184. The Chiral Recognition of Guest Molecules in Trio-*o*-thymotide Clathrates: a Semi-empirical Approach[1])

Preliminary communication

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Summary

The enantiomers of a chiral solvent can be enclathrated to a different extent in a crystal lattice consisting of tri-*o*-thymotide (**1**) molecules of a given handedness. This property affords a mean of studying the stereoselective interaction of a chiral environment with an enclosed chiral component. The general approach to account for the observed differences in stereoselectivity is based on the calculation and comparison of the minimum energies for the respective inclusion of enantiomeric guest molecules within a rigid cage of given chirality. An interpretation of the fair chiral recognition of 2-bromobutane as opposed to the unselective inclusion of 2-butanol is attempted.

Introduction. – The tri-*o*-thymotide molecule (TOT, **1**) exists in chiral conformations of *propeller* type in the crystalline phase. A wide variety of guest molecules can be enclathrated by TOT to form generally chiral crystalline species (cage or channel clathrates) which contain only one conformation, either *P* or *M*, of the host molecule. *Van der Waals* forces alone hold together the components of the crystal lattices of the present clathrates, within which the guest molecules are

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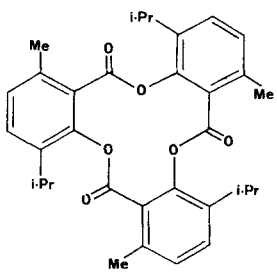

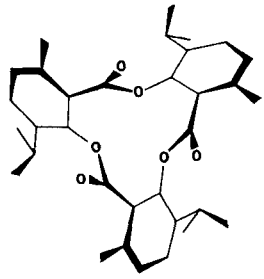

Fig. 1. *Schematic view of tri-*o*-thymotide* (**1**) *and idealized representation of the* (M)*-configuration of* (–)-**1**

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enclosed in separate closed cavities (cages). The presence of dissymmetric cages provides a chiral environment around the trapped molecule and can give rise to the preferential inclusion of one of the enantiomers of a racemic mixture [1]. This correlation between the host and guest configurations demonstrates the ability of the cavities to recognize molecular chirality. A measure of the cavity stereoselectivity is given by the enantiomeric excess (e.e. %) of the guest in a single crystal or in an equivalent homogeneous crop. It has been shown by *Green et al.* [1], and independently by us, that a wide range of figures are observed for the e.e. depending on the nature of the guest around which the cage is built during crystallization. Some of our results are summarized below (the related clathrates form a group of isomorphous crystals).

Guest molecule	2-butanol (**2**)	2-amino-butane	2-chloro-butane	2-bromo-butane (**3**)	ethyl methyl sulfoxide
e.e. (%)	<5	<2	45	35	40–50

We shall attempt here to explore the problem of what controls the stereoselective choice in the enclathration process. The relative 'adaptability' of a pair of enantiomers to the shape of the cage is most simply expressed by the e.e. In turn, this observable parameter is amenable to a semi-quantitative estimation under the assumption that the enantiomer giving rise to the least interaction energy with the cage (greater 'adaptability') will be preferentially enclosed. Our general approach to account for the *differences* in stereoselectivity is based on the calculation and comparison of the minimum energies for the inclusion of enantiomeric molecules within a rigid cage of given chirality. The method is best illustrated by the interpretation of the fair chiral recognition of 2-bromobutane (**3**) (e.e. 35%) as opposed to the unselective enclathration of 2-butanol (**2**) (e.e. $<5\%$).

Recognition of the chirality of 2-bromobutane (3) and 2-butanol (2). – The cage frameworks were taken from the X-ray structures of TOT/2-bromobutane (**4**) [2] and TOT/(*R*)-2-butanol (**5**) [3]. In addition the crystal structure of **5** allowed the assignment of the (*M*)-configuration to (−)-tri-*o*-thymotide *(Fig. 1)* [4]. Both clathrates recrystallize in space group $P3_121$ and therefore the guest molecules assume a two-fold disordered position. This localized disorder resulted in unsatisfactory bond distances and angles in the X-ray structure models for the guests, whose configurations were however unequivocally determined. Improved molecular geometries were calculated by force fields procedures [5]. The resulting structure models, still consistent with the initial crystallographic ones, were used thereafter in the calculations. In addition sets of internal values for the H-atoms positions[3]), which are of the utmost importance in the determination of packing energies, were then available. The position of the guest molecules was optimized by the use of the PCK 6 program [6], which allows the minimization of the energy of a crystal lattice consisting of several distinct rigid bodies.

[3]) Owing to the disorder the localization of the H-atoms of the solvent in the crystallographic model is hopelessly impaired.

a) *2-Bromobutane.* Clathrate **4** was recrystallized from a racemic mixture of **3**. As was apparent in a ΔF synthesis, a weighted two-fold disorder in the cage confirmed that (*R*)-**3** was the predominant enantiomer in the *laevo*-clathrate, in agreement with the chiroptical properties. The guest molecules are randomly distributed over the available sites and, in a single crystal, the same enantiomer is present in about two out of three filled cages. Calculation of the packing energies showed that the association (*M*)-TOT/(*R*)-2-bromobutane is more favorable by 3.5 kcal than the diastereoisomer (*M*)-TOT/(*S*)-2-bromobutane, in good qualitative agreement with experiment. As depicted in *Figure 2* the final calculated position of (*R*)-**3** converged on that observed for the crystallographic model (in both cases, the rigid molecules have the same geometry). Inspection of the close intermolecular contacts around the methyl groups calls for some rotational freedom, by which is meant that slight rotations of the methyl groups do not bring about critical variations of the packing energy.

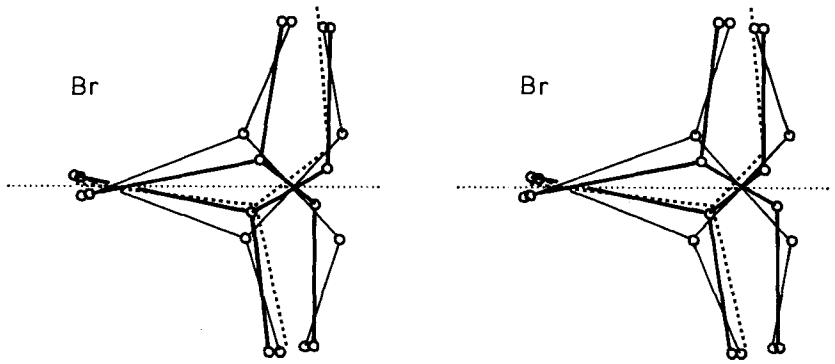

Fig. 2. *Stereoscopic view down the* c*-axis of the calculated positions for* (R)- *and* (S)*-2-bromobutane.* Heavy solid line: (*R*)-enantiomer; dashed line: X-ray model (only one equivalent position shown); horizontal dotted line: crystallographic 2-axis.

b) *2-Butanol.* Substance **5** was recrystallized from the optically pure (*R*)-enantiomer [3]. Both **2** and **3** are enclosed in very similar environments, with the C-atom/heteroatom-bond along the direction of the crystallographic 2-axis (see *Fig. 2*). However **2** possesses an additional torsional degree of freedom, defined by the torsion angle C–C–O–H (θ). Three conformers having about the same energy (minima A, B, and C; *Fig. 3 a*) are generated by internal rotation about the C,O-bond. The ease of their inclusion is however very much dependent on the internal orientation of the O,H-bond as shown by plots of packing energy *versus* θ. The energy profiles for the (*R*)- and (*S*)-enantiomers are different but the curves intersect for two values, θ_1 and θ_2, of the torsion angle. This is best illustrated by plotting the algebraic difference of the potential energy curves as shown in *Figure 3 b*. By comparison with the strain energy profile of **2** it is seen that the values θ_1 and θ_2 are closely related to the minimum energy conformations A and B. The fundamental outcome is that both (*R*)- and (*S*)-**2** can be enclathrated at the expense of about the same energy without any drastic distorsion of the molecular frame, thus pointing to a greatly reduced stereoselectivity of the cage, as observed experimentally.

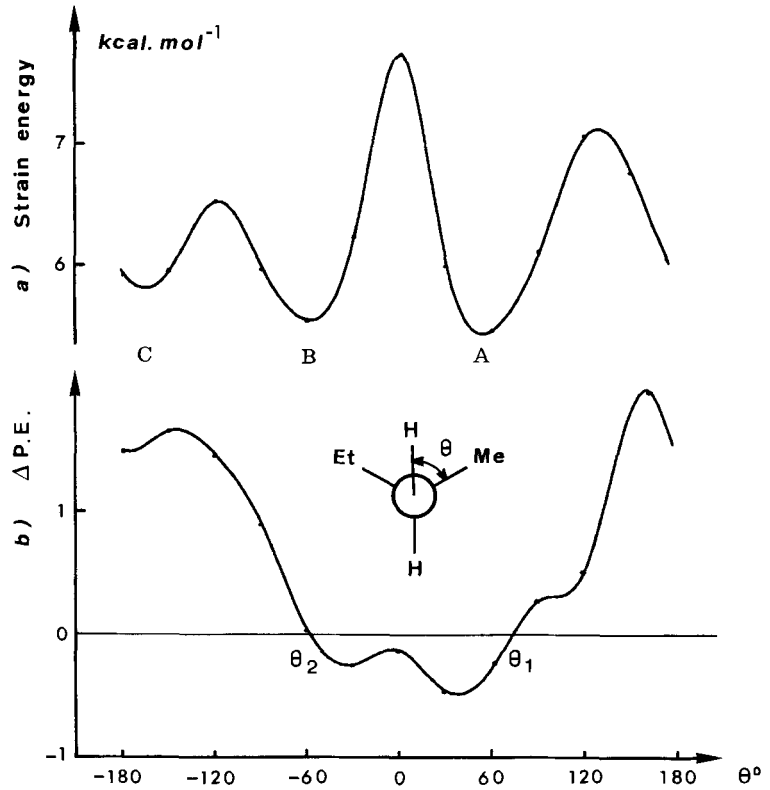

Fig. 3. a) *Strain energy of 2-butanol* (**2**) versus *torsion angle C–C–O–H (θ).* b) *Inclusion of one rotational isomer of* **2** *in one cavity of the* (M)-*TOT lattice:* potential energy of (*S*) *minus* potential energy of (*R*) *versus θ.*

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