718. *The Spontaneous Optical Resolution of Solvated Tri-*o*-thymotide.*

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Crystal-structure examination has shown that tri-*o*-thymotide crystallises as a racemate but that resolution takes place on formation of its crystalline adduct with *n*-hexane, benzene, or chloroform. The crystals do not develop enantiomorphous forms that would permit of hand sorting, but large single crystals of the benzene and hexane compounds have been grown. Each gives a solution showing optical activity which diminishes rapidly through racemisation.

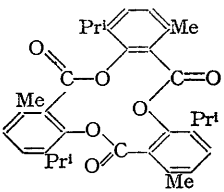
The optical activity arises from hindrance to free rotation about single bonds in a twelve-membered ring. The energy of activation for the racemisation is estimated as 16 kcal./mole.

THE two thymotides derived from thymotic acid (2-hydroxy-6-methyl-3-*iso*propylbenzoic acid) which were described by Spallino and Provenzal (*Gazzetta*, 1909, **39**, II, 325) as isomeric dithymotides have been further examined by Baker, Gilbert, and Ollis (*J.*, 1952, 1443) and one of these has been found to be tri-*o*-thymotide (I).

If the interatomic distances and bond angles are as shown and rotation about single bonds is used to minimise steric interference between the carbonyl groups and the substituents on the benzene rings the atoms are not all coplanar. They may be arranged as in Fig. 1. In this the molecule has no symmetry other than a three-fold axis and is therefore not superposable on its mirror image. It could exist in enantiomorphous forms which are related to each other as right- and left-handed three-bladed propellers. One enantiomorph may be converted into the other by rotations about single bonds but in the process some steric interference must be overcome.

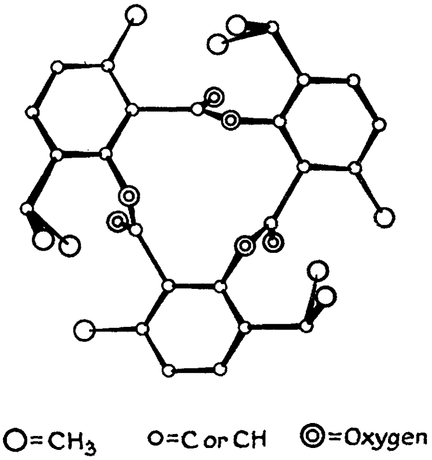
Edgerly and Sutton (*J.*, 1951, 1069) have examined the stereochemistry of the same central ring system found in the related tricresotides and trisalicylide. From measurements of dipole moments and other considerations they conclude that these molecules also are propeller-shaped.

There does not seem to be a simple way of effecting a resolution by combining tri-*o*-thymotide with an optically active substance, but during *X*-ray crystallographic examination it became apparent that this compound which crystallises from methanol as a racemate could be resolved by formation of its molecular compounds. This optical resolution has been carried out.



(I)

FIG. 1. *Scale drawing of a possible form of the trithymotide molecule.*



C–C (*aromatic*) = 1·4, *other* C–C = 1·54, C=O = 1·25, C–O = 1·43 Å. *Bond angles* 120°, *except those of the* iso*propyl group and* C–O–C *which are taken as tetrahedral. The thicker end of a tapered line denotes the end nearer to the observer.*

Tri-*o*-thymotide, crystallised from methanol, has an orthorhombic structure. The absent *X*-ray reflexions are those of the space groups C_{2v}^{9}-*Pbn* or D_{2h}^{16}-*Pbnm*. Of these *Pbnm* may be rejected since with only four molecules in the cell they are required to have either planes or centres of symmetry which are lacking. In the space group *Pbn* the four molecules per unit cell need not have any symmetry and are not restricted to special positions. The structure may be represented as in Fig. 2. Molecule *A* (or *A'*) is derived from *B* (or (*B'*) by a reflexion in the plane *MM* (or *M'M'*) perpendicular to the paper, accompanied by a translation of *b*/2. *A* and *B* must be mirror images of each other and hence if tri-*o*-thymotide is a dissymmetric substance the crystals are those of a racemic form containing equal numbers of *dextro*- and *lævo*-molecules.

Baker, Gilbert, and Ollis who found (*loc. cit.*) that a number of substances such as *n*-hexane or benzene unite with tri-*o*-thymotide to give crystalline adducts of the clathrate type provided a crystalline specimen of composition $2C_{33}H_{36}O_6,C_6H_{14}$. It was found to have a hexagonal unit cell containing six molecules of tri-*o*-thymotide and three of *n*-hexane. Since the lattice is not rhombohedral the absent spectra 000*l* when $l \neq 3n$ must be due to a screw axis of symmetry (3_1, 3_2, 6_2, or 6_4) and the structure belongs to one of the enantiomorphous space groups. The observed equality of *hkil* and *hki*$\bar{l}$ reflexions and the inequality of *hki*0 and *khi*0 limit the space group to the enantiomorphous pair $C6_2$, $C6_4$. In these space groups molecules such as tri-*o*-thymotide lacking a two-fold symmetry axis cannot occupy the special equivalent positions of three-fold multiplicity and therefore the six molecules of the unit cell can only be in the general positions. They are all related to each other by rotation and translation operations only and must be geometrically identical. This does not prove that the molecules are dissymmetric but, if they are, then those in any one unit cell are all of the same kind and hence in the absence of complications such as disorders or twinning the molecules in any one crystal are of the same kind, all *dextro* or all *lævo*. In such a case the separation of the two enantiomorphous forms of the crystals is also a separation of the two molecular antimers.

FIG. 2.

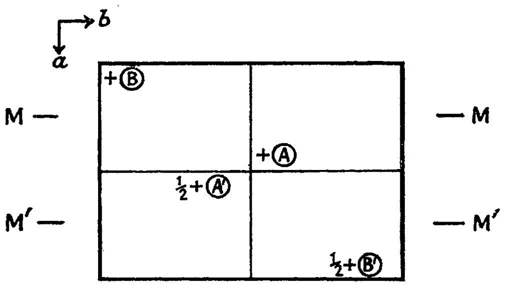


FIG. 3. *Face development shown by large crystals of trithymotide–benzene solvate. It is consistent with the symmetry class 32 but does not include faces which could distinguish right and left enantiomorphs.*

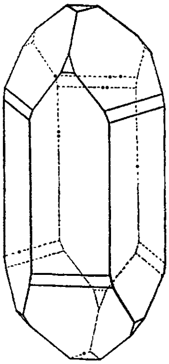
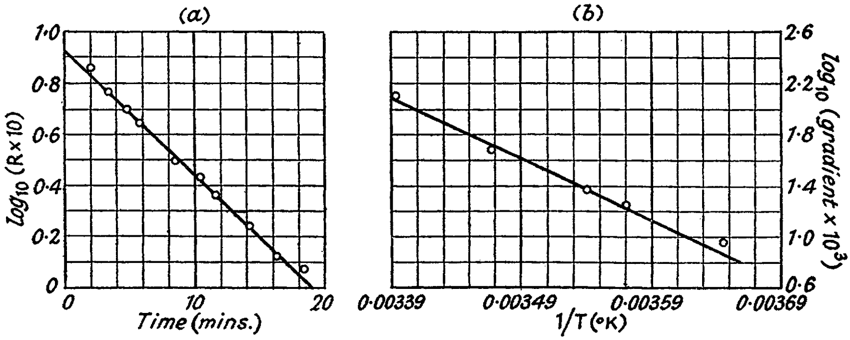


FIG. 4.



Crystals of the *n*-hexane adduct were examined under the microscope and on the optical goniometer but were without trace of enantiomorphous faces. They were also cut, and examined in the direction of the optic axis for signs of rotatory power, but in view of the comparatively small dimensions (1 mm.) and their imperfections the negative result is not of great significance. It was planned therefore to make the optical resolution by growing large single crystals which, in the continued absence of enantiomorphous faces but with greater thickness, could be cut and separated according to the sense of the optical rotation observed in the crystal. Alternatively a single large crystal might contain enough material to give a solution showing rotation. The crystals usually grow in needles elongated parallel to the optic axis. They are frequently of a turbid appearance and are difficult material for optical sorting. However the adducts of tri-*o*-thymotide with benzene or chloroform also give crystals belonging to enantiomorphous space groups. In this case *X*-ray reflexions considered in conjunction with the crystal habit indicate the space groups $C3_121$, $C3_221$. The only special positions require a two-fold symmetry axis in the molecule and are therefore not occupied by tri-*o*-thymotide. Hence the six molecules per unit cell are in general six-fold positions and must be identical, all *dextro* or all *lævo* for any one crystal. No enantiomorphous faces have been observed but crystals of the benzene adduct may be readily grown to the desired size. By slow cooling single crystals up to 1 g. in weight have been obtained.

Solutions in chloroform made in each case from a single crystal rotated the plane of polarisation of light, some to the left and some to the right. The rotation diminished rapidly through racemisation in solution. The rate of racemisation has been determined at temperatures between 0° and 21° and the activation energy estimated. For convenience the main observations have been made on the benzene compound but crystals of the *n*-hexane compound have been obtained large enough (0·019 g.) to give solutions of measurable optical activity.

There are several unusual features of this example of optical resolution. The *possibility* of achieving it was revealed through an *X*-ray structural examination. This is so far a rare occurrence but has been noted by Shoemaker, Donohue, Schomaker, and Corey (*J. Amer. Chem. Soc.*, 1950, **72**, 2328) for DL-threonine. The actual separation is carried out by hand sorting but not in the manner of Pasteur since no enantiomorphous faces are developed. The substance which has been resolved crystallises as a racemate, but its self-resolution has been induced by the formation of a crystalline molecular compound with an optically *inactive* substance. The dissymmetry which causes the molecule to be optically active arises from a lack of free rotation about the single bonds of a puckered ring of twelve atoms with substituents that cause steric hindrance.

EXPERIMENTAL

X-Ray examinations were made with copper K_α-radiation on oscillating single crystals with stationary or moving films (Weissenberg method). Lattice dimensions are to an accuracy of ½%. Densities were measured by flotation. Analyses are by Drs. Weiler and Strauss, Oxford.

*Tri-*o*-thymotide.*—The unsolvated material crystallised from methanol is orthorhombic, having $a = 13{\cdot}5$, $b = 16{\cdot}0$, $c = 13{\cdot}9$ Å, and $\rho = 1{\cdot}17$ g./c.c. Molecules per unit cell = 4. Absent spectra are $0kl$ when k odd and $h0l$ when $h + l$ is odd. Space group, *Pbn*.

*Tri-*o*-thymotide–*n*-Hexane Solvate.*—The composition $2C_{33}H_{36}O_6,C_6H_{14}$ has been established by Baker, Gilbert, and Ollis. The solvate forms colourless crystals, hexagonal, $a = 14{\cdot}2$, $c = 28{\cdot}9$ Å, $\rho = 1{\cdot}069$ g./c.c. The unit cell contains $3C_6H_{14}$ and $6C_{33}H_{36}O_6$. Absent spectra are $000l$ when $l \neq 3n$. Reflexions $hkil$ are of the same intensity as $hki\bar{l}$ but $hki0$ and $khi0$ are not equal. Space group $C6_2$ or enantiomorphous $C6_4$.

*Tri-*o*-thymotide–Benzene Solvate.*—The solvate was obtained in large colourless single crystals by slow cooling of a solution of tri-*o*-thymotide in benzene (Found: C, 76·5; H, 7·0. $2C_{33}H_{36}O_6,C_6H_6$ requires C, 76·2; H, 6·9%). There is no loss of weight at 160°. The composition is confirmed by the weight of the unit cell. The face development (Fig. 3) of pinacoid $\{0001\}$, prisms $\{10\bar{1}0\}$, the large rhombohedron $\{10\bar{1}2\}$, and two small rhombohedra $\{10\bar{1}1\}$ and $\{01\bar{1}2\}$ is consistent with the symmetry class 32 but no enantiomorphous faces were observed. Double refraction is weak, positive. The unit cell has $a = 13{\cdot}7$, $c = 29{\cdot}9$ Å, and contains $3C_6H_6$ and $6C_{33}H_{36}O_6$; $\rho = 1{\cdot}158$ g./c.c. Absent spectra are $000l$ when $l \neq 3n$. Reflexions $hkil$ are not equal to $hki\bar{l}$ but $hki0$ and $khi0$ are equal in intensity. These observations and the crystal habit are consistent with the pair of enantiomorphous space groups $C3_121$, $C3_221$.

Single crystals of about 0·1 g. were powdered and dissolved in 9 c.c. of chloroform, and the resulting solution was examined in a Hilger-Watts Standard polarimeter, Mark III. Some solutions rotated the plane of polarisation to the left, others to the right. The rotation falls to zero owing to racemisation. Table 1 gives rotation against time for a typical experiment. Fig. 4*a* shows a plot of logarithms of rotation against time and from it the value R_0 of the initial rotation is deduced by extrapolation to the estimated zero of time. The straight-line form indicates a reaction of the first order. Table 2 records R_0, calculated for 0·1 g. of material, specific rotations and half-life of the rotation for several temperatures. Five samples were taken from the same crystal; the sixth, from another crystal, gave a specific rotation approximately the same in magnitude but of opposite sense. Specific rotations are calculated as those of the tri-*o*-thymotide complex. If the rotation is regarded as that of the tri-*o*-thymotide alone the numbers should be multiplied by the factor 1·075. In Fig. 4*b* the logarithms of the gradients of five curves similar to those in 4*a* are plotted against $1/T$; from this the energy of activation for the racemisation is calculated to be 16 kcal./mole.

TABLE 1.—*Racemisation at* 15·2°. *Tri-*o*-thymotide* (0·1058 *g.*), *in* 9 *c.c. of chloroform, examined in a* 1-*dm. tube.*

Time, mins....	1·8	3·3	4·5	5·8	8·5	10·2	11·8	14·1	16·1	18·3	21·9	24·5
α	0·73°	0·59°	0·51°	0·44°	0·31°	0·27°	0·235°	0·155°	0·135°	0·12°	0·07°	0·045°

TABLE 2.

Temp. (K)	274·6°	280·2°	283·3°	288·2°	294·6°	294·4°
R_0, calc. for 0·1 g.	0·726°	0·753°	0·743°	0·804°	0·920°	−0·855°
$[\alpha]_D$	+65°	+68°	+67°	+72°	+83°	−77°
Half-life (mins.)	34	17·1	12·4	6·4	2·4	—

*Tri-*o*-thymotide–Chloroform Solvate.*—Obtained by cooling or evaporation of solutions of tri-*o*-thymotide in chloroform, this *solvate* (Found: C, 68·9; H, 6·1; Cl, 9·0; $2C_{33}H_{36}O_6,CHCl_3$ requires C, 68·4; H, 6·2; Cl, 9·05%) does not lose weight at 160°. It forms colourless crystals, trigonal, $a = 13{\cdot}55$, $c = 30{\cdot}3$ Å, $\rho = 1{\cdot}209$ g./c.c. The unit cell contains $3CHCl_3$ and $6C_{33}H_{36}O_6$. Absent spectra are $000l$ when $l \neq 3n$. Reflexions $hkil$ in general are not equal to $hk\bar{i}l$, but $hki0$ is equal to $khi0$ in intensity. The X-ray diffraction patterns are very similar to those of the benzene adduct. The space group is not certain but it must be enantiomorphous.

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