The Study of the Ring Inversion of Tri-*o*-thymotide by Nuclear Magnetic Resonance Spectroscopy

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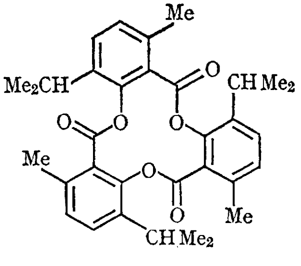
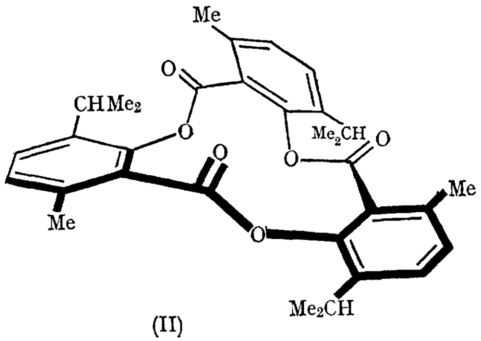
THE spontaneous resolution, and racemisation in solution, of the clathrate complexes of tri-*o*-thymotide[1–4] have been investigated polarimetrically,[2] but the X-ray-crystallographic studies[3] did not establish in detail the conformation of the tri-*o*-thymotide molecules in the solid state. Various suggestions [1–3] have been made regarding the conformation of tri-*o*-thymotide in solution, but the only relevant evidence previously available was its dipole moment (4.13 D in benzene solution)[5] and its racemisation.[2] We now wish to report on the temperature-dependence of the nuclear magnetic resonance (n.m.r.) spectrum of tri-*o*-thymotide in relation to its conformation in solution and its ring inversion.[6]

The n.m.r. spectrum of tri-*o*-thymotide at 60° in pentachloroethane solution shows two doublet signals corresponding to non-equivalent methyl groups of the isopropyl substituents (see I). The n.m.r. spectrum of tri-*o*-thymotide is temperature-dependent (see Figure 1) and above 103° the two doublets (Figure 1a: τ 8·77 and 8·82; $J = 6{\cdot}8$ c./sec.) coalesce to a single doublet (Figure 1b: τ 8·80; $J = 6{\cdot}8$ c./sec.). This coalescence is a result of rapid exchange between different environments of each methyl group of the isopropyl substituents. The examination of line shapes[7] during the coalescence of each pair of corresponding lines of the methyl doublets yields a series of exchange times at different temperatures from which the associated Arrhenius parameters can be approximately calculated as $E_a = 22{\cdot}2$ kcal./mole and $\log_{10}A = 13{\cdot}5$. These values must be regarded as approximate at this stage because the methods which have been used apply only to exchange between equally populated sites and in fact the site populations are slightly different (see Figure 1a). A comparison of observed and computed line shapes is necessary for an exact solution, and this is in progress.[8]

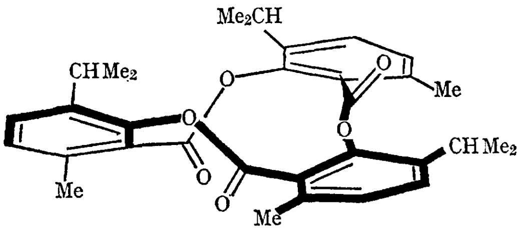


(I)



(II)

Propellor Conformation



(III)

Helical Conformation

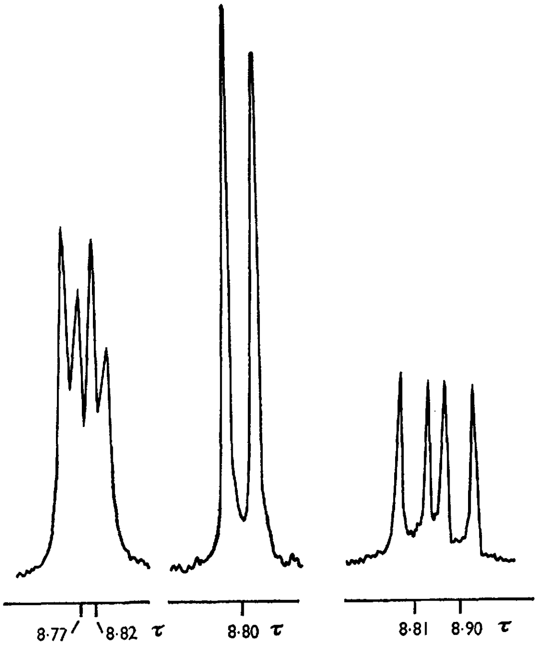
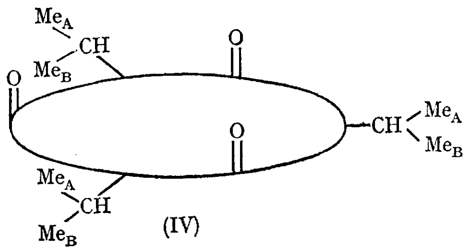
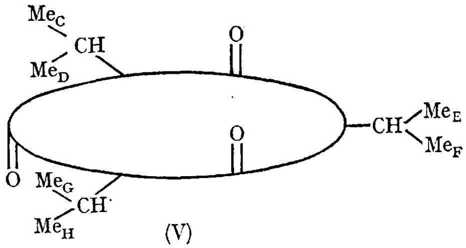


FIGURE 1. *Nuclear magnetic resonance spectra of tri-*o*-thymotide*

(a) *Pentachloroethane solution at* 60°c.
(b) *Pentachloroethane solution at* 140°c.
(c) *Pyridine solution at* 35°c.



(IV)



(V)

At present our results may be considered in terms of two preferred conformations for the tri-*o*-thymotide molecule (I). These have been termed the propellor conformation (II) and the helical conformation (III). Both of these conformations (II and III) are chiral[9] and the racemisation of optically active tri-*o*-thymotide presumably involves the following equilibria:

$$(II) \rightleftharpoons (III) \rightleftharpoons \text{Enantiomer of (III)} \rightleftharpoons \text{Enantiomer of (II)}$$

The Arrhenius parameters ($E_a = 22{\cdot}2$ kcal./mole and $\log_{10}A = 13{\cdot}5$) for the exchange process determined by n.m.r. are similar to those determined* ($E_a = 21{\cdot}2$ kcal./mole, $\log_{10}A = 13{\cdot}3$) for the racemisation of tri-*o*-thymotide by kinetic studies.[2] So far as we are aware, this is possibly the first example of the determination of the

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* The value originally given for the "energy of activation for the racemisation" was 16 kcal./mole and the values given above have been recalculated from the published data. (Ref. 2.)

energy barrier to a conformational change by both the direct observation of racemisation rates and the n.m.r. method.[10] However, it has yet to be established that the exchange process and the racemisation process involve the same conformational changes.

The exact nature of the exchange process detected by the n.m.r. study of tri-*o*-thymotide cannot yet be described in detail and further work is in progress[8] to determine the preferred conformations in solution of tri-*o*-thymotide, the conformational changes which are involved, and the detailed kinetics of these processes. However, our present results clearly exclude consideration of only the propellor conformation (II).

Thus the chiral conformation (II) could give rise only to a pair of isopropyl-methyl doublets of equal intensity;[11] this is not observed (see Figure 1a). If the conformations (II) and (III) are represented diagrammatically by (IV) and (V) respectively, then the line shapes and relative intensities of the isopropyl-methyl n.m.r. signals would be determined by the equilibrium involving the conformations (IV) and (V). This could give rise to a pair of doublets of equal intensity due to Me_A and Me_B and three pairs of doublets of the appropriate intensities due to Me_C, Me_D, Me_E, Me_F, Me_G, and Me_H. Clearly there is an accidental magnetic equivalence of some of these methyl groups which is now being examined, but the observed n.m.r. spectrum of tri-*o*-thymotide requires consideration of an equilibrium involving the helical conformation (V) in addition to the propellor conformation (IV). The n.m.r. study of other macrocyclic systems similar to tri-*o*-thymotide is in progress.[8]

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

[2] A. C. D. Newman and H. M. Powell, *J. Chem. Soc.*, 1952, 3747.

[3] D. Lawton and H. M. Powell, *J. Chem. Soc.*, 1958, 2339.

[4] H. M. Powell, *Nature*, 1952, **170**, 155.

[5] This was kindly determined by Dr. L. E. Sutton and Mr. M. F. Saxby and was quoted in reference 2.

[6] J. E. Anderson, *Quart. Revs*, 1965, **19**, 426.

[7] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance", McGraw-Hill, New York, 1959, ch. 10; H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228.

[8] A. P. Downing, W. D. Ollis, and I. O. Sutherland, forthcoming publication.

[9] R. S. Cahn, *J. Chem. Educ.*, 1964, **41**, 116; R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem. Internat. Edn.*, 1966, **5**, 385.

[10] L. W. Reeves, *Adv. Phys. Org. Chem.*, 1965, **3**, 187.

[11] W. L. Meyer and R. B. Meyer, *J. Amer. Chem. Soc.*, 1963, **85**, 2170; G. M. Whitesides, D. Holtz, and J. D. Roberts, *ibid.*, 1964, **86**, 2628; F. A. L. Anet, A. J. R. Bourn, and Y. S. Lin, *ibid.*, p. 3576.