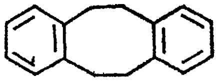
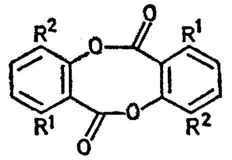
Conformational Behaviour of Di-*o*-thymotide and Di-*o*-carvocrotide

By W. David Ollis* and J. Fraser Stoddart
(*Department of Chemistry, The University, Sheffield* S3 7HF)

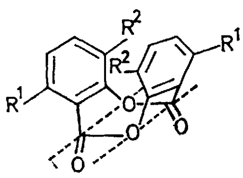
Summary The temperature-dependent ^1H n.m.r. spectra of suitably substituted disalicylides [(**3**) and (**4**)], related lactones [(**8**) and (**9**)], and bislactams [(**10**) and (**11**)], demonstrate their ring inversion ($B \rightleftharpoons B^*$) between enantiomeric boat conformations.

Earlier studies[1–3] have disposed of the alleged existence of isomeric α- and β-disalicylides as conformational diastereomers of the Chair† and Boat† types:[4] the α-disalicylides are dimers whereas the β-compounds are, in fact, trimers. The disalicylides were shown by dipole moment measurements[5] to exist in the Boat† conformation[4] with two *cis*-ester linkages whereas the trisalicylides can adopt[6] propeller and helical conformations, each with three *trans*-ester linkages. The impression has been given[1–4,6] that the resonance demand of two planar ester groups in the *cis*-disalicylides is such that ring inversion would be a relatively slow process compared with the conformational changes which occur[6] in the trisalicylides. Further investigation of this impression was encouraged by the results on 5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclo-octene (**1**). *X*-Ray crystallography has indicated[7] that this hydrocarbon (**1**) adopts the centrosymmetric (C_{2h}) Chair† conformation in the solid state whereas ^1H n.m.r. studies have shown[4] that Chair† and Boat† conformations are approximately equally populated in solution. Examination of the temperature-dependent ^1H n.m.r. spectra of the suitably substituted disalicylides (3) and (4) shows that inversion is detectable.

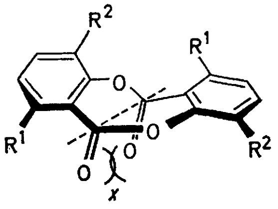

(1)



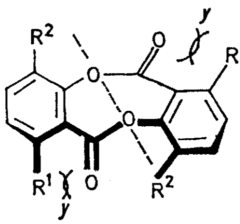
(2) $R^1 = R^2 = H$
(3) $R^1 = Me, R^2 = Pr^i$
(4) $R^1 = Pr^i, R^2 = Me$



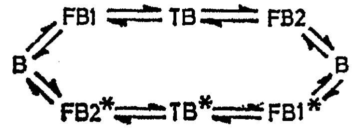
B conformation
(5)



FB1 conformation
(6)

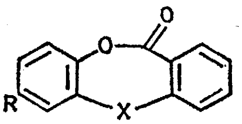


FB2 conformation
(7)

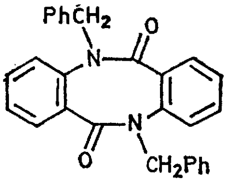


Figure

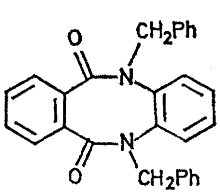
The temperature dependence of the methyl signals for the isopropyl groups (Table) of di-*o*-thymotide[2] (**3**) and di-*o*-carvocrotide[3] (**4**) is ascribed to ring inversions between chiral B conformations[4] (**5**) and their enantiomers (B*). During the conformational itinerary (Figure), involving only torsional changes, the folded boat conformations, FB1 (**6**) and FB2 (**7**), and their enantiomers (FB1* and FB2*) are the most probable transition states for ring inversion ($B \rightleftharpoons B^*$). The stereoelectronic characteristics of the folded boat conformations will be discussed in detail later. They involve three principal factors: (i) steric interactions [*x*, see (**6**); *y*, see (**7**)], (ii) diminished conjugation associated with the non-planar ester groups, and (iii) opposing contributions from *p*–π conjugative interactions of the ester oxygen atoms, and from π–π conjugative interactions of the carbonyl groups, with the aromatic rings. The relative magnitudes of the free energies of activation (Table) for



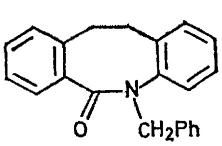
(8) R = H, X = $CH_2{\cdot}CH_2$
(9) R = Me, X = CH_2



(10)



(11)



(12)

---

† The description 'Chair' is non-specific and refers to both of the enantiomeric conformations (C and C*) of the rigid chair type. Similarly, the description 'Boat' refers to any conformation of the flexible boat family. The descriptions B, B*, TB, TB*, FB1, FB1*, FB2, and FB2* used later in the Communication are specific (*cf.* ref. 4).

di-*o*-thymotide [(**3**), $\Delta G^\ddagger$ 17·7 kcal mol^{-1}] and di-*o*-carvocrotide [(**4**) $\Delta G^\ddagger$ 18·4 kcal mol^{-1}] support the view that the FB2 and FB2* conformations are more likely to be the *rate-determining* transition states for B $\rightleftharpoons$ B* inversion. This conclusion is based on the expectation that the steric interaction [*y*, see (**7**)] will be slightly greater when $R^1 = Pr^i$ (**4**) than when $R^1 = Me$ (**3**). It follows that the energy barrier for ring inversion of disalicylide (**2**; $R^1 = H$) will be even lower. It is therefore understandable that attempts to effect its resolution were unsuccessful.[8]

The lactones (**8**)[9] and (**9**)[10] have given results (Table) compatible with relatively low energy B $\rightleftharpoons$ B* inversion processes. In contrast, the isomeric bislactams (**10**) and (**11**) showed no change in their ^1H n.m.r. spectra up to +180° in accordance with the view that the resonance demands of *cis*-amide linkages are considerably greater than those of *cis*-ester linkages.

Free energies of activation ($\Delta G^\ddagger$) *for* B $\rightleftharpoons$ B* *inversion*

Compound	Solvent	Prochiral‡ group	Temp. (°C)	Chemical shifts (τ)[d] J/Hz	$\Delta G^\ddagger$/kcal mol^{-1}
(**3**)	$CDCl_3$	$CHMe_2$	+25 +80	8·84 (A), 8·88 (B), $J_{Me,H}$ 6·9 8·86 (AB), $J_{Me,H}$ 6·9	17·7 ± 0·2[f]
(**4**)	$CDCl_3$	$CHMe_2$	+25 +96	8·74 (A), 8·92 (B), $J_{Me,H}$ 6·9 8·83 (AB), $J_{Me,H}$ 6·9	18·4 ± 0·1[f]
(**8**)	$CDCl_3$–CS_2(1 : 1)	CH_2	−90 +22	6·35 (A), 7·02 (B), *J* 11·5[e] 6·84 (AB)[e]	*ca.* 10[g]
(**9**)	$CDCl_3$–CS_2(3 : 1)	CH_2	−60 +10	5·63 (A), 6·47 (B), *J* 13·8 6·10 (AB)	10·9 ± 0·2[f]
(**10**)[a]	$(CD_3)_2SO$	CH_2	+22 +180	4·77 (A), 5·35 (B), *J* 15·0 4·90 (A), 5·22 (B), *J* 15·0	> 27[g]
(**11**)[b]	$(CD_3)_2SO$	CH_2	+22 +180	5·35 (A), 5·96 (B), *J* 15·0 5·16 (A), 5·71 (B), *J* 15·0	> 27[g]
(**12**)[c]	$C_6D_5NO_2$	CH_2	+63	5·83 (A), 6·32 (B), *J* 14·0[c]	21·4[c,f]

‡ J. F. Stoddart, in 'MTP International Review of Science, Organic Chemistry,' Series One, ed. W. D. Ollis, Butterworths, London 1973, vol. 1, p.1.

[a] M.p. 158—159°. [b] M.p. 208—209°. [c] Ref. 4. [d] With respect to tetramethylsilane as internal standard. Sites are designated A and B for two site systems; sites that represent two time-averaged signals are designated AB. [e] Strictly speaking this is an example of an ABCD system coalescing to an AA′BB′ system. However, the higher temperature spectrum was almost a singlet and the low temperature spectrum was approximately an AB system. Accordingly, it has been treated as an AB system coalescing to a singlet. [f] By line shape methods. [g] At the coalescence temperature by using the approximate equation $k_{coal.} = \pi[(\nu_A - \nu_B)^2 + 6\,J_{AB}{}^2]^{\frac{1}{2}}/2^{\frac{1}{2}}$.

(*Received*, 30*th April* 1973; *Com.* 620.)

[1] W. Baker, W. D. Ollis, and T. S. Zealley, *J. Chem. Soc.*, 1951, 201; W. Baker, B. Gilbert, W. D. Ollis, and T. S. Zealley, *ibid.*, p. 209.

[2] W. Baker, B. Gilbert, and W. D. Ollis, *J. Chem. Soc.*, 1952, 1443.

[3] W. Baker, J. B. Harborne, A. J. Price, and A. Rutt, *J. Chem. Soc.*, 1954, 2042.

[4] 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.

[5] P. G. Edgerley and L. E. Sutton, *J. Chem. Soc.*, 1951, 1069.

[6] A. P. Downing, W. D. Ollis, and I. O. Sutherland, *J. Chem. Soc.* (*B*), 1970, 24.

[7] W. Baker, R. Banks, D. R. Lyon, and F. G. Mann, *J. Chem. Soc.*, 1945, 27.

[8] L. Anschütz and R. Neher, *Ber.*, 1944, **77**, 634.

[9] W. Baker, W. D. Ollis, and T. S. Zealley, *J. Chem. Soc.*, 1952, 1447.

[10] W. Baker, D. E. Clark, W. D. Ollis, and T. S. Zealley, *J. Chem. Soc.*, 1952, 1452.