04.5-04 TRI-O-THYMOTIDE CLATHRATES: A CONFORMATIONAL APPROACH TO THE CHIRAL RECOGNITION OF GUEST MOLECULES.

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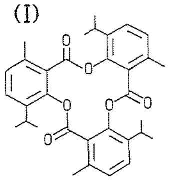
The presence of dissymetric cavities in chiral crystals of tri-o-thymotide (TOT,I) can give rise to the preferential enclathration of one of the enantiomers of a racemic mixture. A measure of the stereoselectivity is experimentally given by the enantiomeric excess, and the best figures observed range between 30-50% (e.g. guests 1-4, Table). Besides, many enantiomeric pairs are undistinctively enclathrated (5-8, Table). Our approach (R. Gerdil and J.Allemand, Helv. Chim. Acta,63,1750(1980)) is based on the calculation of the nonbonded potential energy difference ΔRS (kcal/mol) for the respective inclusion of the R and S enantiomers in a cavity of given handedness. The cage is made up of rigid TOT molecules allowed to move independently. It is assumed that the chiral recognition will be roughly proportional to ΔRS. Predictions for unknown crystal structures are facilitated by the fact that the cage clathrates are isostructural (space group $P3_121$). A simple measurement of the cell parameters permits an adequat optimization of the cage dimensions, using an average conformation for TOT.

By way of illustration the clathrates including the guest components (II) are reported here (the dotted line denotes the crystallographic C_2 axis). The calculated energies reported in the Table are accurate enough to serve as a starting point for estimating the observed degrees of stereoselectivity. Allowance is made, in the calculations, of the conformational energy variations of the guest and it is seen that the presence of a rigid "rotor" alongside the C_2 axis tends to cause a substantial levelling of the ΔRS values.

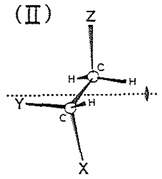
Guests	X	Y	Z	ΔRS	
1) 2-chlorobutane	CH_3	Cl	CH_3	3.2	a
2) 2-bromobutane	CH_3	Br	CH_3	4.9	a
3) 2-iodobutane	CH_3	I	CH_3	2.6	b
4) ethylmethylsulfoxide	CH_3	(*)	CH_3	2.7	a
5) 2-butanol	CH_3	OH	CH_3	<0.5	a,c
6) 1,2-dibromopropane	Br	CH_3	Br	<0.5	a,c
7) 2-butylamine	CH_3	NH_2	CH_3	<0.5	b,c
8) 2-amino-1-butanol	NH_2	CH_2OH	CH_3	<0.5	b,c,d

a) known crystal structure; b) only the cell parameters are known; c) ΔRS is calculated as a function of the torsion angle about C-Y for various rotational orientations of Y. Minimum values for ΔRS are associated with low energy rotamers; d) X and Y may be exchanged with each other.

(I)



(II)



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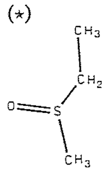

04.5-05 CHIRAL DISCRIMINATION IN MOLECULAR AND CRYSTALLINE SYSTEMS.

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Chiral recognition may operate at different levels. The primary recognition procedure operates generally at the molecular level. This can already be achieved in solution ; a novel illustration is described in Part.A. Next, in certain systems, the molecular recognition is achieved only within the unit cell of a crystal. This is the case of chiral TOT clathrates (Part B) ; it may finally happen that in almost racemic crystalline compounds the chiral entities to be associated are already crystalline blocks of several microns (Part C).

A. Chiral recognition in solution : Bilirubin, Biliverdin and related molecules in association with cyclodextrines. The above molecules, may present different conformers; enantiomers cannot be separated in solution of pure compounds. However, it will be shown that, in presence of chiral cyclodextrine molecules, both bilirubin (BR) and biliverdin (BV) exhibit a very intense circular dichroïsm recalling the well known phenomenon of chiral association with the serum albumin. Crystals of simpler model compounds composed of α or β cyclodextrine and benzil or biacetyl have been obtained. CD spectra will be presented as well as molecular models allowing the interpretation of these phenomenon.

B. Chiral discrimination in TOT clathrates. Cocrystallization of Tri-o-thymotide (TOT) with a racemic mixture provides after a single crystallization an enantiomeric excess ranging from 5% to 50% (JACS,102,1157, (1980)). Moreover, there is a correlation of guest and host chirality, which in turn has allowed the determination of the absolute configuration of TOT (Tet. Let. 21, 387,(1980)). Crystal structure determinations to be presented have allowed a rationalization at the molecular level of this phenomenon.

C. Chiral blocks in almost racemic crystals. It has usually been taken for granted that crystallization in a chiral space group is sufficient to allow resolution of enantiomers by sorting crystals according to a chirality observation such as sign of optical rotation. The hexahelicene case exemplifies a situation which may have been overlooked in other systems as well, where crystals grow as nearly racemic mixtures of enantiomers and are indistinguishable from genuinely chiral material by standard X-ray diffractometry. We have shown that hexahelicene almost racemic "single" crystals consist of alternating (+) and (-) layers. A rationalization based on crystal packing will be presented.