DEVIATIONS FROM C_3 SYMMETRY OF THE TRI-O-THYMOTIDE MOLECULE IN DIFFERENT
CRYSTALLINE ENVIRONMENTS.

X-RAY DETERMINATIONS OF THE UNSOLVATED FORM AND OF TYPICAL CAVITY AND CHANNEL
INCLUSION COMPOUNDS.

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Tri-o-thymotide (TOT, $C_{33}H_{36}O_6$)(I) is of interest in connection with current
studies of medium-ring dynamics.[1,2] It has been cited as one of the few, if not the 'unique'
example of an organic molecule having C_3 symmetry.[3] It has been proposed on the basis
of dipole-moment measurements[4] and n.m.r. spectra[1,5] that, in the solid state the molecule
has a propellor conformation, i.e. all three carbonyl oxygens lie on the same side of
the 12-membered ring. The energy barrier for inversion of this chiral conformation was
estimated at 21.2 kcal mole^{-1} from polarimetric measurements,[6] and 23.6 kcal mole^{-1} from
n.m.r. studies which showed that the process occurs stepwise, one carbonyl group at
a time via a 'helical' configuration.[1,5]

TOT is also remarkable as it not only crystallises in a pure, unsolvated form,
but is known to form crystalline inclusion complexes with a very large number of assorted
substances, (∿80 so far characterised).[7,8,9] The majority of these complexes are hexagonal
or trigonal and are either of the channel or the cavity type, depending on the shape and
length of the guest molecule.[8] Each type has a distinctive host structure that is virtually
independent of the guest molecules.[8] We report here X-ray structure determinations of the
pure unsolvated form, and of the ethanol and cetyl alcohol complexes which we regard as
typical of the cavity and channel forms respectively. Detailed aspects of the host-guest
relationship, the shape and dimensions of the cavity, and of the unsolvated structure were
given at the H.M.Powell Symposium, Oxford, April 1974.[†] These together with those of
the channel will be published elsewhere. Here we compare the conformations of the 12-
membered TOT ring in these three structures.

[†] At the same meeting Mme S. Brunie (Universite de Paris-Sud) reported an independent
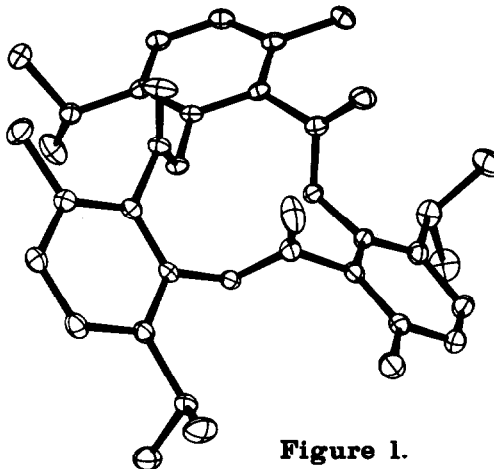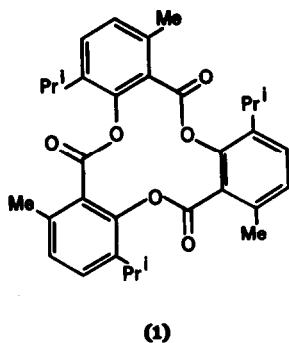determination of the structure of the unsolvated form.

(1)

Figure 1.

Crystals of TOT/ethanol (II) are trigonal, $\underline{a}$=13.443, $\underline{c}$=30.143Å, space group $\underline{P3_1}21$ (or enantiomorphous $\underline{P3_2}21$); cell contents $6(C_{33}H_{36}O_6)3(C_2H_5OH)$. Those of TOT/cetyl alcohol (III) are hexagonal, $\underline{a}$=14.308, $\underline{c}$=29.016Å, space group $\underline{P6_1}$ (or enantiomorphous $\underline{P6_5}$); cell contents $6(C_{33}H_{36}O_6)1.3(C_{16}H_{33}OH)$. Those of unsolvated TOT (I) are orthorhombic, $\underline{a}$=16.049, $\underline{b}$=13.424, $\underline{c}$=13.969Å, space group $\underline{Pna}2_1$, Z=4. For all three substances intensity data were measured (to θ=70°) on a Siemens four-circle diffractometer, using filtered Cu-$\underline{K}_\alpha$ radiation. The structure of the ethanol complex was solved by inserting the coordinates of the TOT host structure found in the CH_2I_2 complex.[10] The structures of the cetyl alcohol complex and the unsolvated form were obtained by direct methods. All three structures have been refined anisotropically.

In all three structures the TOT molecule has the predicted propellor conformation;[1,4,5] Fig.1 shows the configuration found in the ethanol complex. To facilitate comparison all three molecules have been converted to a common arbitrary chirality and rotated relative to each other to give the best fit. The nonbonded distances and torsion angles have been labelled as in fig.2. Fig.3 shows a series of graphical comparisons of the three chemically equivalent values of a parameter found in each of the three structures as well as mean values. It is immediately evident that, apart from the group a,e,i and two minor exceptions (q,u;D,F), the jointed lines, which indicate the variations in a given parameter, never cross, i.e. there is a marked element of consistency in the deformations of these molecules. The kinks in any line indicate the influence of the very different packing environments: the variation is considerable, thus indicating a marked flexibility in the molecule. The deviations from C_3 symmetry are sometimes large, particularly in the unsolvated structure (I) where they reach 32° (d,ℓ) and 0.77Å (D,E). It is also clear, however, that the average value of the three equivalent parameters in each molecule is remarkably consistent.
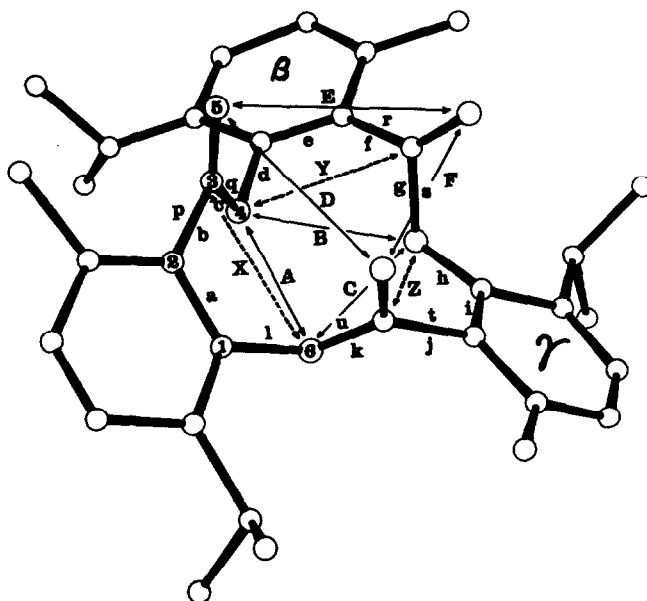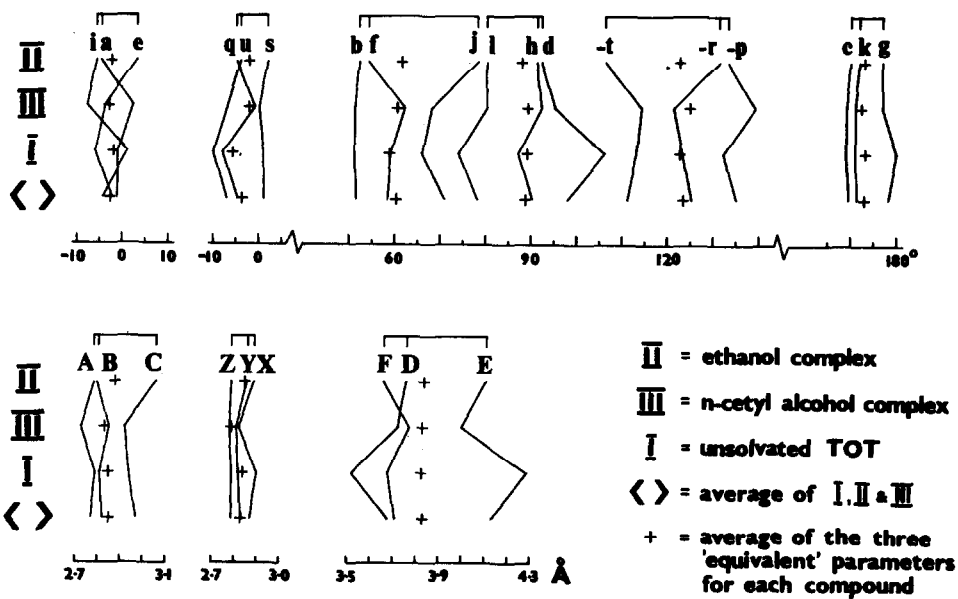
Figure 2.

Figure 3.

The mean values in fig.3 suggest the ideal C_3 molecule would have a torsion angle of $60°$ about b etc., and of $90°$ about d, etc. It is noteworthy that the sequence of adjacent torsion angles e,f,g,h,i is in all three structures nearly ideal and much less distorted than the rest of the molecule. This suggests that rings β and γ (fig.2) are nearly ideally related and that when the carbonyl $C(3),O(5)_{1,5}$ flips over during the process of inter-conversion to produce the propellor form, it has to make the best of a conformationally uncomfortable situation. Hence b cannot attain its ideal value of $60°$ and E is consequently large. Thus strict C_3 symmetry is energetically a little less favourable than the lopsided form we have consistently found in these structures.

We have also considered the possibilities of ring stabilisation by carbonyl-carbonyl interactions[11] and carbonyl-ether interactions.[12] The carboxylic carbon atoms deviate from the planes of their associated atoms towards the nearer opposing ether oxygen (i.e. deviation of C(3) from the plane of C(2),O(4),O(5) towards O(6) and so on fig.2) by distances ranging from 0.00 to 0.07Å, but there is no correlation between deviation and the corresponding distance X,Y or Z. We do not consider this a significant contributor to the lopsidedness and consequently also discount the likelihood of carbonyl-carbonyl interactions as the distances involved are somewhat greater, (above 3.3Å).

It is this very flexibility of the TOT molecule which enables it to form such a wide range of crystalline compounds.

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