The Determination of the Solid-state Conformation and the Absolute Configuration of Tri-o-thymotide

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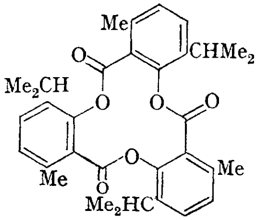
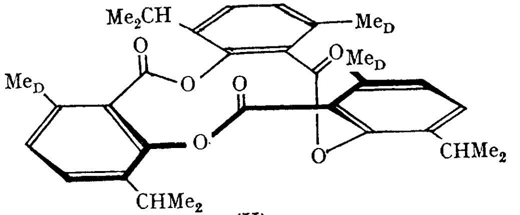
IN an earlier communication[1] we reported evidence for the existence of two different enantiomeric pairs of conformations for tri-*o*-thymotide (I) in solution. This suggestion was based upon the nuclear magnetic resonance (n.m.r.) spectral characteristics of tri-*o*-thymotide which could be interpreted in terms of conformations of the propeller (II) and helical (III) types. However, it was not possible at that time to comment upon the relative proportions of these conformations in solution or upon the relationship between the conformations in solution and the conformation in the solid state of tri-*o*-thymotide. We now report further spectroscopic evidence (A.P.D., W.D.O., and I.O.S.) which establishes the proportions of helical and propeller conformations in solution and which proves that tri-*o*-thymotide in the solid state in both the cavity and the channel clathrates[2] adopts the propeller conformation(II).

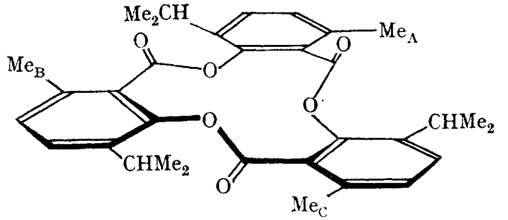


(I)

The experiments now reported are of general interest in that the examination of the n.m.r. spectrum of a *solution* of tri-*o*-thymotide, formed at low temperatures, permits discussion of the conformation adopted by tri-*o*-thymotide ***in the solid state.*** This information then allows the interpretation of the circular dichroism of tri-*o*-thymotide (J.M. and S.F.M.) and the deduction of the absolute configuration of tri-*o*-thymotide.



(II)



(III)

Tri-*o*-thymotide cavity and channel clathrates were prepared by crystallising tri-*o*-thymotide from chloroform and n-hexane, respectively, and their n.m.r. spectra in solution confirmed the presence of the included molecules. The n.m.r. spectra of the clathrates in deuteriochloroform solution, freshly prepared at low temperature, show a singlet signal (τ 7·52) which is assignable to the three aryl-methyl groups (Me_D) of the propeller conformation (II). At −7° this spectrum is time-dependent and a second low-intensity aryl-methyl signal (τ 7·43) slowly appears. This second signal we assign to two of the three aryl-methyl groups (Me_A, Me_B, and Me_C) of the helical conformation (III) and the signal due to the third methyl group (Me_A, Me_B, or Me_C) must lie under the signal due to Me_D of the propeller conformation.[†] These assignments are based upon the temperature-dependence of the low-field signal [see (a) in Figure 1] which is discussed below. The rate of appearance of this second signal[‡] (τ 7·43) agrees well with the rate constant expected from the reported[3] racemisation rates of optically active tri-*o*-thymotide in chloroform solution. The temperature-dependence of the aryl-methyl signals of an equilibrium mixture of the propeller and helical conformations of tri-*o*-thymotide is shown in Figure 1. The shape of the high intensity signal is virtually temperature-independent up to 50°, but above this temperature the rate of propeller to helix interconversion becomes sufficiently fast to affect the signal shape. However, the low-intensity signal is markedly temperature-dependent below 50° and this signal must therefore be assigned to the helical conformation (III) associated with Me_A, Me_B, and Me_C. The initial broadening of the low-field signal is the result of the interconversion of enantiomeric helical conformations and the two sharp signals observed at 50° (τ 7·49 and 7·52) must be assigned to the time-averaged signals from the aryl-methyl groups of the helical conformation (Me_A, Me_B, and Me_C) and to the aryl-methyl groups of the propeller conformation (Me_D) respectively. The relative intensities of the two signals suggest that the low temperature signal at τ 7·43 should be assigned to two of the three helical aryl-methyl groups. The existence of the propeller conformation only in the solutions freshly prepared at low temperatures indicates that this is the only conformation present in both the channel- and the cavity-type clathrates.

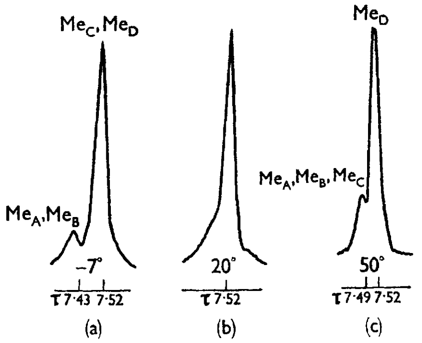


FIGURE 1. *The temperature-dependent aryl-methyl signals of the n.m.r. spectra of tri-*o*-thymotide after its solution in deuteriochloroform and conformational equilibrium is established.*

The circular dichroism and absorption spectra of tri-*o*-thymotide in ether solution at −78° or in a potassium chloride disc at 20° (Figure 2) show that the particular propeller conformation adopted by the (+)-isomer in solution at low temperature or in the solid state has the *M*-configuration[4]

[†] In Figure 1(a) the assignment of Me_A and Me_B to the low-field signal and Me_C to the high-field signal of the spectrum at −7° is arbitrary.

[‡] The details of the kinetics of these conformational changes will be discussed in the full paper.

(minus, or left-handed propeller form) (II). The dipole moment evidence[5] indicates that in the trisalicylides with *ortho*-alkyl substituents, there is little conjugation between the three benzene rings, each carbonyl group being perpendicular, or nearly so, to the plane of the phenoxy-group to which it is bonded. Accordingly, the spectroscopic properties of tri-*o*-thymotide approximate to those of three thymotide chromophores arranged, in the propeller conformation, in a structure with a three-fold axis of symmetry, C_3. In the trimer, a given monomer excitation is triply degenerate in the zero-order, but dipole–dipole interactions between the three excitation moments partially split the degeneracy and give two optically active resultant transitions,[6] one with A and the other with E in symmetry in C_3. For $\pi \rightarrow \pi^*$ transitions of the thymotide monomer, which are necessarily directed in the molecular plane of the chromophore, the resultant A and E transitions of the trimeric isomer with the M-conformation (II) have negative and positive rotational strengths, respectively. The circular dichroism of tri-*o*-thymotide has the expected general form, a positive and a negative dichroism associated with each isotropic absorption band system (Figure 2), and the determination of the relative frequencies of the A and the E components of each band system fixes the particular absolute configuration of the isomer studied. The calculation of the relative frequencies of the A and E components requires in general a knowledge of the directions of the excitation moments in the monomer chromophore. However, the moments of the transitions responsible for the lower- (α) and higher-frequency (*p*) bands of benzene derivatives are found experimentally and theoretically to be mutually perpendicular.[7] This condition, and the observation that the circular dichroism of tri-*o*-thymotide follows the pattern positive and then negative to higher frequencies for both the α- and the *p*-band system (Figure 2), requires that the α- and *p*-transition moments in the thymotide monomer have the relative orientation (IV) within ±10°, and that in tri-*o*-thymotide with the propeller conformation the resultant transition with A symmetry lies at a higher frequency than that with E symmetry for both the α- and the *p*-band systems. In principle the direction of the α-transition moment of the thymotide monomer may be obtained by vector addition of the spectroscopic moments[8] induced by each substituent in the 2600 Å absorption of benzene. However, the values of the spectroscopic moments listed by Platt[8] are not directly applicable in the present case, as the conjugation of the ester group with the benzene rings is sterically hindered in tri-*o*-thymotide, which shows, for example, only one-third of the isotropic absorption intensity of three salicylate chromophores in the quartz ultraviolet region. If Platt's values[8] for the spectroscopic moment of the ester group are reduced to account for the observed reduction in absorption intensity, the calculated direction of the α-transition moment of the thymotide monomer agrees with one of the two possible directions (IV) derived above and supports the assignment of the relative frequencies of the resultant A and E transitions giving a particular band system and the associated circular dichroism in tri-*o*-thymotide. For both the α- and the *p*-band systems of the (+)-isomer of tri-*o*-thymotide, the circular dichroism absorption at lower frequency, due to the E transition, is positive whilst that at higher frequency, deriving

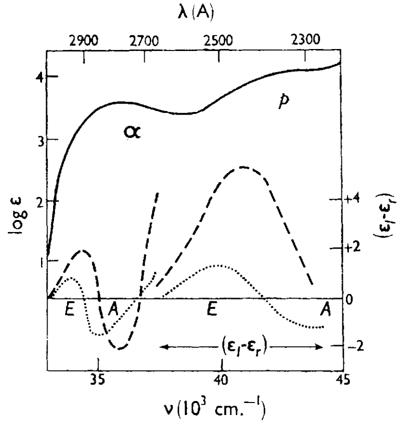
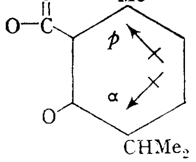


FIGURE 2. *The circular dichroism of a* (+)-*crystal of the tri-*o*-thymotide–ethanol clathrate dissolved in ether at* −78° (— — —) *or dispersed in a potassium chloride disc at* 20° (. . .). *The absorption spectrum of tri-*o*-thymotide in ether solution* (——).



(IV)

from the *A* transition, is negative, and it is concluded that the (+)-isomer has the *M*-propeller configuration (II) in solution at low temperature and in the solid state.

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