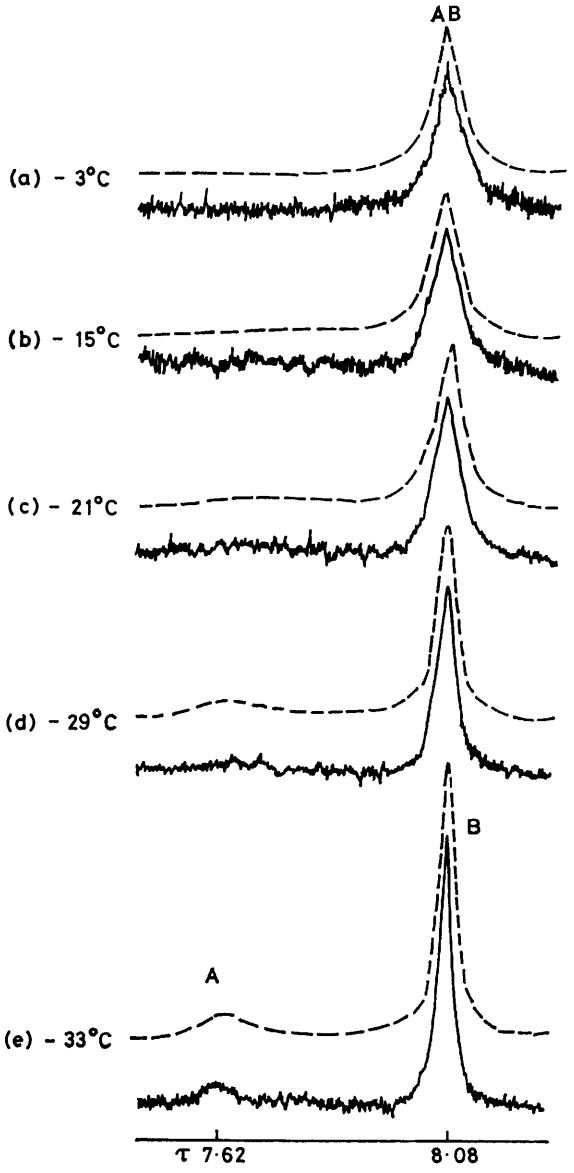


FIGURE 1 Observed (full line) and computed (broken line) spectra of the aromatic methyl protons of 10-methyl-7*H*,14*H*-benzo[*b*]naphtho[1,8-*fg*][1,4]dithionin (2d): (a) at −3 °C, k_{AB} =628 s^{-1}, p_A = 0.20, p_B = 0.80; (b) at −15 °C, k_{AB} = 82 s^{-1}, p_A = 0.20, p_B = 0.80; (c) at −21 °C, k_{AB} = 63 s^{-1}, p_A = 0.20, p_B = 0.80; (d) at −29 °C, k_{AB} = 37 s^{-1}, p_A = 0.20, p_B = 0.80; (e) at −33 °C, k_{AB} = 29 s^{-1}, p_A = 0.20, p_B = 0.80

and A2B2) characteristic of the presence of two diastereoisomeric conformations in solution. Calculated and observed spectra are shown in Figure 2.

Method III. For compounds (2a, e, and f), (3), and (4) site exchange rate constants, k_c, were calculated (see Table 2)

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

at coalescence temperatures, T_c, by using the approximate relationship (i), 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}.

RESULTS AND DISCUSSION

At low temperature, a single AB system is observed in the ^{1}H n.m.r. spectra of compounds (2a, e, and f), (3), and (4) for their ring methylene protons. In all cases, the AB system coalesces to a singlet at higher temperatures. This means (i) that the single AB system must be associated with either *enantiotopic* or *homotopic* ring methylene groups and (ii) that only one conformation is present in solution in the case of all of these compounds. The spectral changes associated with the signals for their ring methylene protons are summarised in Tables 1 and 2. Table 1 gives chemical shifts and coupling constants of the high- and low-temperature spectra. Table 2 records the spectral data which permit calculation by method III (see Experimental section) of the rate constants at the coalescence temperatures and the associated free energies of activation for the ring inversion processes.

The temperature dependent ^{1}H n.m.r. spectra of the compounds (2c and d) demonstrate that two diastereoisomeric conformations are populated in solution. At low temperatures, the ring methylene protons of compound (2c) give rise to two AB systems of unequal intensities which may be assigned to a major and a minor conformation. The signals coalesce to a singlet as the temperature is increased. Three exchange processes were identified by line-shape analyses (Figure 2) and these may be associated with conformational interconversion of the two diastereoisomeric conformations and slow inversion of each of the diastereoisomers with its enantiomer. In the low temperature spectra of compound (2d), two signals of unequal intensities are observed (Figure 1) for the aromatic methyl protons. Their coalescence behaviour permits independent line-shape analysis of the interconversion process involving the two diastereoisomeric conformations. The spectral changes associated with the signals for the ring methylene protons and the aromatic methyl protons are summarised in Tables 1 and 3. Table 1 gives the chemical shifts and coupling constants of the high- and low-temperature spectra. Table 3 gives details of the site exchanges affecting the signal line-shapes and some thermodynamic parameters associated with the conformational changes. These are derived by comparison (see Figures 1 and 2) of observed and calculated spectra over a range of temperatures by methods I and II (see Experimental section). Good agreement is attained for the thermodynamic parameters associated with the interconversion process involving two diastereoisomeric conformations of compounds (2c and d) by using methods I and II on signals arising from two different ^{1}H n.m.r. probes. However, line-shape analysis (Figure 2) was relatively insensitive to the value of the rate constants employed to simulate the exchange process associated with the signals arising from the minor conformation. Accordingly, some uncertainty

surrounds the thermodynamic parameters for this ring inversion.

The observation of isochronous ring methylene groups in compounds (2) and (3) at low temperatures requires that the observable ground state conformation must have either C_s or C_2 symmetry. The chair C (15a) and boat B (16a) conformations both have C_s symmetry whereas the twist-boat TB conformation (17a) has C_2 symmetry. In the case of the C (15a) and B (16a) conformations, it is necessary to consider degenerate C* (15b) and B* (16b) conformations as participants in possible ring inversion processes. With the TB conformation (17a), however, ring inversion would have to involve the enantiomeric TB* conformation (17b). These conformations are conveniently [1-3,15] described by using the usual + and − notation [16] for torsional angles and referring in turn to the bonds 6a–7, 7–8, 8–8a, 12a–13, 13–14, and 14–14a.

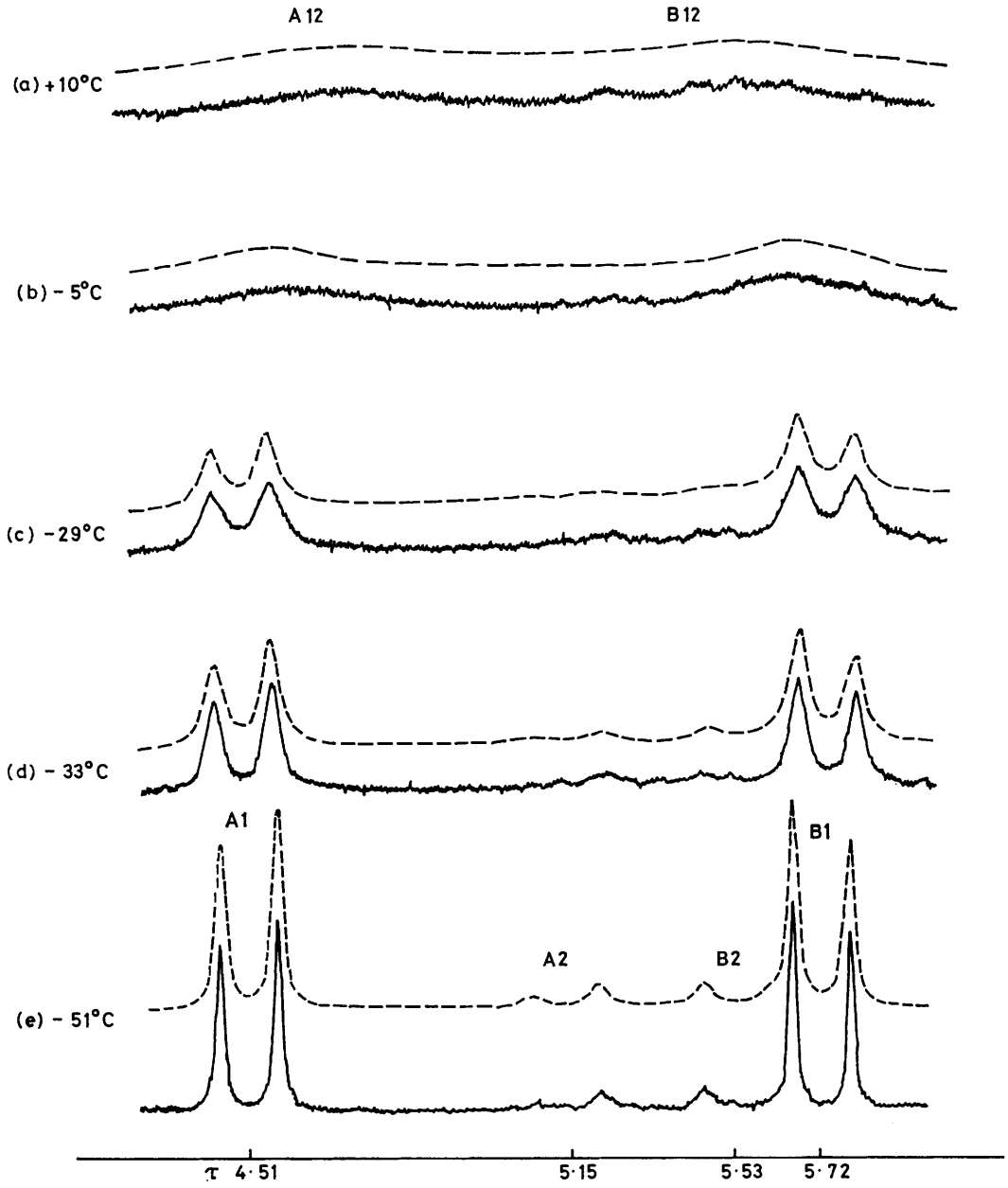


FIGURE 2 Observed (full line) and computed (broken line) spectra of the C-7 and C-14 methyl protons of 7*H*,14*H*-benzo[*b*]naphtho-[1,8-*fg*][1,4]dithionin (2d); (a) at +10 °C, $k_1 = 125\ s^{-1}$, $k_2 = 125\ s^{-1}$, $k_{12} = 250\ s^{-1}$, $p_1 = 0.86$, $p_2 = 0.14$; (b) at −5 °C, $k_1 = 25\ s^{-1}$, $k_2 = 25\ s^{-1}$, $k_{12} = 50\ s^{-1}$, $p_1 = 0.86$, $p_2 = 0.14$; (c) at −29 °C, $k_1 = 2.5\ s^{-1}$, $k_2 = 2.5\ s^{-1}$, $k_{12} = 5.0\ s^{-1}$, $p_1 = 0.86$, $p_2 = 0.14$; (d) at −33 °C, $k_1 = 1.5\ s^{-1}$, $k_2 = 1.5\ s^{-1}$, $k_{12} = 3.0\ s^{-1}$, $p_1 = 0.86$, $p_2 = 0.14$; (e) at −51 °C, $k_1 = 0.05\ s^{-1}$, $k_2 = 0.05\ s^{-1}$, $k_{12} = 0.1\ s^{-1}$, $p_1 = 0.86$, $p_2 = 0.14$

[16] W. Klyne and V. Prelog, *Experientia*, 1960, **16**, 521; J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1961, **83**, 4537; 1962, **84**, 3355; 1964, **86**, 4854; 1967, **89**, 7036, 7043, 7047.

TABLE 1

Temperature-dependent ^1H n.m.r. spectral parameters (100 MHz) for compounds (2a—f), (3), and (4)

Compound	R	X	Y	Solvent	Temp. (°C)	Group	τ (*J* in Hz) [a]
(2a)	H	O	CH_2	$CDCl_3$–CS_2 (1 : 4)	−97	OCH_2	4.56(A1), 4.86(B1) (*J* 11.1)
					−50		4.72(s) (AB1)
(2b)	CH_3	O	CH_2	$CDCl_3$–CS_2 (1 : 2)	−90	OCH_2 [b]	4.52(A1), 4.86(B1) (*J* 12)
							4.58(C1), 4.86(D1) (*J* 12)
						$ArCH_3$	7.74(s)
					+30	OCH_2 [b]	4.68(s) (AB1)
							4.72(s) (CD1)
						$ArCH_3$	7.64(s)
(2c)	H	S	CH_2	$CDCl_3$–CS_2 (2 : 1)	−51	SCH_2	4.51(A1), 5.72(B1) (*J* 12) [c,d]
							5.15(A2), 5.53(B2) (*J* 14) [d]
					−33	SCH_2	4.50(A12), 5.73(B12) (*J* 12)
					+37	SCH_2	5.12(s) (AB12)
(2d)	CH_3	S	CH_2	$CDCl_3$	−45	SCH_2 [b]	4.32(A1), 5.62(B1) (*J* 12) [e]
							5.10(A2), 5.44(B2) (*J* 14) [f]
							4.50(C1), 5.66(D1) (*J* 12) [c,e]
							5.10(C2), 5.47(D2) (*J* 14) [f]
						$ArCH_3$	7.62(s) (A)
							8.08(s) (B) [e]
					+44	SCH_2 [b]	5.08(br s) (ABCD12)
						$ArCH_3$	8.01(s) (AB)
(2e)	H	NMe	CH_2	$CDCl_3$	−20	NCH_2	4.25(A1), 6.64(B1) (*J* 14)
						NCH_3	7.10(s)
					+30	NCH_2	5.46(br s) (AB1)
						NCH_3	7.14(s)
(2f)	H	NTs	CH_2	$CDCl_3$	+30	NCH_2	4.24(A1), 5.10(B1) (*J* 13)
					+70	NCH_2	4.66(br s) (AB1)
(3)	H	CH_2	O	$CDCl_3$–CS_2	−85	OCH_2	4.81(A1), 5.13(B1) (*J* 10.7)
				(1 : 2)	−30	OCH_2	5.02(s) (AB1)
(4)				$CDCl_3$–CS_2	−80	OCH_2	4.26(A1), 4.54(B1) (*J* 10)
				(2 : 1)	−20	OCH_2	4.33(s) (AB1)

[a] The designations A1, B1, *etc.*, correspond to the site exchanges cited in Tables 2 and 3 (see note *a* in Table 2). Sites are designated A and B for uncoupled two-site systems. Sites that represent two time-averaged signals are designated AB. Sites are designated A1 and B1 for coupled AB systems. Sites are designated A1, B1, A2, and B2 for four-site systems where there is coupling in the form of two AB systems. Sites that represent two time-averaged signals are designated AB1 (average of A1 and B1), A12 (average of A1 and A2), *etc.* [b] The C-7 and C-14 methylene groups are constitutionally heterotopic. [c] The signal(s) for the major conformation. [d] The chemical shift differences $\nu_{A1} - \nu_{B1}$ and $\nu_{A2} - \nu_{B2}$ equal 121 and 38 Hz, respectively. [e] The chemical shift assignments to AB systems A1B1 and C1D1 are arbitrary. [f] The chemical shift assignments to AB systems A2B2 and C2D2 are arbitrary.

TABLE 2

Free energies of activation for ring inversion (TB ⇌ TB *) in compounds (2a, e, and f), (3), and (4)

Compound	Solvent	Prochiral group	$(\nu_A - \nu_B)$/Hz [a]	J_{AB}/Hz	T_c/K	k_c [b]/s^{-1}	$\Delta G^{\ddagger}$ (at T_c)/ kcal mol^{-1}
(2a) [c]	$CDCl_3$–CS_2 (1 : 4)	OCH_2	33.0	11.1	194	95	9.5
(2e) [d]	$CDCl_3$	NCH_2	241.0	14.0	303	541	14.0
(2f)	$CDCl_3$	NCH_2	87.0	13.0	330	216	15.9
(3)	$CDCl_3$–CS_2 (1 : 2)	OCH_2	32.0	10.7	199	93	9.7
(4)	$CDCl_3$–CS_2 (2 : 1)	OCH_2	28.0	10.0	212	26	10.4

[a] Details of chemical shifts are given in Table 1 where the AB system is denoted as A1B1. [b] Calculated by method III (see Experimental section). [c] The singlet for the aromatic methyl group in the 10-methyl derivative (2b) remains sharp down to −100 °C, thus indicating the absence of exchange between diastereoisomeric conformations. [d] The singlet for the *N*-methyl group remains sharp down to −50 °C, thus indicating the absence of exchange between diastereoisomeric conformations.

TABLE 3

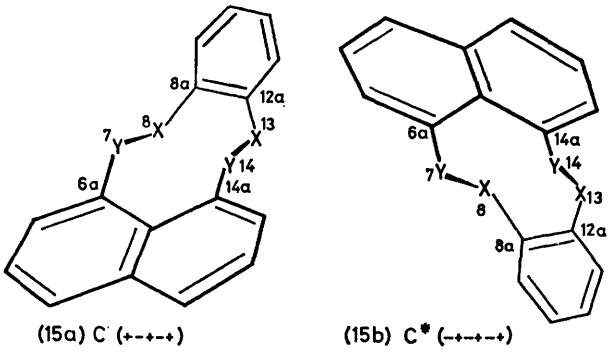
Site exchanges and thermodynamic parameters associated with conformational changes in compounds (2c and d)

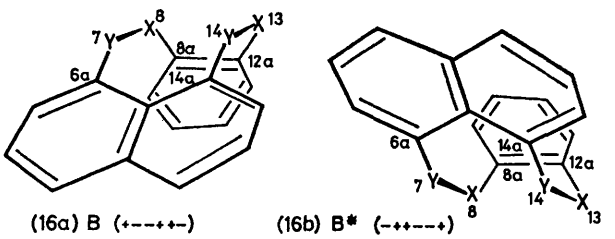
Compound	Solvent	Program	Site exchanges [a]	p_1 or p_A	p_2 or p_B	$\Delta G°$/ kcal mol^{-1} [b]	$\Delta G^{\ddagger}$/ kcal mol^{-1}	Process
(2c)	$CDCl_3$–CS_2 (2 : 1)	III	A1 ⟶ A2	0.86	0.14	0.80 (−51 °C)	13.3	TB ⟶ C
			B1 ⟶ B2					
			A1 ⇌ B1				13.7	TB ⇌ TB *
			A2 ⇌ B2				13.7 [c]	C ⇌ C *
(2d)	$CDCl_3$	I	A ⟶ B	0.20	0.80	0.63 (−45 °C)	12.6	C ⟶ TB
			B ⟶ A				13.2	TB ⟶ C

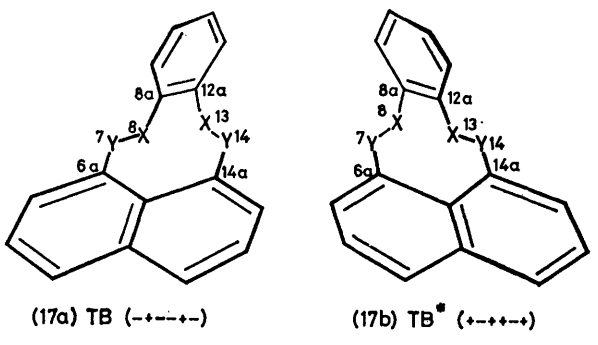
[a] Details of chemical shifts and coupling constants are given in Table 1. In compound (2c), the AB system A1B1 refers to the C-7 and C-14 methylene protons of the twist-boat (major) conformation (17) and the AB system A2B2 refers to the C-7 and C-14 methylene protons of the chair (minor) conformation (15). In compound (2d), the singlet A refers to the aromatic methyl protons of the chair (minor) conformation (15) and the singlet B refers to the aromatic protons of the twist-boat (major) conformation (17). [b] The $\Delta G°$ values are for the process TB ⟶ C. [c] Some uncertainty surrounds this value for C ⇌ C * ring inversion (see text).

Molecular models indicate that the *peri*-interaction between methylene groups of the ring in the chair (15) and boat (16) conformations (2a—f) is particularly large. This transannular steric interaction is relieved partially

in the twist-boat conformation (17) where the principal non-bonded interactions are between the ring methylene groups and the heteroatoms (X = O, S, NMe, or NTs).







We therefore propose that the twist-boat conformation (17) is the ground state conformation and that ring inversion involves a TB ⇌ TB* pseudorotational process (see Figure 3). Four observations support this

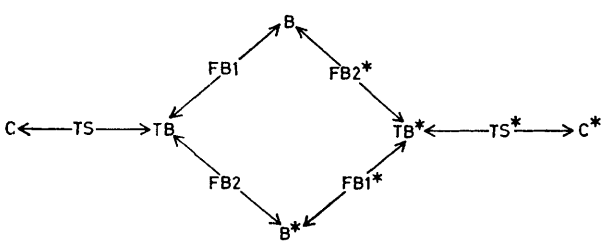
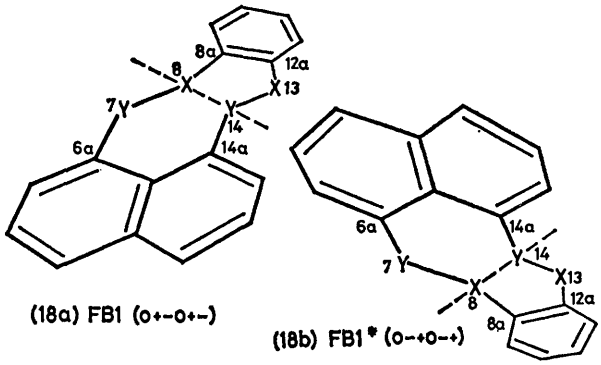
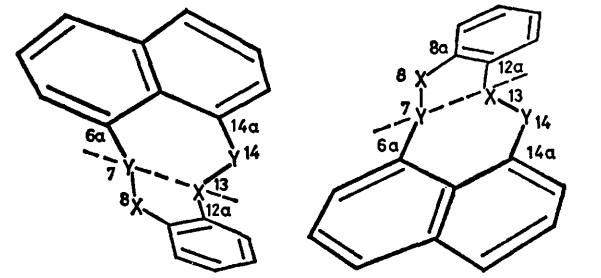
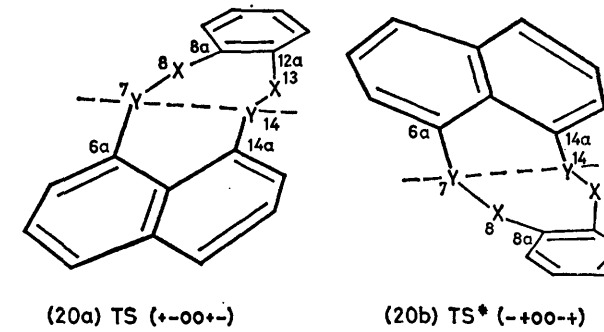


FIGURE 3 Conformational changes in heterocyclic analogues of 7,8,13,14-tetrahydrobenzo[6,7]cyclonona[1,2,3-*de*]naphthalene

proposal. (i) The magnitudes (33 Hz for X = O, 87 Hz for X = NTs, 121 Hz for X = S, and 241 Hz for X = NMe) of the chemical shift of differences [$(\nu_A - \nu_B)$ in Tables 2 and 3] for the ring methylene protons is found to depend significantly upon the nature of the ring heteroatoms. There are a number of examples [8,17] where van der Waals interactions between heteroatoms and proximate protons lead to deshielding of the proton involved. The expectation [18] that the deshielding influence of heteroatoms will be related to their polarisabilities also appears to be fulfilled by the data recorded in Tables 2 and 3, (ii) The fact that the free energies of activation ($\Delta G^{\ddagger}$ 13.7—15.9 kcal mol^{-1}) for TB ⇌ TB* ring inversion in the dithionins (2c and d) and diazonines (2e and f) are larger than those (9.5 kcal mol^{-1}) for the dioxonins (2a and b) is consistent with the pseudorotational process shown in Figure 3 where the FB1 (18a and b) and







FB2 (19a and b) conformations correspond to the transition state conformations. The main component of strain in these folded boat transition states (18) and (19) arises from non-bonded interactions between the ring

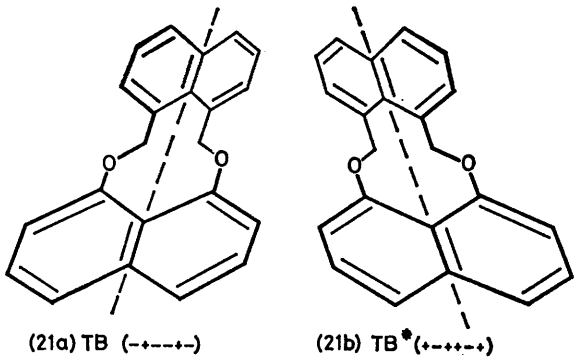
[17] S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Amer. Chem. Soc.*, 1965, **87**, 5239; T. Sato and K. Uno, *J.C.S. Perkin I*, 1973, 895.

[18] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy to Organic Chemistry,' Pergamon, London, 1969, p. 71.

methylene (Y = CH_2) groups and the heteroatoms (X = O, S, NMe, or NTs). (iii) The fact that the free energies of activation ($\Delta G^{\ddagger}$ 9.5—9.7 kcal mol^{-1}) for the dioxonins (2a and b) and (3) are almost identical is compatible with twist-boat (17) ground state conformations and folded boat [(18) and (19)] transition state conformations with very similar energy contents. Molecular models reveal that this is the case whether X = O and Y = CH_2 as in dioxonin (2a) or X = CH_2 and Y = O as in dioxonin (3). (iv) When the heteroatoms are both sulphur (X = S) as in the dithionins (2c and d), then transannular nonbonded interactions with the ring methylene groups (Y = CH_2) destabilise the twist-boat conformation (17) sufficiently to permit the observation of *ca.* 20% of a second conformation at low temperatures. The minor conformation * is presumably the chair conformation (15). Molecular models indicated that the most probable transition state conformation for ring interconversion is the TS conformation (20a and b) with C_s symmetry on the pathway between the chair (15) and boat (16) conformations (see Figure 3). The chair conformation (15) can therefore be regarded as a detectable intermediate in the TB $\rightleftharpoons$ TB* ring inversion of the dithionins (2c and d). In principle, the free energy of activation for TB $\longrightarrow$ C interconversion should be reduced by $RT\ln 2$ relative to that for TB $\rightleftharpoons$ TB* inversion since $k_{TB \rightleftharpoons TB^*} = 0.5\, k_{TB \longrightarrow C}$ if the inversion process involves intermediate chair conformations (15). Qualitatively, this feature is evident (see Table 3) in the dithionins (2c and d) where the only criteria exercised in the determination of $k_{TB \rightleftharpoons TB^*}$ and $k_{TB \longrightarrow C}$ by line-shape analysis using two different ^1H n.m.r. probes were the matches between observed and calculated spectra (see Figures 1 and 2).

It is noteworthy that when a *peri*-annelated naphthalene ring replaces an *ortho*-annelated benzene ring in '6,8,6' systems (1), chair-like conformations are destabilised relative to boat-like conformations. Also, the increase in transannular non-bonded interactions associated with the *peri*-positions of the naphthalene rings leads to much higher barriers to ring inversions involving pseudorotational processes.

At low temperatures, the dioxecin (4) exhibits an AB system for the ring methylene protons in its ^1H n.m.r. spectra. Since chair and boat conformations would both be even more unstable relative to a twist-boat conformation (21) in a ten-membered ring containing two *peri*-interactions, we proposed that the ground state conformation is once again of this type. The notation



for torsional angles in the TB (21a) and TB* (21b) conformations refers in turn to the bonds 6a–7, 7–8, 8–8a, 14a–15, 15–16, and 16–16a. Two observations support the proposal that the observable ground state conformation is a twist-boat conformation (21). (i) The magnitude (28 Hz) of the chemical shift difference [($\nu_A - \nu_B$) in Table 2] for the ring methylene protons is very similar to those of 33 and 32 Hz observed for the dioxonins (2a) and (3). (ii) The value of 10.4 kcal mol^{-1} for the free energy of activation to TB $\rightleftharpoons$ TB* ring inversion is very similar to those of 9.5 and 9.7 kcal mol^{-1} observed for this process in the dioxonins (2a) and (3), and is entirely in accord with a pseudorotational process.

We acknowledge the award of an S.R.C. Research Studentship (to D. J. B.).

[7/1690 *Received*, 26*th September*, 1977]

* We assign as the major conformation the twist-boat conformation (17) because the more intense AB system (A1B1) has a larger chemical shift difference ($\nu_{A1} - \nu_{B1}$) of 121 Hz associated with it [see observation (i)] than has the less intense AB system (A2B2) where the chemical shift difference ($\nu_{A2} - \nu_{B2}$) is only 38 Hz.