

THE ABSOLUTE CONFIGURATION OF TRI-O-THYMOTIDE AND ITS
"CAGE" CLATHRATE INCLUSION CAVITY

R. Arad-Yellin,^a B.S. Green,^{a,b} M. Knossow,^c and G. Tsoucaris^c

(a) Department of Structural Chemistry, Weizmann Institute of
Science, Rehovot, Israel

(b) Israel Institute for Biological Research, Ness-Ziona, Israel

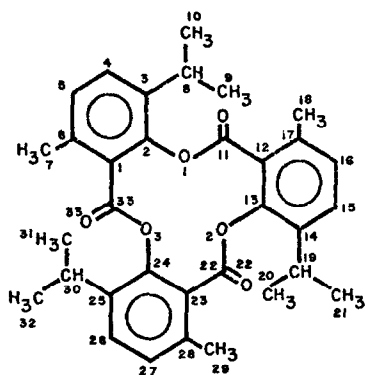
(c) Laboratoire de Physique, Centre Pharmaceutique, 92290
Chatenay-Malabry, France

The absolute configuration of tri-o-thymotide (TOT) has been determined by X-ray crystal structure determinations of two cage-type clathrate inclusion compounds, (+)-TOT·S-(+)-2-bromobutane and (-)-TOT·RR-(+)-2,3-dimethylthiirane; (+)-TOT has a P propeller-like configuration

Clathrate inclusion compounds¹ comprise two different species, guest and host, which associate to form stable crystalline compounds; there are no covalent or ionic bonds linking the two species. Tri-o-thymotide (TOT) enclathrates a wide variety of guest molecules and generally affords chiral crystalline complexes.² Crystal structure analysis of these clathrates was first reported by Powell, who recognised the possibility of using the chirality of the clathrate crystals to discriminate between enantiomers of guest molecules^{3,4}. Powell also pointed out that the absolute configuration of a clathrate inclusion complex could define both the TOT absolute configuration as well as the absolute configuration of the chiral cavities in each enantiomorphous form of a TOT clathrate crystal³. Such information could then be used to establish the absolute configurations of included guests in other TOT clathrate compounds.

More detailed descriptions of TOT crystal structures have since become available⁵ and it has been confirmed that the TOT molecule has a P- or M-propeller configuration in the crystal. The absolute configuration of TOT had been assigned by circular dichroism measurements in the solid state and solution⁶; however, such determinations may be problematic, especially when data are lacking on related molecules⁷.

A crystallographic study of the TOT·R-2-butanol clathrate has just been published⁸ and these results establish the absolute configuration of TOT as opposite to that reported in the CD studies. We have also determined the X-ray crystal structures and absolute configurations of several cage-type TOT clathrate inclusion complexes as part of a study to better understand the chiral discrimination when TOT clathrate single crystals are grown from various racemic

Tri-*o*-thymotide (TOT)

guests⁴ and the nature of the guest-host chiral interactions. Our results (Figure 1) with two clathrates containing guests of known configuration are fully consistent with one another and with that of the TOT·R-2-butanol clathrate. It is therefore unequivocally established that (+)-TOT has the \underline{P} (right-handed propeller) absolute configuration.

TOT clathrate crystals were grown from slowly cooled solutions of 34% optically enriched S-(+)-2-bromobutane, $\underline{1}$ (prepared by TOT enclathration⁹), and optically pure RR-(+)-2,3-dimethylthiirane, $\underline{2}$,¹⁰ respectively. Single crystals were selected and the same specimen was used for X-ray analysis and for establishing the sign of rotation of TOT. The latter is very conveniently measured polarimetrically using chloroform solutions of crystals dissolved at ca. 0°; at higher temperatures, the $\underline{P} \rightleftharpoons \underline{M}$ enantiomerization of TOT is rapid, $E_{act} \sim 21$ Kcal/mole.¹¹

The data for both crystals were collected at -50° on an Enraf-Nonius CAD-4 four circle diffractometer, using Ni-filtered Cu-K α radiation and the ω -2 θ scan mode. For (+)-TOT·S(+)- $\underline{1}$, $\underline{a}=\underline{b}=13.70(1)$, $\underline{c}=30.25(1)\text{\AA}$, $\underline{Z}=6$ (6 TOT: 3 $\underline{1}$), space group $P3_221$; $D_c=1.195$, $D_m=1.191$ g-cm⁻³; $R_{obs}=7.6\%$; 2397 unique reflections ($\theta < 55^\circ$) were measured¹². For (-)-TOT·RR(+)- $\underline{2}$, $\underline{a}=\underline{b}=13.60(1)$, $\underline{c}=30.28(1)\text{\AA}$, $\underline{Z}=6$ (6 TOT: 3 $\underline{2}$), space group $P3_121$; $D_c=1.161$, $D_m=1.158$ g-cm⁻³; $R_{obs}=8.6\%$; 3143 unique reflections ($\theta < 65^\circ$) were measured¹². The host:guest ratio was established as 2:1 for both complexes by NMR analysis of solutions prepared from polycrystalline clathrate samples. All non-hydrogen ordered host atoms were refined anisotropically, starting from the coordinates of the isomorphous cage-type TOT·pyridine clathrate^{5c}; hydrogen atoms were introduced in calculated positions or refined as rigid methyl groups using the SHELX program¹³. Guest atoms were located on Fourier difference maps and refined isotropically. Guest atoms in both structures exhibit larger thermal motion than that of most TOT atoms and TOT atoms in contact with guest molecules exhibit either two-position disorder or temperature factors higher than normal in both structures¹⁴.

It has been shown⁴ that, without any recourse to the absolute configuration of TOT, the sign of rotation can be well-correlated with the guest absolute configuration within a series of related TOT clathrate inclusion complexes. The unambiguous absolute configuration assignment of TOT makes it now possible to determine absolute configurations of guests by a standard X-ray structure analysis, even if they are unrelated to previously studied molecules.

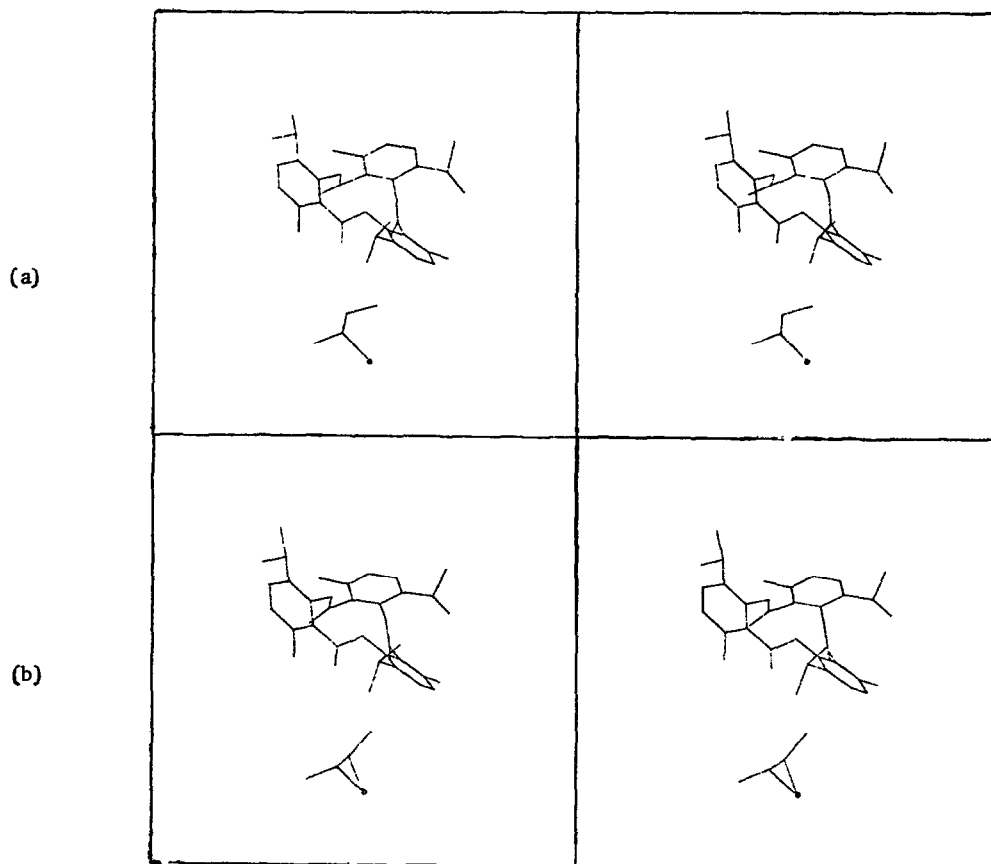


Figure 1. Stereoviews indicating the absolute configurations of guest and host in (a) the (+)-TOT·S-(+)-2-bromobutane clathrate and (b) the (-)-TOT·RR-(+)-2,3-dimethylthiirane clathrate. Bromine and sulfur atoms are shown as solid circles.

References and Notes

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9. Large single TOT clathrate crystals were grown from racemic $\underline{1}$ and then several individual (+)-TOT· $\underline{1}$ crystals were powdered and heated in vacuo to release S-(+)- $\underline{1}$, $[\alpha]_D = +11.2^\circ$ (neat liquid). Configuration assignment of $\underline{1}$: W.A. Cowdrey, E.D. Hughes, C.K. Ingold, S. Masterman, and A.D. Scott, J. Chem. Soc. 1252 (1937). Since each subsequent crystallization significantly increases the enantiomeric excess of the included guest compared to that in the starting solution (unpublished results), the crystal used for analysis contains S-(+)- $\underline{1}$ with appreciably higher optical purity.
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12. The calculated and measured densities are for room temperature.
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(Received in UK 16 October 1979)