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CONFORMATIONAL SELECTION BY CLATHRATION

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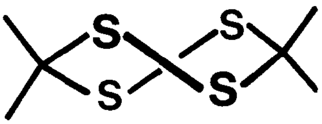
Summary. As an illustration of the potential use of multi-molecular host systems in conformational analysis, it is demonstrated that, after guest release from host (III), the normally disfavoured chair form of 3,3,6,6-tetramethyl-s-tetrathiane (II) can be obtained in solution with a purity of $\gtrsim$ 95%.

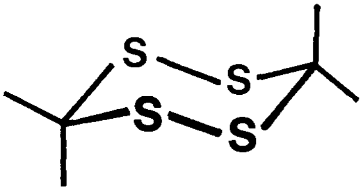
An intriguing challenge in conformational analysis is the production and detection of conformers strongly disfavoured in the normal solution equilibrium. Recently, Anet and coworkers,[1,2] employing an elegant cryogenic deposition technique, have observed the axial-methyl chair form of methylcyclohexane and the twist-boat conformer of cyclohexane itself. In this method, the gaseous form of substance under study is rapidly condensed on to a cold surface, trapping the conformer proportions corresponding to the high temperature equilibrium, typically at 500-800°C. In the present work we describe a different strategy, potentially applicable to thermally labile compounds, based on guest inclusion in a suitable multi-molecular host lattice, followed by appropriate release of the guest which has been subjected to conformational selection.

The detailed studies of Bushweller[3] have established that the twist-boat form (I) of 3,3,6,6-tetramethyl-s-tetrathiane is substantially favoured over the less stable chair conformer (II).



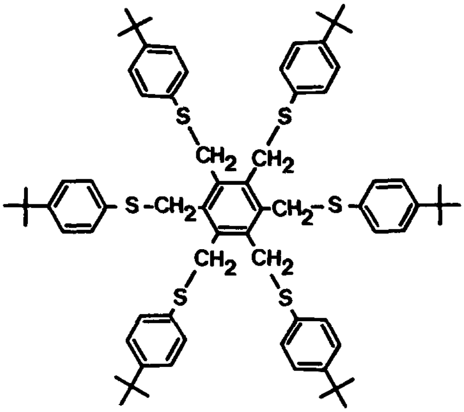
(I)

(one enantiomer shown)



(II)

The symmetry distinction between the centrosymmetric chair form (II) and the chiral twist-boat (I), suggested that guest location at a crystallographic centre of inversion[4] in an appropriate inclusion compound might constrain the guest to be centrosymmetric, hence yielding (II).[5] The versatile hexa-host[6] hexakis(*p*-*t*-butylphenylthiomethyl)benzene (III) was selected as potential host,



(III)

and recrystallisation of equimolar proportions of (III) and guest employing mesitylene[7] as solvent yielded an adduct of (III) with 3,3,6,6-tetramethyl-*s*-tetrathiane. On dissolving a sample of this adduct[8] in a precooled mixture of CS_2 and CD_2Cl_2 (*ca.* 4:1, v./v.) in an n.m.r. tube, and quickly transferring this to the precooled probe of the spectrometer at -90°C, the guest proton n.m.r. spectrum shown in the Figure (a) was observed. That conformational selection

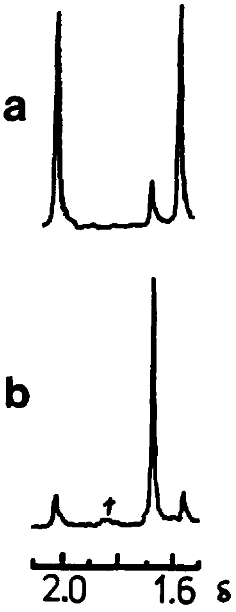


Figure (a) ^1H n.m.r. spectrum of guest 3,3,6,6-tetramethyl-*s*-tetrathiane released from its adduct with host (III) showing the predominance of chair form (II) (-90°C, solvent CS_2/CD_2Cl_2, *ca.* 4:1, v./v.);

(b) corresponding spectrum for a sample warmed to room temperature, and recooled (to -80°C), illustrating the normal predominance of the twist-boat form (I). (Peak denoted † is a spinning side band of the host *t*-butyl resonance).

had indeed been achieved is shown by the predominance of the chair form (92%)

with resonances from the non-equivalent methyl groups at 1.59 δ and 2.00 δ, a low proportion (8%) of twist-boat giving rise to the signal at 1.69 δ. For comparison Figure (b), illustrates the guest spectrum for a similar sample warmed to room temperature, then cooled to -80°C, the normally encountered[3] predominance of the twist-boat form now being apparent. Suspecting that some of the twist-boat form, apparent in Figure (a), might have come from co-crystallisation of the tetrathiane along with the adduct,[9] samples prepared as described above were heated in vacuo (e.g. for 10 hours at 80°C, and 0.5 mm Hg) to remove, or minimise, any 'free' tetrathiane by sublimation. After such treatment, the normally disfavoured chair form[10] of 3,3,6,6-tetramethyl-*s*-tetrathiane (I) could be obtained routinely in solution with a purity of $\gtrsim$ 95%.

The present availability of families of related hosts with known, and varying, void geometries, for example Dianin's compound and related systems,[11] the cyclodextrins,[12] and the hexa-hosts,[13] suggests the attractive possibility of employing a series of selection experiments to elucidate more complex conformational situations. Work along these lines is in progress.

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References and Notes

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3. C.H. Bushweller, J. Amer. Chem. Soc., 1969, 91, 6019; and references therein.

4. It is interesting to note that in the 1,4-dioxan clathrates of hexakis(benzylthiomethyl)benzene and hexakis(2-phenylethylthiomethyl)benzene, the guest is located at a point of $\bar{1}$ symmetry and has a chair conformation: A.D.U. Hardy, D.D. MacNicol, S. Swanson, and D.R. Wilson, J.C.S. Perkin II, 1980, 999; K. Burns, C.J. Gilmore, P.R. Mallinson, D.D. MacNicol, and S. Swanson, J. Chem. Research, in press.

5. In the general case, void dimensions and geometry, as well as symmetry, should be considered for efficient, planned, conformational selection. All these factors were taken into account in the production of the pure staggered conformations of 2,5,5-trimethylhex-3-yn-2-ol and di-*t*-butylacetylene trapped in the clathrate cages of 4-*p*-hydroxyphenyl-2,2,4-

trimethylthiachroman: D.D. MacNicol and F.B. Wilson, Chem. Comm., 1971, 786; A.D.U. Hardy and D.D. MacNicol, unpublished results.

6. A.D.U. Hardy, D.D. MacNicol, and D.R. Wilson, J.C.S. Perkin II, 1979, 1011.
7. Mesitylene does not form an adduct with (III), ref. 6.
8. Samples were placed in the bottom of a precision glass tube (length 28 cm, 7 mm o.d., 5 mm i.d.) closed at the lower end by a medium porosity sintered glass disc, and fitted with a plunger. The lower end of this tube was immersed in cold solvent in a 10 mm o.d. n.m.r. tube permitting precooling of the sample crystals before contact with the solvent. Drawing up and expelling solvent, in several cycles, through the disc provided a filtered solution. ^{1}H n.m.r. spectra were measured on a Varian XL-100 instrument in the pulsed Fourier transform mode.
9. As shown independently (ref. 3) dissolving the molecular crystal of the tetrathiane gives rise to the conformationally pure twist-boat form at low temperature; however, see also, A. Fredga, Acta Chem. Scand., 1958, 12, 891.
10. It may be noted that while the present results are consistent with location of the (geometrically rigid) chair at a point of $\bar{1}$ symmetry in the adduct, the possibility that the guest is situated in a general position cannot be discounted.
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12. W. Saenger, Angew. Chem. Int. Ed. Engl., 1980, 19, 344.
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