

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

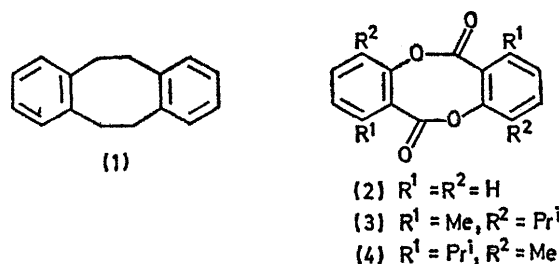
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Summary The temperature-dependent ^1H n.m.r. spectra of suitably substituted disalicylides [(3) and (4)], related lactones [(8) and (9)], and bislactams [(10) and (11)], demonstrate their ring inversion ($B \rightleftharpoons B^*$) between enantiomeric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

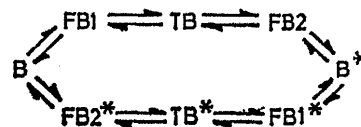
EARLIER studies¹⁻³ have disposed of the alleged existence of isomeric α - and β -disalicylides as conformational diastereomers of the Chair \dagger and Boat \dagger types:⁴ the α -disalicylides are dimers whereas the β -compounds are, in fact, trimers. The disalicylides were shown by dipole moment measurements⁵ to exist in the Boat \dagger conformation⁴ with two *cis*-ester linkages whereas the trisalicylides can adopt⁶ propeller

which occur⁶ 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 indicated⁷ that this hydrocarbon (1) adopts the centrosymmetric (C_{2h}) Chair \dagger conformation in the solid state whereas ^1H n.m.r. studies have shown⁴ that Chair \dagger and Boat \dagger 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.

The temperature dependence of the methyl signals for the isopropyl groups (Table) of di-*o*-thymotide² (3) and di-*o*-carvocrotide³ (4) is ascribed to ring inversions between chiral B conformations⁴ (5) and their enantiomers (B^*). During the conformational itinerary (Figure), involving

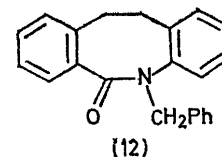
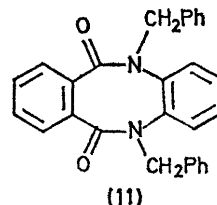
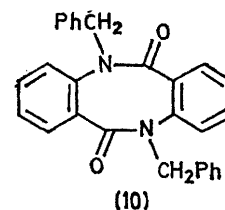
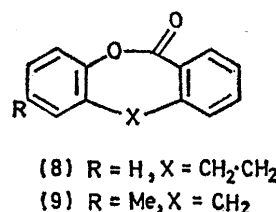
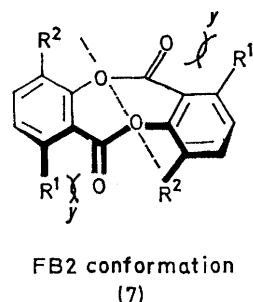
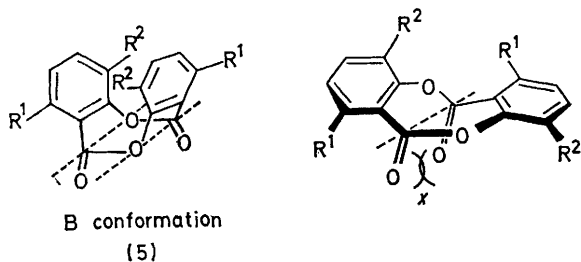


and helical conformations, each with three *trans*-ester linkages. The impression has been given^{1-4,6} that the resonance demand of two planar ester groups in the *cis*-disalicylides is such that ring inversion would be a relatively slow process compared with the conformational changes



FIGURE

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



\dagger 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), ΔG^\ddagger 17.7 kcal mol⁻¹] and di-*o*-carvocro-tide [(4) ΔG^\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

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

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

Compound (3)	Solvent CDCl ₃	Prochiral† group CHMe ₂	Temp. (°C) +25 +80	Chemical shifts (τ) ^d J/Hz 8.84 (A), 8.88 (B), $J_{Me,H}$ 6.9 8.86 (AB), $J_{Me,H}$ 6.9	ΔG^\ddagger /kcal mol ⁻¹ 17.7 ± 0.2'
(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'
(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'
(10) ^a	(CD ₃) ₂ SO	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) ₂ SO	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 ₆ D ₆ NO ₂	CH ₂	+63	5.83 (A), 6.32 (B), J 14.0 ^e	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 $k_{\text{coal.}} = \pi[(\nu_A - \nu_B)^2 + 6 J_{AB}^2]^{1/2}$.

interaction [γ , see (7)] will be slightly greater when R¹ = Pr¹ (4) than when R¹ = Me (3). It follows that the energy barrier for ring inversion of disalicylide (2; R¹ = H) will be even lower. It is therefore understandable that attempts to effect its resolution were unsuccessful.⁸

demands of *cis*-amide linkages are considerably greater than those of *cis*-ester linkages.

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