

THE DETERMINATION OF THE ABSOLUTE CONFIGURATION OF TRI-O-THYMOTIDE
BY CRYSTAL STRUCTURE ANALYSIS AND OPTICAL ROTATION.

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The absolute configuration of tri-o-thymotide was obtained from the crystal structure of the solvate with (R)-2-butanol in association with optical measurements.

The large number of solvates formed by tri-o-thymotide (TOT) and its attractive geometry has encouraged many structural investigations. Recent crystallographic work¹ has confirmed that TOT exists in chiral conformations of "propeller" type in the crystalline phase. NMR spectroscopy has demonstrated the occurrence of an equilibrium between the latter type and conformations of "helical" type². Ollis et al³ had previously deduced that the chiroptical properties of the (+)-isomer of TOT in the solid state were consistent with the M-configuration⁴ (left-handed propeller form). Recent crystallographic results obtained in our Laboratory contradict this configuration assignment and therefore prompt the present communication.

An absolute conformation of TOT could be obtained from the crystal structure of the solvate with 2-butanol whose absolute configuration is known. The solvate is of the cavity type and all the TOT molecules in a single crystal adopt the same chiral configuration. The Friedel law prevents any distinction between associations such as (\pm)-TOT/(R)-2-butanol and (\mp)-TOT/(S)-2-butanol. If however TOT is recrystallised from an optically pure solvent the knowledge

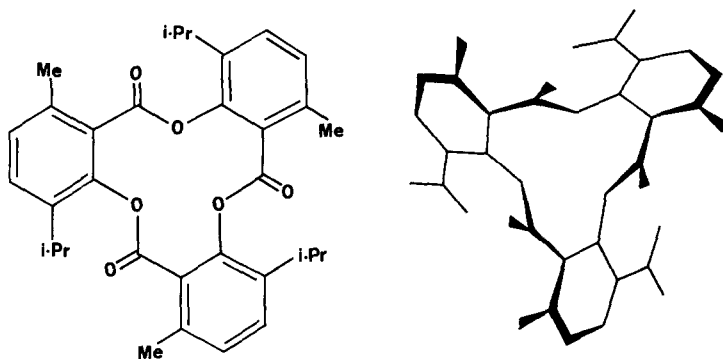


Fig. 1. Idealized view of the M-configuration of (-)-tri-o-thymotide.

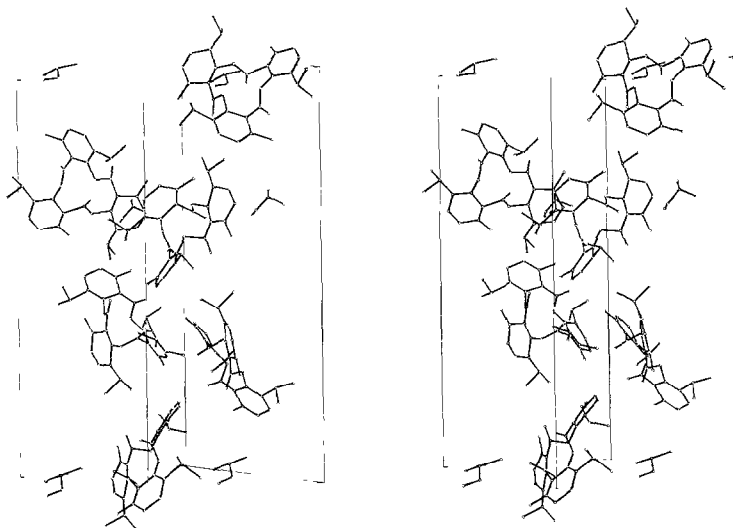


Fig. 2. Stereoview of the molecular packing of (M)-tri-o-thymotide with (R)-2-butanol.

of the absolute configuration of the guest molecule would lead to the absolute configuration of the host molecule provided an univocal structural relationship exists between them (e.g. stereospecific cavity). Following this approach we have determined the crystal structure of the solvate with (R)-2-butanol on the basis of 2384 unique reflexions recorded at -150°C on a Philips PW1100 four-circle automatic diffractometer using $\text{MoK}\alpha$ -radiation. The structure was anisotropically refined and the final $R = 0.069$. From a body of optical

measurements it had become apparent that associations such as (-)-TOT/(R)-2-butanol and (+)-TOT/(R)-2-butanol could be isolated as single crystals: an unfortunate sign of "host-guest" non-stereospecificity. Although in the crystallographic model arrived at ((M)-TOT/(R)-2-butanol; see Fig. 2) the atomic positions of the guest molecules had been determined without ambiguity by Fourier difference syntheses, it was of central importance to check the possible validity of the diastereoisomeric model (P)-TOT/(R)-2-butanol or of its crystallographic equivalent (M)-TOT/(S)-2-butanol. Five single crystals were selected (some cut off from larger samples) and 1500 reflections were collected at -150°C from each one of them. Structure factors were calculated for both models and the tests of the R-factor ratio⁵ revealed that the (M)-TOT/(R)-2-butanol model was significantly better for the five samples investigated. The rotatory power ($\lambda = 546\text{nm}$, $T = 16.2^{\circ}\text{C}$) extrapolated at the time $t=0$ was separately measured⁶ in chloroform for each single crystal and the remaining crystalline fragments of larger size. The observed values ranged from $-0.019 \pm 0.002^{\circ}$ to $-0.140 \pm 0.006^{\circ}$ depending on the sample size (0.2 to 1.9 mg) and it can be concluded that the (-)-isomer has the M-configuration whose left-handedness is clearly visible in Fig. 2. Consideration of the torsion angles and other conformational parameters afford of course a more rigorous means of determining to the actual chirality⁷. An idealised view of the M-configuration associated with the (-)-isomer is shown in the right side of Fig. 1.

Acknowledgment. We thank the Swiss National Science Foundation (2.926-0.77) for support of this work.

References and Notes

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(Received in Germany 18 June 1979)