The Study of the Conformational Behaviour of Tri-o-carvacrotide by Nuclear Magnetic Resonance Spectroscopy

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RECENTLY we examined[1] the temperature dependence of the nuclear magnetic resonance (n.m.r.) spectrum of tri-*o*-thymotide (I) and found that consideration of an equilibrium involving both propeller (II) and helical (III) conformations was required. On the basis of the data then available, it was not possible to make definite assignments of the observed isopropyl methyl n.m.r. signals to each of the eight geometrically non-equivalent methyl sites associated with the propeller and helical conformations. This uncertainty prevented the

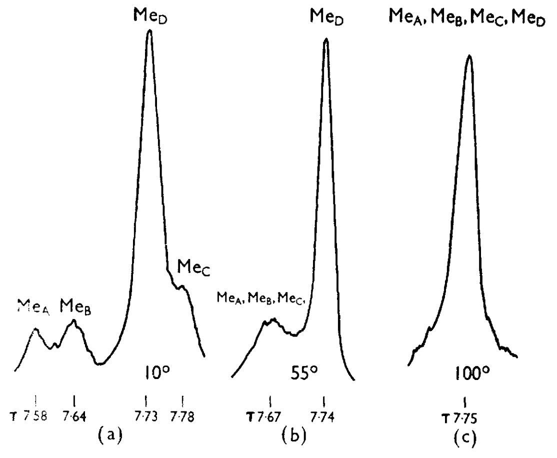
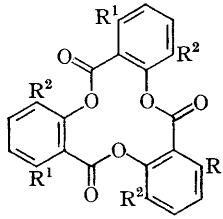
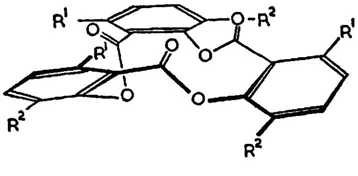


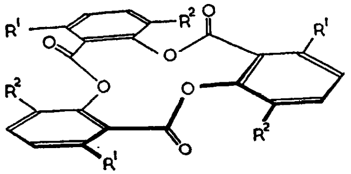
FIGURE. *Nuclear magnetic resonance spectrum due to the aromatic methyl groups of tri-*o*-carvacrotide* (IV). *The spectra were determined in pyridine solution at the indicated temperatures.*



(I) and (IV)



Propeller Conformation
(II) and (V)



Helical Conformation
(III) and (VI)

In formulae (I), (II), and (III), $R^1 = Me, R^2 = CHMe_2$
In formulae (IV), (V), and (VI), $R^1 = CHMe_2, R^2 = Me$

determination of the three rate constants associated with the equilibria [(II) $\leftrightarrows$ (III) $\leftrightarrows$ enantiomer of (III) $\rightleftharpoons$ enantiomer of (II)] for tri-*o*-thymotide (I), but considerable progress has now been made in the analysis of this complex situation and will be reported shortly.[2]

Meanwhile a similar study of tri-*o*-carvacrotide (IV)[3] has been made and the non-equivalence of its aromatic methyl groups observable at low temperatures (see the Figure) permits unambiguous signal assignments and the determination of activation parameters for each of the conformational changes (propeller → helix, helix → propeller, and helix → enantiomeric helix).

The n.m.r. spectrum of tri-*o*-carvacrotide (IV) in pyridine solution at 10° shows [Figure (a)] three low intensity singlet signals (τ 7·58, 7·64, and 7·78) which may be assigned to the three non-equivalent aromatic methyl substituents (Me_A, Me_B, and Me_C) of the helical conformation (VI), and a high intensity singlet signal (τ 7·73) assignable to the three equivalent aromatic methyl substituents (Me_D) of the three-fold axially symmetrical propeller conformation (V). As the temperature is raised, the three low intensity singlets due to Me_A, Me_B, and Me_C form a broad singlet (τ 7·67) at 55° [Figure (b)]. This partial coalescence is due to the increased rate of the exchange process, helix (VI) $\rightleftharpoons$ enantiomeric helix. At higher temperatures the rate of the exchange process, helix (VI) $\rightleftharpoons$ propeller (V), becomes sufficiently fast to cause complete coalescence to a broad singlet which becomes sharp as the temperature is raised [Figure (c)].

The rate constants (k_1, k_2, and k_3) for the conformational equilibria:

$$\begin{tikzcd}
\begin{array}{c}\text{Propeller (V)}\\ {[3 \times \text{Me}_\text{D}]}\end{array} \arrow[r, shift right, "k_1"'] & \begin{array}{c}\text{Helix (VI)}\\ {[\text{Me}_\text{A}, \text{Me}_\text{B}, \text{Me}_\text{C}]}\end{array} \arrow[l, shift right, "k_2"'] \arrow[d, shift left, "k_3"] \\
\begin{array}{c}\text{Enantiomer of propeller (V)}\\ {[3 \times \text{Me}_\text{D}]}\end{array} \arrow[r, shift right, "k_1"'] & \begin{array}{c}\text{Enantiomer of helix (VI)}\\ {[\text{Me}_\text{A}, \text{Me}_\text{B}, \text{Me}_\text{C}]}\end{array} \arrow[l, shift right, "k_2"'] \arrow[u, shift left, "k_3"]
\end{tikzcd}$$

are related to the following rate constants for methyl-site exchange:

[$\text{Me}_\text{D} \rightarrow \text{Mr}_\text{A}$, $\text{Me}_\text{D} \rightarrow \text{Me}_\text{B}$, $\text{Me}_\text{D} \rightarrow \text{Me}_\text{C}$. Rate constant $= k_1/3$]

[$\text{Me}_\text{A} \rightarrow \text{Me}_\text{D}$, $\text{Me}_\text{B} \rightarrow \text{Me}_\text{D}$, $\text{Me}_\text{C} \rightarrow \text{Me}_\text{D}$. Rate constant $= k_2$]

[$\text{Me}_\text{A} \rightarrow \text{Me}_\text{B}$, $\text{Me}_\text{A} \rightarrow \text{Me}_\text{C}$, $\text{Me}_\text{B} \rightarrow \text{Me}_\text{A}$, $\text{Me}_\text{B} \rightarrow \text{Me}_\text{C}$, $\text{Me}_\text{C} \rightarrow \text{Me}_\text{A}$, $\text{Me}_\text{C} \rightarrow \text{Me}_\text{B}$. Rate constant $= k_3$].

It therefore followed that the rates and activation parameters for the conformational changes of tri-*o*-carvacrotide (IV) could be obtained from a study of the temperature dependence of the n.m.r. characteristics of its aryl-methyl groups.

The modified form of the Bloch equations introduced by McConnell[4] was used to calculate line shapes for the aromatic methyl signals using various values of k_1, k_2, and k_3. Comparison of calculated* and observed line shapes obtained at

TABLE

*Activation parameters for the conformational changes of tri-*o*-carvacrotide* (IV) *in pyridine solution*

Process	E_a[a] (kcal./mole)	$\log_{10}A$[a,b]	$\Delta G_0\ddagger$[a] (kcal./mole)
Propeller → Helix	22·8 ± 1·5	14·5 ± 1·0	20·6 ± 0·2
Helix → Propeller	22·8 ± 1·5	14·7 ± 1·0	20·3 ± 0·2
Helix → Enantiomeric helix	21·4 ± 1·3	15·9 ± 1·0	17·6 ± 0·2

[a] The errors quoted refer to 90% confidence limits.
[b] Rate constants and A values are based upon sec.$^{-1}$ units.

* A Mercury Autocode programme based directly on the McConnell equations was used for the computation of line shapes. Details on the methods used to obtain input parameter values will be given in our full Paper.

various temperatures enabled values for k_1 and k_2 (from 62·5° to 76°) and k_3 (from 20·5° to 42·5°) to be determined, thus leading to the Arrhenius parameters given in the Table.

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[3] W. Baker, J. B. Harborne, A. J. Price, and A. Rutt, *J. Chem. Soc.*, 1954, 2042.

[4] H. M. McConnell, *J. Chem. Phys.*, 1958, **28**, 430; J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance", McGraw-Hill, New York, 1959.