Conformational Behaviour of Medium-sized Rings. Part 9.[1] Disalicylides and Trisalicylides

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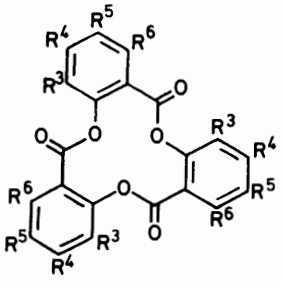
The temperature dependences of the ^{1}H n.m.r. spectra of di-*o*-thymotide (13) and di-*o*-carvacrotide (14) have been interpreted in terms of ring inversion (12a) ⇌ (12b) between enantiomeric boat conformations. Comparison of the $\Delta G^{\ddagger}$ values (17.7 and 18.4 kcal mol^{-1}, respectively) for this conformational change suggests that it takes place by a pseudorotational process involving folded boat conformations (17) in which the substituents (methyl and isopropyl, respectively) on C-3 enter into 1,5-interactions with the carbonyl oxygen atoms in the eight-membered rings at the rate-determining transition states. The temperature dependences of the ^{1}H n.m.r. spectra of tri-*o*-cresotide (6) and tri-*m*-cresotide (7) provide further evidence that a mechanism involving pedalling of *trans*-ester linkages through the mean plane of the twelve-membered ring accounts for the conformational changes between enantiomeric propeller (4) and helical (5) conformations. The $\Delta G^{\ddagger}$ values for interconversion and inversion processes of eight- and twelve-membered ring compounds show an informative dependence upon the steric demands of the *ortho*-substituents on the aromatic rings.

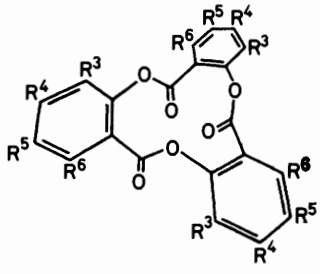
TWELVE years ago we reported[2] a detailed investigation of the conformational properties of tri-*o*-thymotide (1), tri-*o*-carvacrotide (2), and tri-3,6-dimethylsalicylide (3) by dynamic ^{1}H n.m.r. spectroscopy. These cyclic



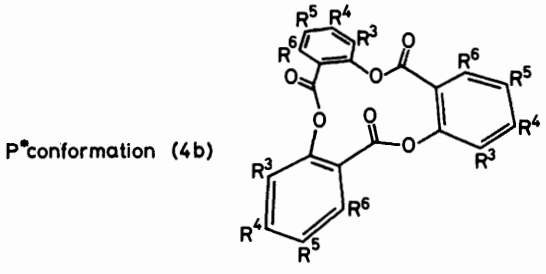
(1) $R^3 = CHMe_2$; $R^4 = R^5 = H$; $R^6 = Me$
(2) $R^3 = Me$; $R^4 = R^5 = H$; $R^6 = CHMe_2$
(3) $R^3 = R^6 = Me$; $R^4 = R^5 = H$

(6) $R^3 = Me$; $R^4 = R^5 = R^6 = H$
(7) $R^3 = R^5 = R^6$; $R^4 = Me$
(8) $R^3 = R^4 = R^5 = R^6 = H$

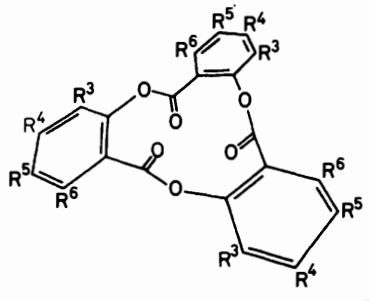
trianhydro-derivatives were all shown to exist in solution as an equilibrium mixture of conformational isomers in which the three ester linkages all assume *trans*-geometries. Two chiral non-planar conformational types were identified as ground-state conformations: (i) the enantiomeric propeller † conformations (4a and b)



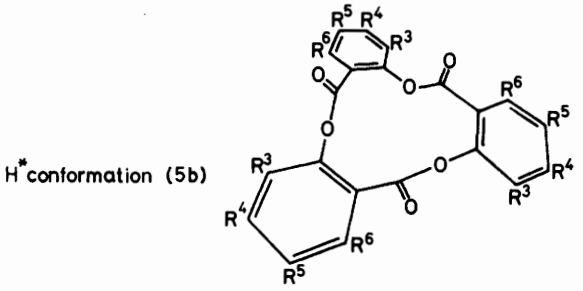
P conformation (4a)



P* conformation (4b)



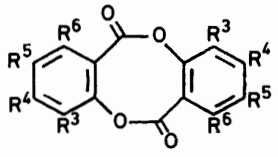
H conformation (5a)



H* conformation (5b)

† Originally, the terms ' propeller ' and ' helix ' were chosen [3] as conformational descriptors of the relative dispositions of the three benzene rings in molecular models of compounds of this type without any particular reference to *molecular* symmetry considerations. In retrospect, this was a fortunate decision! Deviations from C_3 symmetry are quite large in the crystal structure of the propeller conformation of tri-*o*-thymotide [4] (1). This is not surprising because, on statistical grounds (*i.e.* for entropic reasons), a lopsided asymmetrical (C_1) conformation is energetically more favourable. The fact that the low-temperature ^{1}H n.m.r. spectra of tri-*o*-thymotide (1) do not reveal [2,3] this lack of symmetry in solution no doubt reflects the extremely low barriers associated with this averaging process on the time scale of this means of observation.[5] The propeller conformations of tri-*o*-thymotide (1)—and related compounds—should be regarded as examples of homochiral molecules [6] to which the analogy can be drawn with say the right hands belonging to different people where the hands are alike but not identical! Thus, any confusion surrounding the original choice of conformational descriptors that might have arisen from the fact that the propeller conformation which belongs to point group C_3 has helical symmetry becomes academic. By the same token, the helical conformations of tri-*o*-thymotide (1)—and related compounds—with time-averaged C_1 symmetry are undoubtedly also examples of homochiral [6] molecules.

denoted by P and P* in which all three carbonyl oxygen atoms of the *trans*-ester linkages are oriented above and below the two faces of the macrocyclic ring, and (ii) the enantiomeric helical † conformations (5a and b) denoted by H and H* in which the three *trans*-ester linkages are oriented relative to each other such that one carbonyl oxygen atom projects from one face of the twelve-membered ring whereas the other two carbonyl oxygen atoms project from the opposite face. The relative populations in solution of the conformational isomers are summarised in Table 1 for compounds (1)—(3) together with the free energies of activation for the conformational changes associated with the equilibrium: P ⇌ H ⇌ H* ⇌ P*. The results in this Table suggest that the $\Delta G^{\ddagger}$ values for conformational changes in trisalicylide derivatives are highly dependent upon the nature of the substituents in the *ortho*-positions of the aromatic rings, *cf.* the situation [7] for the parent hydrocarbon, 5,6,11,12,17,18-hexahydrotribenzo[*a*,*e*,*i*]cyclododecene and its 1,4,7,10,13,16-hexamethyl derivative. We decided to investigate this structure–energy relationship in more detail by examining the conformational behaviour of tri-*o*-cresotide [8] (6) and tri-*m*-cresotide [8] (7) in solution. The *meta*-isomer (7) can be regarded as a suitable model compound for trisalicylide [9] (8) itself, with a good ^{1}H n.m.r. probe in the form of the aryl methyl groups.



(9) R^3 = Me; R^4 = R^5 = R^6 = H
(10) R^3 = R^5 = R^6 = H; R^4 = Me
(11) R^3 = R^4 = R^5 = R^6 = H
(13) R^3 = $CHMe_2$; R^4 = R^5 = H; R^6 = Me
(14) R^3 = Me; R^4 = R^5 = H; R^6 = $CHMe_2$

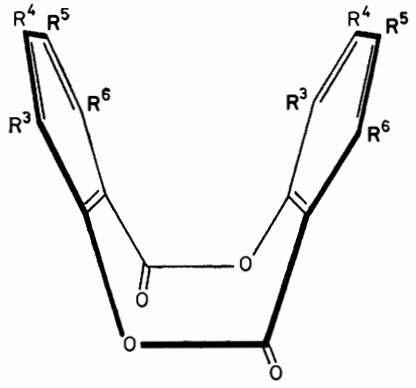
The corresponding cyclic dianhydro-analogues (9)—(11) of compounds (6)—(8) have been shown to exist in benzene solution as boat conformations which we shall denote by the descriptors B (12a) and B* (12b) to distinguish between the enantiomeric pairs. Disalicylide (11) and di-*o*-cresotide [8] (9) have dipole moments of 6.26 and 6.34 D which are close to the calculated [10] range of 6.00—6.20 D for the boat conformation (12). In the case of the di-*m*-cresotide [8] (10), the predicted range of from 6.75 to 6.95 D corresponds [10] closely with the experimentally measured dipole moment of 6.74 D for the boat conformation (12) of this compound. The enantiomeric boat conformations (12a and b) are characterised by two *cis*-ester linkages which might be expected to undergo ester bond rotation during B ⇌ B* ring inversion. The prochirality of the isopropyl substituents in di-*o*-thymotide [11] (13) and di-*o*-carvacrotide [12] (14) provides

TABLE 1

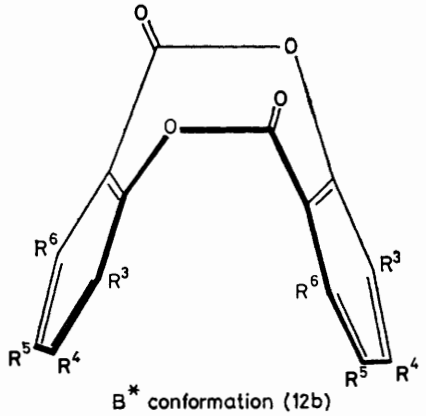
Thermodynamic parameters [a] associated with conformational changes in tri-*o*-thymotide (1), tri-*o*-carvacrotide (2), and tri-3,6-dimethylsalicylide (3)

Compound	Solvent	Propeller (%)	Helix (%)	$\Delta G^{\ddagger}$/kcal mol^{-1}	Process
Tri-*o*-thymotide (1)	Pentachloroethane	86 (68 °C)	14 (68 °C)	21.4 ± 0.9 [b]	P ⟶ H
		80 (90 °C)	20 (90 °C)	20.7 ± 0.9 [b]	H ⟶ P
				21.8 ± 0.9 [b]	P ⇌ P*
Tri-*o*-carvacrotide (2)	Pyridine	64 (20 °C)	36 (20 °C)	20.6 ± 0.2 [b]	P ⟶ H
		58 (90 °C)	42 (90 °C)	20.3 ± 0.2 [b]	H ⟶ P
				17.6 ± 0.2 [b]	H ⇌ H
Tri-3,6-dimethylsalicylide (3)	Deuteriochloroform	67 (−10 °C)	33 (−10 °C)	18.0 ± 0.5 (60 °C) [c]	P ⟶ H
				14.3 ± 0.5 (−10 °C) [c]	H ⇌ H*

[a] Data taken from ref. 2. [b] Determined by ^{1}H n.m.r. line-shape methods. [c] These values are approximate and are based upon the coalescence temperatures only.



B conformation (12a)



B* conformation (12b)

† See footnote on page 1629.

the opportunity to probe this ring-inversion process in these two derivatives by variable-temperature ^{1}H n.m.r. spectroscopy. Our observations on the conformational behaviour of these two compounds in solution have been reported in preliminary form in a communication [13] and in a review.[14]

EXPERIMENTAL

The following compounds were prepared and isolated as described previously: (i) tri-*o*-cresotide [8] (6), m.p. 264—265 °C (lit.,[8] m.p. 264—265 °C), (ii) tri-*m*-cresotide [8] (7), m.p. 206—207 °C (lit.,[8] m.p. 207—207.5 °C), (iii) di-*o*-thymotide [11] (13), m.p. 206—207 °C (lit.,[11] m.p. 207 °C), and (iv) di-*o*-carvacrotide [12] (14), m.p. 176—178 °C (lit.,[12] m.p. 174 °C).

Determination of Rates of Conformational Changes by Dynamic ^{1}H *N.m.r. Spectroscopy.*—The methods used have been described in Part 6.[7] The computer programs (coded in FORTRAN IV) used to generate the theoretical line-shapes are now described for the general methods I and II.

Method I. A program (V) † for exchange of nuclei between four unequally populated sites A, B, C, and D with no mutual coupling. This computer program (MASTER FOUR SITE) has already been discussed by us at some length in our previous publications [2,3] on the conformational behaviour of the trisalicylide derivatives (1)—(3). This program was used to simulate the spectral line shapes of the aryl methyl protons in the temperature-dependent ^{1}H n.m.r. spectra (see Figure 1) of tri-*o*-cresotide (6) recorded in dideuteriodichloromethane–carbon disulphide (4 : 1) solution. At +20 °C, a high intensity singlet was observed for the three aryl methyl groups at τ 7.77. At lower temperatures (*i.e.* in the range −23 °C down to −38 °C), this singlet broadened and, eventually at −38 °C, two singlets of un-

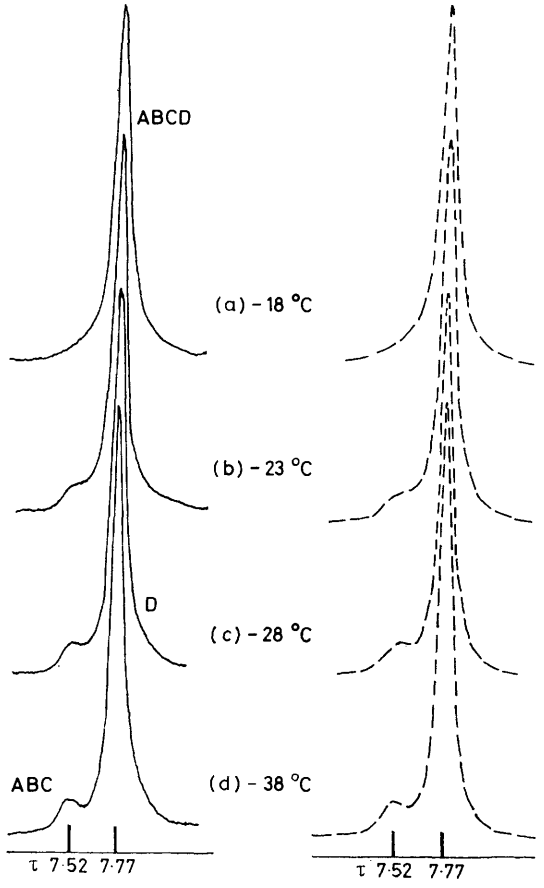


FIGURE 1 Observed (full line) and computed (broken line) spectra of the aryl methyl protons of tri-*o*-cresotide (6) using program V for exchange of protons between three equally populated (time-averaged) sites A, B, and C and a fourth differently populated site D: (a) at −18 °C, k = 22.3 s^{-1}; (b) at −23 °C, k = 11.7 s^{-1}; (c) at −28 °C, k = 6.9 s^{-1}; (d) at −38 °C, k = 2.3 s^{-1}

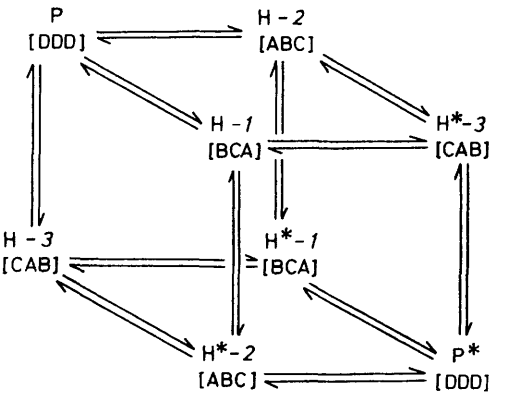


FIGURE 2 Cubic array diagram showing the site exchanges for the aryl methyl groups in the P (4a), P* (4b), H (5a), and H* (5b) conformations (R^3 = Me; R^4 = R^5 = R^6 = H) of tri-*o*-cresotide (6). The sites indicated in square brackets read from left to right corresponding to the aryl methyl groups associated with the aromatic rings *12*, *23*, and *31* in the formulae in Figure 3. The rate constants $k_{P \rightarrow H}$, $k_{H \rightarrow P}$, and $k_{H \rightleftharpoons H^*}$ are related to the rate constants for site exchanges according to equations (1)—(3). The rate constants k_{AB} *etc.* refer to the rate constants for site exchange between sites A and B *etc.* [The aromatic rings are given the descriptors *12*, *23*, and *31* according as to whether they lie between the ester linkages *1* and *2*, *2* and *3*, and *3* and *1*]

equal intensity were observed. The low intensity singlet (ABC) was assigned—on the basis of evidence which materialises below—to the three diastereotopic aryl methyl groups of the enantiomeric helical conformations (5a and b; R^3 = Me; R^4 = R^5 = R^6 = H). The rate of the H ⇌ H* ring-inversion process must be sufficiently rapid at −38 °C on the ^{1}H n.m.r. time scale for the three diastereotopic aryl methyl groups to give a time-averaged signal (ABC). The high intensity singlet (D) was assigned to the three homotopic aryl methyl groups of the enantiomeric propeller conformations (4a and b; R^3 = Me; R^4 = R^5 = R^6 = H). At temperatures above −38 °C the two signals broadened as a result of the increased rate of the P ⇌ H ring interconversion process until eventually at −18 °C only a broad singlet was observed. At temperatures below −38 °C the rate of the H ⇌ H* ring inversion process becomes slower and at −62 °C substantial broadening of the low intensity singlet was observed. This broadening continued down to −92 °C and it appeared that a splitting of the low intensity singlet into three further singlets of equal intensity was occurring. Unfortunately, these changes in the line shapes were obscured by the high inten-

† The program number (*viz.* V) established in Part 6 [7] is adhered to in this paper, and together with the additional program (VII) described here, these programs will form the basis of a collection for reference in future Parts of this series.

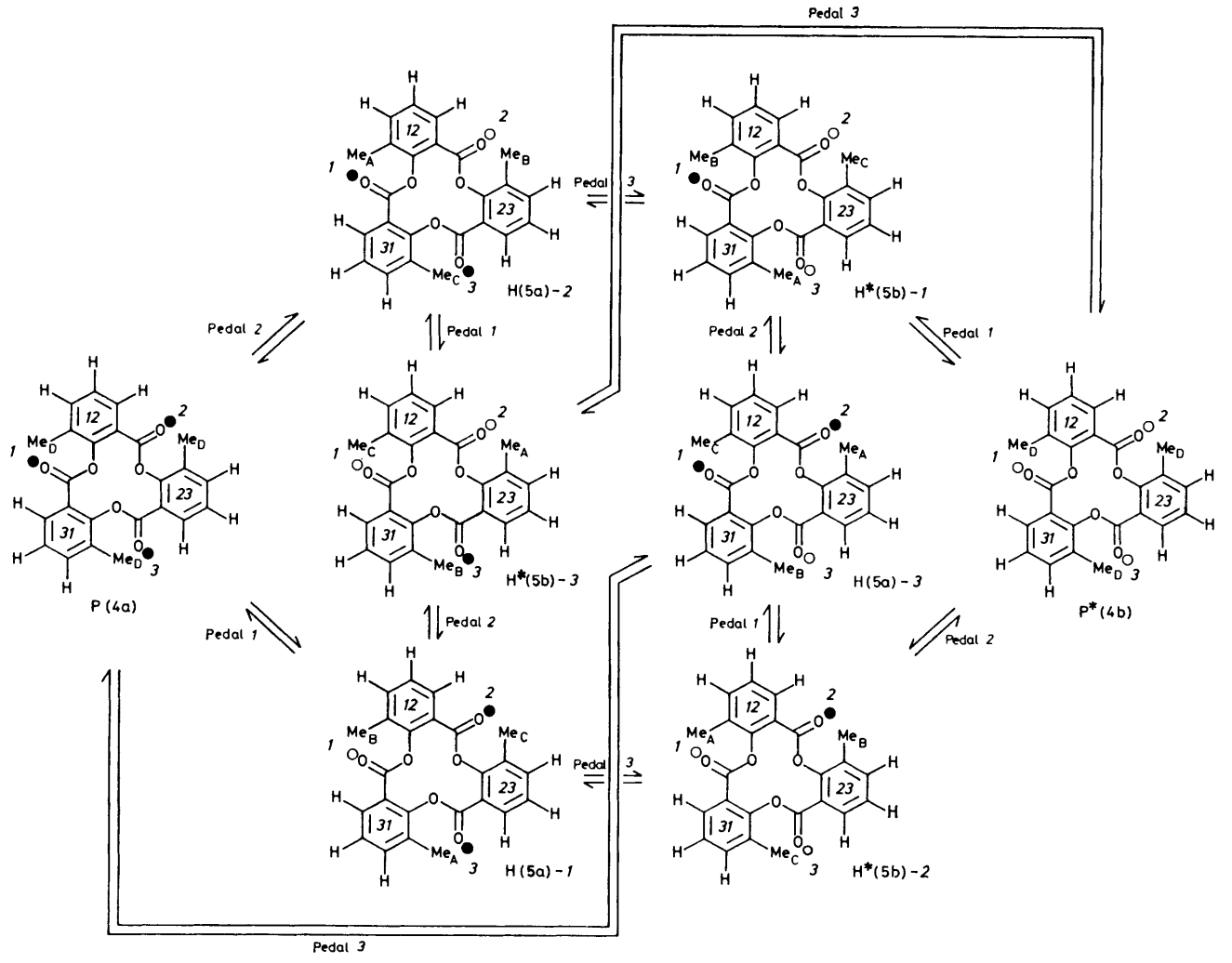


FIGURE 3 Conformational itinerary and site exchange scheme for the aryl methyl groups in the P (4a), P* (4b), H (5a), and H* (5b) conformations (R^3 = Me; R^4 = R^5 = R^6 = H) of tri-*o*-cresotide (6); ● ≡ a carbonyl group above the mean plane of the ring and ○ ≡ a carbonyl group below the mean plane of the ring

sity singlet for the homotopic aryl-methyl groups in the propeller conformations (4a and b). The ring interconversions and inversions,† *i.e.* P ⟶ H, H ⟶ P, and H ⇌ H*, are associated with first-order constants $k_{P \longrightarrow H}$, $k_{H \longrightarrow P}$, and $k_{H \rightleftharpoons H^*}$ (Figure 2) which may be related to the rate constants for the site exchanges of the aryl methyl groups (as a consequence of the conformational changes indicated in Figure 3) according to equations (1)—(3). Good

$$k_{P \longrightarrow H}/3 = k_{DA} = k_{DB} = k_{DC} \quad (1)$$

$$k_{H \longrightarrow P} = k_{AD} = k_{BD} = k_{CD} \quad (2)$$

$$k_{H \rightleftharpoons H^*} = k_{AB} = k_{BA} = k_{AC} = k_{CA} = k_{BC} = k_{CB} \quad (3)$$

matches (see Figure 1) were obtained between the experimental and computed spectra when $k_{AD} = k_{DA} = k_{BD} = k_{DB} = k_{CD} = k_{DC} = k$ were varied whilst $k_{AB} = k_{BA} = k_{AC} = k_{CA} = k_{BC} = k_{CB}$ were set equal to 10 000 s^{-1}.

Method II. A program (VII) ‡ for exchange of nuclei (which are coupled to an independent but common nucleus) between two equally populated sites A/A′ and B/B′ with no mutual coupling.[15] The constitutionally homotopic isopropyl groups of di-*o*-thymotide (13) and di-*o*-carvacrotide (14) both gave two overlapping doublets of equal intensities at low temperatures which coalesced in each case to afford a single doublet at higher temperatures. The prochiral methyl groups within the two isopropyl groups of compounds (13) and (14) are clearly behaving as diastereotopic probes at room temperature on the ^{1}H n.m.r. time scale. Thus, spectral line shapes could be simulated in both cases by using this program. Calculated and observed spectra for the isopropyl methyl groups of compounds (13) and (14) are shown in Figures 4 and 5 respectively.

† We find it convenient to refer to pseudorotational processes (i) connecting enantiomers as *inversions* and (ii) connecting diastereoisomers as *interconversions*.

‡ As † on page 1631.

RESULTS AND DISCUSSION

The temperature-dependent ^{1}H n.m.r. spectra and the conformational properties of di-*o*-thymotide (13) and di-*o*-carvacrotide (14) are presented first, and the discussion of the corresponding results for tri-*o*-cresotide (6) and

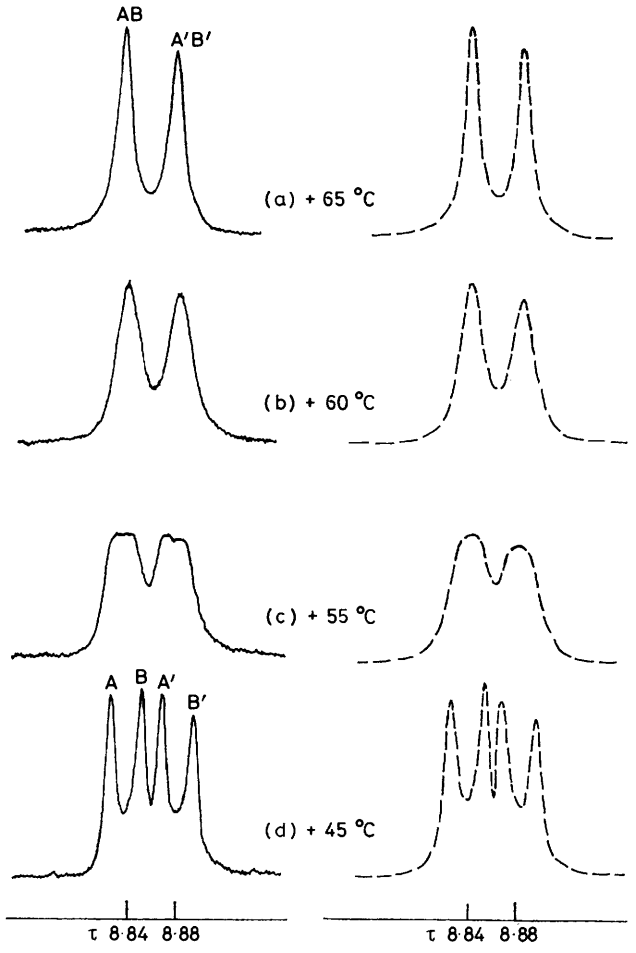


FIGURE 4 Observed (full line) and computed (broken line) spectra of the isopropyl methyl groups of di-*o*-thymotide (13) using program VII for exchange of protons (which are coupled to another common proton) between two equally populated sites A/A′ and B/B′: (a) +65 °C, $k = 34.6\ s^{-1}$; (b) +60 °C, $k = 18.0\ s^{-1}$; (c) +55 °C, $k = 9.3\ s^{-1}$; (d) +45 °C, $k = 2.6\ s^{-1}$.

tri-*m*-cresotide (7) follows. Finally, the present situation governing the conformational behaviour of the trisalicylides in solution is summarised.

The Temperature-dependent ^{1}H *N.m.r. Spectra and the Conformational Properties of Di-o-thymotide* (13) *and Di-o-carvacrotide* (14).—The ^{1}H n.m.r. spectrum † of di-*o*-thymotide (13) in deuteriochloroform exhibits two overlapping doublets (A/A′ and B/B′) centred upon τ 8.84 and 8.88 for the isopropyl methyl groups at ambient temperature. In the range +45 °C to +65 °C, coalescence of these signals occurs to give (see Figure 4) one doublet (AB/A′B′) at higher temperatures. The ^{1}H n.m.r. spectrum ‡ of di-*o*-carvacrotide (14) in deuteriochloroform exhibits two resolved doublets (A/A′ and B/B′) centred upon τ 8.74 and 8.92 for the isopropyl methyl groups at ambient temperature. In the range +60 °C to +86 °C, coalescence of these signals occurs to give (see Figure 5) one doublet (AB/A′B′) at higher temperatures. The designations $Me_{A/A'}$ and $Me_{B/B'}$ of the two pairs of diastereotopic methyl groups in the enantiomeric boat conformations (12a and 12b) where $R^3 = CHMe_{A/A'}Me_{B/B'}$; $R^4 = R^5 = H$; $R^6 = Me$ for

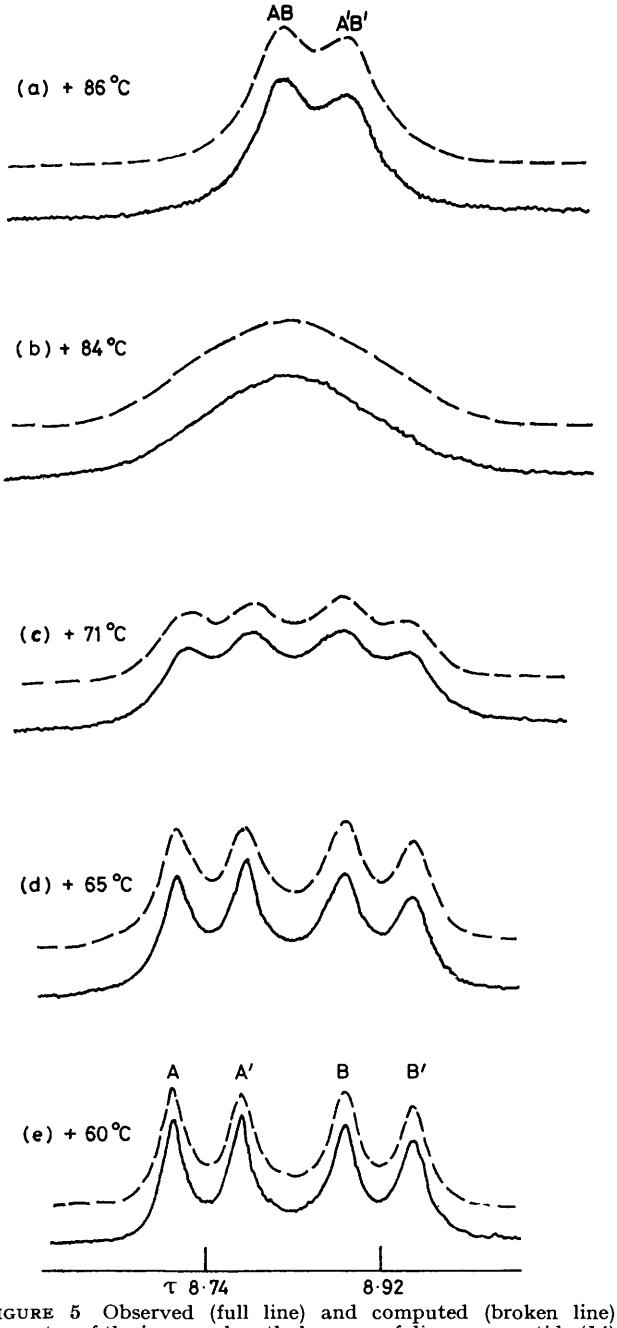


FIGURE 5 Observed (full line) and computed (broken line) spectra of the isopropyl methyl groups of di-*o*-carvacrotide (14) using program VII for exchange of protons (which are coupled to another common proton) between two equally populated sites A/A′ and B/B′: (a) +86 °C, $k = 91.6\ s^{-1}$; (b) +84 °C $k = 30.5\ s^{-1}$; (c) +71 °C, $k = 15.3\ s^{-1}$; (d) +65 °C; $k = 9.5\ s^{-1}$; (e) +60 °C, $k = 6.0\ s^{-1}$

† ^{1}H N.m.r. spectral data for di-*o*-thymotide (13): τ($CDCl_3$) 2.88 and 3.06 (4 H, 2 × AB system, J_{AB} 8.3 Hz, ArH), 6.80 (2 H, m, *J* 6.9 Hz, 2 × C*H*Me$_2$), 7.70 (6 H, s, 2 × Ar*Me*), and 8.84 and 8.88 (2 × 6 H, 2 × d, *J* 6.9 Hz, 2 × CH*Me*$_2$).

‡ ^{1}H N.m.r. spectral data for di-*o*-carvacrotide (14): τ($CDCl_3$) 2.86 and 2.98 (4 H, 2 × AB system, J_{AB} 8.3 Hz, ArH), 7.02 (2 H, *J* 6.9 Hz, 2 × C*H*Me$_2$), 7.76 (6 H, s, 2 × Ar*Me*), and 8.74 and 8.92 (2 × 6 H, 2 × d, *J* 6.9 Hz, 2 × CH*Me*$_2$).

di-*o*-thymotide (13) and where R^3 = Me; R^4 = R^5 = H; R^6 = $CHMe_{A/A'}Me_{B/B'}$ for di-*o*-carvacrotide (14) must, of course, be arbitrary in relation to the relative chemical shifts in Figures 4 and 5, respectively. Line-shape analyses (see Figures 4 and 5) employing method II (see Experimental section) afforded average $\Delta G^{\ddagger}$ values of 17.7 ± 0.2 and 18.4 ± 0.1 kcal mol^{-1} respectively for di-*o*-thymotide (13) and di-*o*-carvacrotide (14).

The temperature dependences of the methyl signals for the isopropyl groups of compounds (13) and (14) can be ascribed to ring inversions between chiral B conformations (12a) and their enantiomers (12b). Despite the fact that disalicylide derivatives must experience restricted torsional freedom around their *cis*-ester linkages as a result of *p*-π conjugative interactions, we believe that the ring-inversion process is a pseudo-rotational one in which the twist boat conformations TB and TB* (15a and b) are relatively high-energy intermediates on the conformational itinerary (see Figure 6)

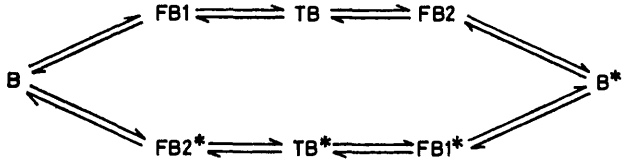
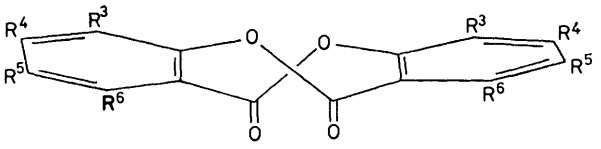
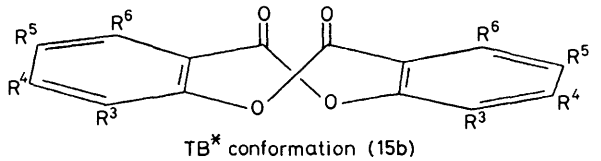


FIGURE 6 The conformational itinerary for B ⇌ B* ring inversion of di-*o*-thymotide (13) and di-*o*-carvacrotide (14)

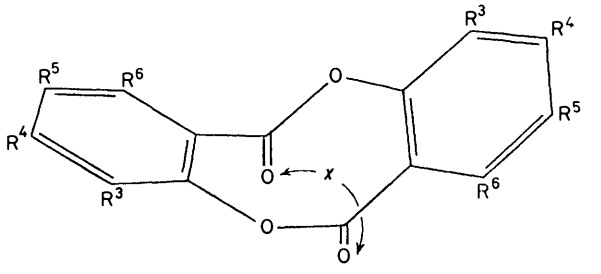
involving the folded boat conformations FB1, FB1*, FB2, and FB2* (16a), (16b), (17a), and (17b) respectively as transition states. In other words, we favour a mechanism for conformational inversion of compounds (13) and (14) which is reminiscent of the itinerary mapped out by the family of Boat conformations of 5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclo-octene [7,16] and its 1,4,7,10- and 2,3,8,9-tetramethyl derivatives [7] in solution. The stereoelectronic characteristics of the folded boat conformations FB1 and FB2, (16) and (17), can be analysed qualitatively in terms of the following principal features. (i) There is a transannular steric interaction (*x*) involving the carbonyl oxygen atoms in the FB1 conformations (16) whilst there are two non-bonded interactions (*y*) of a 1,5-type between a carbonyl oxygen atom and an *ortho*-alkyl substituent on the neighbouring aromatic ring in the FB2 conformations (17). (ii) In both the FB1 and FB2 conformations, (16) and (17), the π-systems associated with the carbonyl groups become orthogonal to the *p*-orbitals on the neighbouring ethereal oxygen atoms with the consequent loss of the electronic stabilisation associated with the *p*–π conjugative interactions of the planar *cis*-ester linkages in the ground-state B conformations (12). (iii) In the FB1 conformations (16), the *p*–π conjugative interactions between the ester oxygen atoms and the aromatic rings become maximised as a result of the parallel alignments of the *p*-orbitals with the π-systems while the π–π conjugative interactions between the carbonyl groups and the aromatic rings become minimised in view of the orthogonal relationships



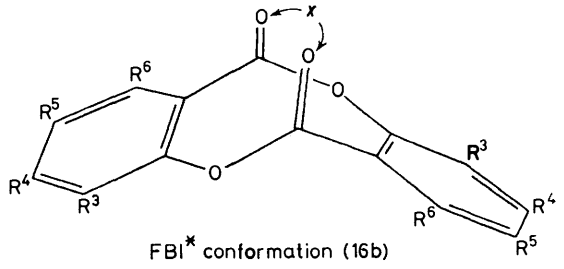
TB conformation (15a)



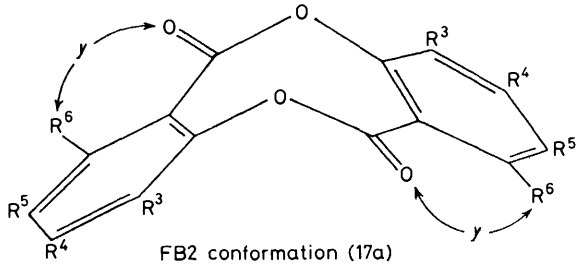
TB* conformation (15b)



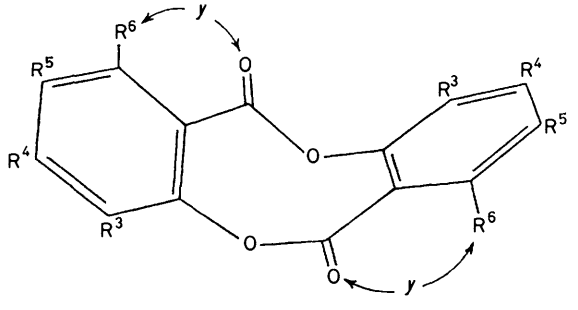
FB1 conformation (16a)



FB1* conformation (16b)



FB2 conformation (17a)



FB2* conformation (17b)

between the two systems. (iv) In the FB2 conformations (17), the π–π conjugative interactions between the carbonyl groups and the aromatic rings become maximised as a result of their parallel alignments while the *p*–π conjugative interactions between the ester oxygen atoms and the aromatic rings become minimised in view of the orthogonal relationships between the *p*-orbitals and the π-systems. In summary, it appears from a consideration of the interplay between (i), (ii), (iii), and (iv) that the FB1 conformations (16) are the more destabilised electronically while the FB2 conformations (17) are the more destabilised sterically. The fact that the free energies of activation for B ⇌ B* ring inversion are higher by 0.7 kcal mol^{-1} for di-*o*-carvacrotide (14) than for di-*o*-thymotide (13) indicates that steric interactions are dominant. This conclusion is based upon the expectation that the 1,5-interactions (*y*) in the FB2 conformations (17) will be larger when R^3 is an isopropyl group than when it is a methyl group. This supports the view that the rate-determining transition states are the FB2 conformations (17). By the same token, it follows that the energy barrier for B ⇌ B* ring inversion in di-*o*-cresotide (9) should be similar to that found for di-*o*-thymotide (13) whereas those in di-*m*-cresotide (10) and disalicylide (11) should be substantially less.

The Temperature-dependent ^{1}H *N.m.r. Spectra and the Conformational Properties of Tri-o-cresotide* (6) *and Tri-m-creosotide* (7).—The temperature-dependent ^{1}H n.m.r. spectra (see Figure 1) for tri-*o*-cresotide (6) have already been interpreted (see Experimental section) in terms of the conformational equilibria: P ⇌ H ⇌ H* ⇌ P*. The rate constants and derived free energies of activation for the H ⟶ P and P ⟶ H interconversion processes at different temperatures are listed in Table 2. These activation parameters were obtained for populations of the propeller (4) and helical (5) conformations of 90 and 10%, respectively, and for an H ⇌ H* ring inversion process with a $\Delta G^{\ddagger}$ value of less than 10 kcal mol^{-1}. At −38 °C, the free-energy difference ($\Delta G°$) between the two conformations was calculated to be 1.0 kcal mol^{-1} from the relationship $\Delta G°_{P \rightarrow H} = -RT \ln [H]/[P]$. The fact that this value is considerably higher than the difference of 0.5 kcal mol^{-1} between the average $\Delta G^{\ddagger}$ values in Table 2 merely reflects the relatively insensitive nature of line-shape analyses on equilibria where the conformational bias is strongly weighted towards one isomer. Nonetheless, the average $\Delta G^{\ddagger}$ values in Table 2 are sufficiently reliable for us to be able to draw a comparison with the corresponding data presented in Table 1 and conclude that the less sterically demanding the size of the substituents in the *ortho*-positions of the aromatic rings, the smaller will be the $\Delta G^{\ddagger}$ values for H ⇌ H* inversion, and P ⟶ H and H ⟶ P interconversions. Further support for this conclusion comes from an investigation of the temperature dependence of the ^{1}H n.m.r. spectrum of tri-*m*-cresotide (7) in deuteriochloroform–carbon disulphide (1 : 1). At ambient temperature, one singlet resonating at τ 7.58 was observed for the aryl methyl groups in addition to a singlet (τ 2.72) and an AB system (τ_A 2.20, τ_B 2.85, J_{AB} 8.0 Hz) for the aromatic protons. At −90 °C, broadening of the aromatic proton singlet resulted in its overlapping and merging with the B portion of the AB system while the aryl methyl signal exhibited an increase in its half-peak

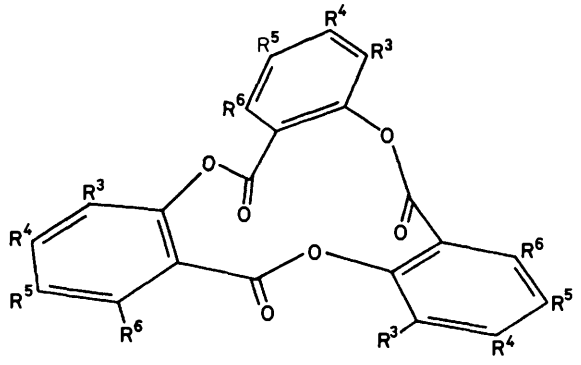
TABLE 2

Rate constants (k s^{-1}) and free energies of activation ($\Delta G^{\ddagger}$ kcal mol^{-1}) for the P ⟶ H and H ⟶ P interconversion process in tri-*o*-cresotide (6) at different temperatures

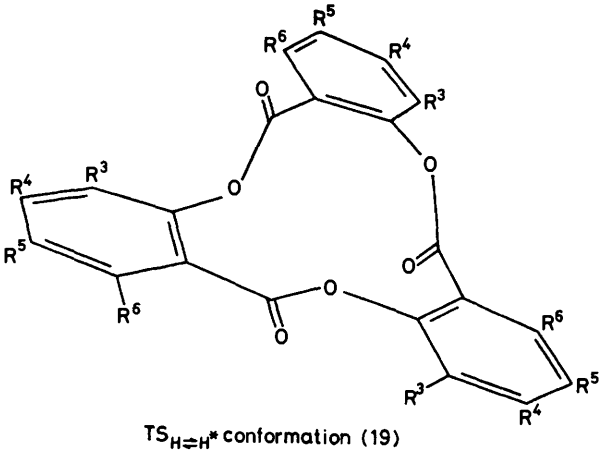
T/°C	$k_{H \rightarrow P}$	$\Delta G^{\ddagger}_{H \rightarrow P}$	$k_{P \rightarrow H}$	$\Delta G^{\ddagger}_{P \rightarrow H}$
−38	2.3 [a]	13.3	0.8	13.8
−32	4.1	13.3	1.4	13.8
−28	6.9 [a]	13.3	2.3	13.8
−23	11.7 [a]	13.4	3.9	13.9
−18	22.3 [a]	13.3	7.4	13.9
−8	63.6	13.2	21.2	13.8
	Average $\Delta G^{\ddagger}$ = 13.3 ± 0.5		Average $\Delta G^{\ddagger}$ = 13.8 ± 0.5	

[a] For line-shape analyses, see Figure 1.

line width without resolving itself into more than one singlet. If these changes in line shapes are attributable to the slowing down of conformational changes in tri-*m*-cresotide (7) on the ^{1}H n.m.r. time scale then we can conclude that the associated $\Delta G^{\ddagger}$ values are less than 8 kcal mol^{-1}. The results for both tri-*o*-cresotide (6) and tri-*m*-cresotide (7) are entirely in accord (*cf.* ref. 2) with a mechanism for the conformational changes involving



$TS_{P \rightleftharpoons H}$ conformation (18)



$TS_{H \rightleftharpoons H^*}$ conformation (19)

pedalling [7] of *trans*-ester linkages through the mean plane of the twelve-membered ring to afford transition states $TS_{P \rightleftharpoons H}$ (18) and $TS_{H \rightleftharpoons H^*}$ (19) for the interconversion and inversion processes, respectively.

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