Tetrahedron Letters Vol. 21, pp 4207 - 4210
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0040-4039/80/1022-4207$02.00/0

X-RAY STRUCTURE DETERMINATIONS OF THE SOLID STATE CONFORMATIONS OF TRI-o-CARVACROTIDE AND OF TRI-3- AND TRI-6-METHYLTHIOSALICYLIDES

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Summary In the solid state, tri-6-methylthiosalicylide (5) adopts only one helical conformation, tri-3-methylthiosalicylide (4) exists as both enantiomeric helical conformations, and tri-o-carvacrotide (2) provides the first example of the unique situation where both enantiomeric propeller conformations and both enantiomeric helical conformations coexist

Variable temperature ^{1}H n m r spectroscopy has shown[3] that in solution the trisalicylide derivatives (1) – (3) undergo ring inversions and interconversions involving enantiomeric and diastereoisomeric conformations of the propeller (P and P*) and helical (H and H*) types according to the scheme outlined in Figure 1. Each conformational change involves the reorientation of a trans-ester linkage

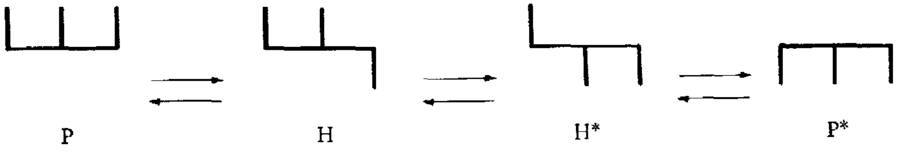
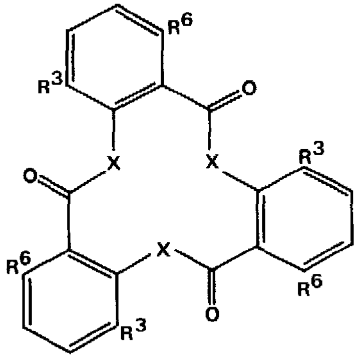


Figure 1 A schematic representation of the ring inversion and interconversion processes. The four diagrams formally depict the relative orientations of the carbonyl groups with respect to the mean plane of the macrocycle in four conformations.

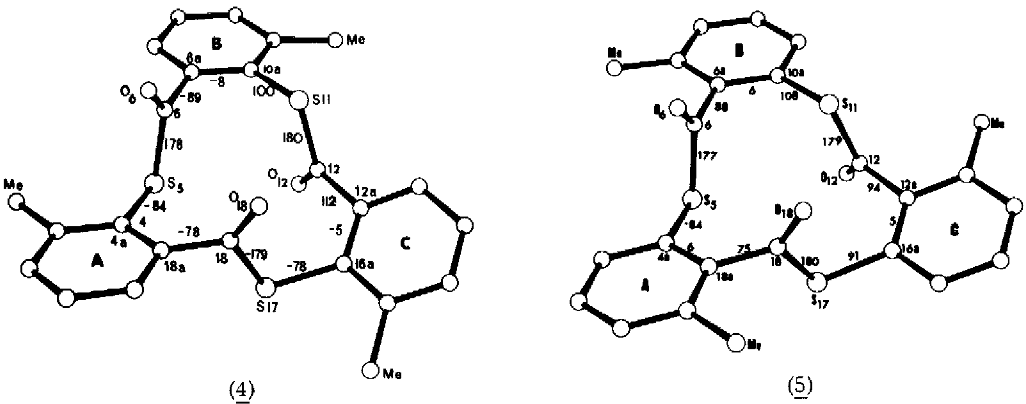


	X	R^3	R^6
1	O	CHMe$_2$	Me
2	O	Me	CHMe$_2$
3	O	Me	Me
4	S	Me	H
5	S	H	Me

accompanied by alterations in the relative inclinations of the planes of the aromatic rings and the ester functions In the three trisalicylides (1) – (3), the propeller conformations with averaged $\underline{C}_3$ symmetry have been shown[3] to predominate in solution. As a consequence of its exceptional inclusion compound forming properties,[4] and the exhibition of spontaneous resolution on crystallisation which can lead to stereospecific entrapment[5] of chiral solvent molecules, tri-*o*-thymotide (1) has been the subject of numerous single-crystal X-ray structure analyses[5,6] These investigations have shown that in the solid state <u>only</u> the propeller conformation has been identified it is unlikely that the helical conformation exists other than in solution In this communication, we draw attention to three examples of closely related compounds where conformations of the helical type have been found to exist in the solid state

Since dynamic ^{1}H n m r spectroscopy had demonstrated[7] that the tri-3- and tri-6-methylthiosalicylides (4) and (5) exist in solution <u>only</u> as ring inverting (H ⇌ H*) helical conformations, it was of considerable interest to establish the nature of their solid state conformations X-Ray structure analyses of (4) and (5) have indeed established that the molecules in both these compounds adopt helical conformation in the solid state However, as shown in Figure 2, the conformations differ[8] significantly from each other Analyses of the inter- and intra-molecular distances lead to the conclusion that the conformational differences are not a result of satisfying any intermolecular nonbonded repulsive interactions, but are a consequence of the different packing requirements in the crystals Although there is no evidence of inclusion compound formation by either compound, tri-6-methylthiosalicylide (5) exhibits spontaneous resolution on crystallisation.

In marked contrast with tri-*o*-thymotide (1), tri-*o*-carvacrotide (2) has not been observed to form <u>any</u> inclusion complexes on crystallisation Variable temperature ^{1}H n m r spectroscopy shows[3] that the population[9] of the helical conformations is proportionately greater for tri-*o*-carvacrotide (2) than for tri-*o*-thymotide (1) For the first time within this series of 12-membered ring compounds, an X-ray



(4)

(5)

Figure 2 The solid state conformations of the trithiosalicylide derivatives (4) and (5) crystal structure analysis has revealed a unique situation where *all four conformational isomers*, P, P*, H, and H*, *coexist in the solid state*. The differences in the torsional angles between the *trans*-ester linkages and the aromatic rings in the propeller and helical conformations are evident from inspection of Figure 3. In particular, it should be noted that there are significant departures from $\underline{C}_3$ symmetry in the solid state in the propeller conformation of tri-*o*-carvacrotide (**2**), just as is found[6] for the propeller conformation of tri-*o*-thymotide (**1**) in the solid state.

A general feature of the conformational behaviour of 12-membered ring compounds such as (**1**) – (**5**) is now emerging: helical conformations are observed[10] more often than propeller conformations in the solid state as well as in solution.

Crystallographic Data. Crystals of tri-3-methylthiosalicylide (**4**) are monoclinic, $\underline{a}$ = 18.772 (1), $\underline{b}$ = 7.465 (1), $\underline{c}$ = 16.303 (1) Å, β = 109.59 (1)°, $\underline{U}$ = 2152 Å^3, space-group $\underline{P}2_1/\underline{c}$, $\underline{Z}$ = 4, $\underline{D}_c$ = 1.39 g cm^{-3}. Crystals of tri-6-methylthiosalicylide (**5**) are orthorhombic, $\underline{a}$ = 8.298 (1), $\underline{b}$ = 15.582 (1), $\underline{c}$ = 16.327 (1) Å, $\underline{U}$ = 2148 Å^3, space-group $\underline{P}2_12_12_1$, $\underline{Z}$ = 4, $\underline{D}_c$ = 1.39 g cm^{-3}. Crystals of tri-*o*-carvacrotide (**2**) are monoclinic, $\underline{a}$ = 14.197 (1), $\underline{b}$ = 31.685 (2), $\underline{c}$ = 13.398 (1) Å, β = 95.06 (1)°, $\underline{U}$ = 6003 Å^3, space-group $\underline{P}2_1/\underline{c}$, $\underline{Z}$ = 8, $\underline{D}_c$ = 1.17 g cm^{-3}. Data for all three compounds were obtained from a diffractometer using Cu–K$_\alpha$ radiation. The numbers of independent reflections measured for (**4**), (**5**), and (**2**) were 4081, 2379, and 8930, respectively. All three structures were solved by direct methods and refined to give $\underline{R}$ values of 0.046, 0.026, and 0.052 for (**4**), (**5**), and (**2**), respectively.

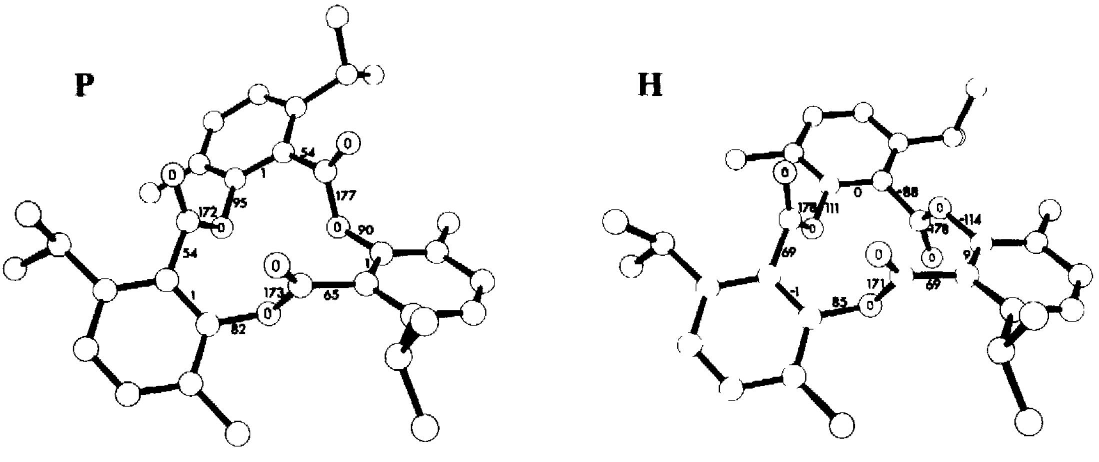


Figure 3. The solid state conformations of tri-*o*-carvacrotide (**2**)

References and Notes

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8. There are differences of 18°, 10°, and 13° respectively in the torsional angles about the C(12)–C(12a), C(12a)–C(16a), and C(16a)–S(17) bonds. These differences are accompanied by changes in the relative tilts of each of the aromatic rings with respect to each other. Compare 6°, 31°, and 30° for (**4**) with 8°, 18°, and 20° for (**5**) These changes result in (**5**) being significantly 'flatter' than (**4**).

9 The molar ratios of propeller helix are[3] (*i*) 80 20 for tri-*o*-thymotide (**1**) in pentachloroethane at 90° and (*ii*) 58 42 for tri-*o*-carvacrotide (**2**) in pyridine at 90°.

10 Helical conformations have been observed in the solid state for 6*H*, 12*H*, 18*H*-tribenzo[*b*, *f*, *j*][1, 5, 9]-trithiacyclododecin (L. Párkányi, A Kálmán, and M. Nógrádi, *Acta Cryst*, 1975, **B31**, 2716) and 5, 11-dibenzyl- and 5, 11-dimethyl-tribenzo[*b*, *f*, *j*][1, 5, 9]triazacyclododecine-6(5*H*), 12(11*H*), 18(17*H*) trione (D. J. Williams, *J Chem. Soc Chem Comm.*, 1977, 170).

(Received in UK 9 June 1980)