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# Conformational Isomerism of the Host as a Factor in Molecular Recognition in Host–Guest Inclusion Complexes: Example of Tris(5-acetyl-3-thienyl)methane

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## Abstract

The tripod molecule tris(5-acetyl-3-thienyl)methane (TATM) is a flexile molecule, *i.e.* one that can occur in many conformationally isomeric states (conformers), which forms host–guest inclusion complexes with a large variety of guests (solvents). Some 40-odd different types of guest have been reported to form inclusion complexes. Five different types of crystal structure (all racemic), with nine different guests, have been reported in the literature and structural information is available for 17 crystallographically independent TATM molecules; most of the guests are disordered. Our analysis of this (substantial but, nevertheless, incomplete) database shows that each group of crystallographically isomorphous structures contains a particular TATM conformer with characteristic torsion angles about the bonds between methane carbon and the three thienyl rings ($\tau_1$, $\tau_2$ and $\tau_3$); the range of torsion angles in a particular structural group does not exceed 10°. Conformers are in addition distinguished *via* the stereochemistry of the acetyl group; there are approximately equal numbers of examples with carbonyl oxygen *syn* or *anti* to ring sulfur, intermediate conformations not being found. So far three different types of conformer have been encountered for the TATM molecule considered as an entity. A necessary condition for the occurrence of a particular conformer type is that the torsion angles $\tau_1$, $\tau_2$ and $\tau_3$ are such that ring hydrogens should not approach more closely than (say) 2.4 Å, but this is not sufficient as considerably larger distances are found in some conformer types. Crystallization of the inclusion complex from a particular solvent can be envisaged to occur as follows. The TATM solution will contain a Boltzmann distribution of host conformers, the distribution depending on temperature but not on the nature of the solvent. Under suitable temperature and solubility conditions, the solvent will crystallize together with the *appropriate* conformer to form the inclusion complex–nuclei formed at this *recognition* stage, then grow into crystallites of the inclusion complex. The perturbed Boltzmann distribution (depleted in appropriate conformer) will continuously revert to its equilibrium form by conversion of the non-appropriate into the appropriate conformer as the crystallization proceeds.

## 1. Introduction

In crystalline 'host–guest inclusion complexes' the details of the interaction of the larger 'host' molecule with the smaller guest are optimally delineated by studying a *family* of complexes; when a particular host interacts with a variety of chemically different guests it is often possible to discern those structural features (molecular and/or crystallographic) which are required for the formation of the complexes. This process is often described as 'molecular recognition', which can be defined as follows:

> "Recognition of molecules, singly or in groups, of one kind or a number of kinds, by each other implies the formation of an aggregate of substantially lower energy than the sum of the energies of the separated molecules. The aggregate must have a lifetime substantially greater than that of a 'contact pair (or group)' and there must be definite orientation relationships among the molecules of the aggregate."

This definition covers everything from binary adducts in solution or the vapour phase to poly-component crystals, but 'substantially' is deliberately not defined and the concept of 'energy' is also left somewhat vague. In a unary (one component) system crystallization requires self-recognition, while in a binary (two component) system crystallization requires both self-recognition (host–host) and other-recognition (host–guest); in a crystalline host–guest inclusion complex guest–guest interactions are generally considered to be negligible. When the host molecule is 'flexile'* (conformationally versatile) and the guest rigid, then the host conformational isomer (conformer) found in a particular complex will depend both on the relative energies of the possible conformers and the nature of the guest. If the guest is flexile, then the conformational possibilities of the guest must also

* 'Flexile': supple, mobile; tractable; versatile. 'Versatile' is appropriate in the present context.

be taken into account. In this context 'rigid' means that conformational isomerism is not possible, while 'flexile' means the converse.

When the host molecule is rigid, as has been the situation in most studies, the possibilities of mutual host–guest adaptation are severely limited. However, the preparation of many inclusion complexes of tris(5-acetyl-3-thienyl)methane (TATM), which has a tripod shape, and determination of a number of their crystal structures now provides information about the mutual adaptation of a flexile host molecule and its guests. This allows correlations to be made between the conformers found for TATM and the crystal structures of different groups of isomorphous inclusion complexes, with the target of understanding the relationship between host conformation in the inclusion complex and the chemical nature of the guest.

The formation of crystalline TATM inclusion complexes has been reported so far for 43 different types of guest. Five different types of crystal structures have been reported in the literature, with nine different guests; structural information is available for 17 crystallographically independent TATM molecules. Specifically, the following questions can be asked and answered within the confines of the available information:

(i) Is there a correlation between the TATM conformer and the crystal structure of the inclusion complexes, *i.e.* is the same TATM conformer found in all the members of a group of isomorphous crystals?

(ii) If so, then which TATM conformers occur in the various groups of isomorphous inclusion complexes and what is the range of TATM molecular structural variation (specifically torsion angles) found within the several groups?

(iii) What is the range of structural variation when there is more than one TATM molecule in the crystallographic asymmetric unit?

(iv) What are the energy differences among the various TATM conformers and which molecular structural factors account for these energy differences?

The answers to (i), (ii) and (iii) are obtained from an analysis of the published crystallographic results. Answers to question (iv) from 'molecular mechanics' computations are clearly essential for further understanding of TATM systems, but are not considered here as they are preferably tackled separately in the broader context of the structures taken up by flexile tripod molecules. Potentially one can also hope to study how the nature of the guest influences the conformation taken up by the host, but this is not generally possible at present because the guests are disordered in most of the crystal structures that have been determined. Repetition and extension of the crystal structure determinations at low temperatures should be rewarding.

Obviously the general validity of the conclusions drawn from the limited sample currently available will depend on how representative this sample is of the whole population. Here we wish to draw attention to what can already be extracted from the available information.

Table 1. *Crystalline {(TATM)$_x$.[guest]$_y$} inclusion complexes, classified according to the host–guest ratio and chemical nature of the guest*

TATM host–guest inclusion complexes have so far been reported in the literature with 43 different types of guest; five different types of crystal structures have been reported, with nine different guests. Asterisks denote complexes for which crystal structures have been reported.

| Host–guest ratios | | |
|---|---|---|
| 1:1 | 2:1 | 3:1 |
| Cyclononanone[c]* | $C_6H_5R$ with $R$ = F, Cl, Br, I, $CH_3$, $C_2H_5$, $CH(CH_3)_2$ (cumene), *o*-, *m*- and *p*-xylene, mesitylene | *tert*-Butylbenzene, *n*-hexane[d]* |
| | Benzene,[a]* naphthalene | |
| | Cyclohexane (two polymorphs*), | |
| | Cycloheptane,[b]* cyclooctane,[b]* cyclooctene | |
| | Methanol, ethanol[a]* *iso*-propanol | |
| | *sec*-butanol, *tert*-butanol, *n*-decanol | |
| | Acetone, methyl ethyl ketone, methyl phenyl ketone | |
| | Methyl phenyl ether | |
| | Dichloromethane, chloroform, $CCl_4$* | |
| | Pyridine,[a] piperidine, triethylamine | |
| | Ethyl acetate,* acetonitrile, acetic acid, nitromethane, dimethyl sulfoxide, $HCON(CH_3)_2$, decalin | |

References: (*a*) Yakubov, Sudarushkin, Belenkii & Gold'farb (1973); (*b*) Pang & Brisse (1994*b*); (*c*) Pang & Brisse (1994*a*); (*d*) Roos & Dillen (1992); the other complexes were reported by Bin Din & Meth-Cohn (1977).

## 2. Tris(5-acetyl-3-thienyl)methane (TATM) – chemical background

Tris(5-acetyl-3-thienyl)methane [$C_{19}H_{16}O_3S_3$; TATM; indexed in *Chem. Abstr.* under 'ethanone, 1,1′,1″-(methylidyntri-4,2-thiophendiyl)tris'] was first synthesized by Yakubov, Sudarushkin, Belenkii & Gold'farb

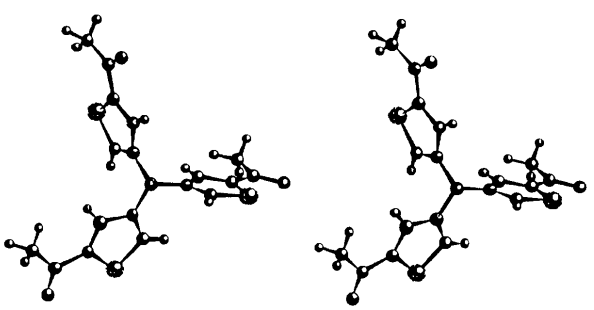


Fig. 1. Stereodiagram model of the TATM molecule as found in its $CCl_4$ complex (only molecule *A* of the two independent molecules in the asymmetric unit is shown). The view is along the methane CH bond, the hydrogen being behind the plane of the page. The hydrogens have been inserted in calculated positions [*d*(CH) = 1.1 Å]. Two oxygens (of C=O groups) are *syn* to S and one *anti*.

Table 2. *Crystallographic data (Å, °, Å$^3$) for some inclusion complexes of TATM*

The compositions are expressed as {TATM. [*n*(guest)]}. Triclinic cells have been reduced. E.s.d.'s of cell lengths are ~0.002–0.006 Å, of angles ~0.01–0.04° and of cell volumes ~0.4–2 Å$^3$. Analyses were at room temperature unless stated otherwise.

| *n* (guest) | *a* | *b* | *c* | $\alpha$ | $\beta$ | $\gamma$ | Cell volume | *Z* |
|---|---|---|---|---|---|---|---|---|
| Group I: channel axis along [100] | | | | | | | | |
| 0.5(ethyl acetate)[a] | 8.229 | 11.229 | 12.329 | 99.05 | 106.43 | 98.42 | 1057 (1) | 2 |
| Group II: channel axis along [100] | | | | | | | | |
| 0.5(ethanol)[b] | 8.335 | 10.372 | 12.488 | 81.49 | 71.26 | 84.95 | 1010 (1) | 2 |
| 0.5(cyclohexane), polymorph *A* at 220 K[c] | 8.622 | 10.194 | 12.795 | 79.09 | 72.74 | 84.89 | 1053.9 (4) | 2 |
| Group III: channel axis along [001] | | | | | | | | |
| 0.5(benzene)[d] | 11.538 | 13.560 | 14.197 | 89.68 | 76.60 | 75.50 | 2089 (1) | 4 |
| 0.5($CCl_4$)[e] | 11.638 | 13.684 | 14.235 | 88.90 | 77.46 | 78.77 | 2170 (1) | 4 |
| 0.5(cyclohexane), polymorph *B*[c] | 11.668 | 13.729 | 14.227 | 89.40 | 77.15 | 76.24 | 2157 (1) | 4 |
| 0.5(cycloheptane) at 220 K[c] | 11.721 | 13.734 | 14.177 | 89.22 | 76.84 | 76.01 | 2154 (2) | 4 |
| 0.5(cyclooctane) at 220 K[c] | 11.914 | 14.013 | 13.986 | 89.46 | 77.15 | 75.22 | 2198.4 (4) | 4 |
| Group IV: | | | | | | | | |
| 1/3(*n*-hexane)[f] | 12.647 | 12.694 | 20.604 | 85.89 | 74.31 | 86.36 | 3173 (1) | 6 |
| Group V: | | | | | | | | |
| Cyclononanone at 220 K[g] | 10.994 | 19.464 | 13.417 | 90 | 109.4 | 90 | 2708.1 (8) | 4 |

(i) Space groups for the ethanol and ethyl acetate complexes were originally given as $P1$, but Marsh (1994) has corrected these to $P\bar{1}$; (ii) the complexes of Groups I and II are not isomorphous, however, there are resemblances between the two structure types and both have channels along [100]; (iii) the space group for the cyclononanone complex is $P2_1/c$. References: (*a*) van Rooyen & Roos (1991*a*); (*b*) Dillen & Roos (1992); (*c*) Pang & Brisse (1994*b*); (*d*) van Rooyen & Roos (1991*b*); Pang, Hynes & Whitehead (1994); (*f*) Roos & Dillen (1992); (*g*) Pang & Brisse (1994*a*).

(1973); these authors reported that the sublimed compound was an amorphous solid (m.p. 50–58°C), which gave crystalline 2:1 adducts with benzene, ethanol and pyridine. An impressive list of inclusion complexes is due to Bin Din & Meth-Cohn (1977), who extended the earlier work and noted that 'a systematic study has so far not revealed a solvent which is *not* incorporated' (my italics). Other workers have reported a few more complexes and these are all collected together, classified in terms of the host:guest ratio and chemical nature of the guest, in Table 1. Only binary TATM systems are considered here.

## 3. Analysis of experimental results from the literature

### 3.1. *Crystallography of the inclusion complexes of TATM*

The currently available crystallographic data are summarized in Table 2. We emphasize, following Marsh (1989) and many other authors, that it is essential that comparisons of triclinic cells be made on the basis of the reduced cells (an introduction to cell reduction is given by Macicek & Yordanov, 1992). The complexes can be divided into a number of groups on the basis of the cell dimensions and further detail is obtained from the full structure analyses.

The terms 'clathrate', 'cage' and 'channel' have been used to describe different varieties of these complexes. Structure analyses of the ethyl acetate complex (Group I) by van Rooyen & Roos (1991*a*) and of the polymorph *A* and polymorph *B* complexes of cyclohexane (representatives of our Groups II and III) by Pang & Brisse (1994*b*) show clearly that these are all channel complexes, with the linear channel axis of Groups I and II along the shortest cell dimension and the zigzag channel axis of Group III along the longest. The cyclohexane guest of the Group II (polymorph *A*) complex is located about a centre of symmetry and is ordered; the cyclohexane of the Group III (polymorph *B*) complex is at a general position and takes up three orientations with occupations in a 40:35:25 ratio. The cycloheptane and cyclooctane molecules of the Group III complexes take up two orientations in an approximate 2:1 ratio. Further distinctions can sometimes be made within a group, for example, the benzene and $CCl_4$ complexes are both in Group III, but the benzene molecules are ordered (only the second example of ordering of guests among the published crystal structures), while the $CCl_4$ molecules have partially disordered arrangements in which one Cl atom is ordered and the three remaining Cl atoms are trigonally disordered in two orientations with a 2:1 ratio. It is perhaps not surprising that the three alicyclic guests cyclohexane (Group III – polymorph *B*), cycloheptane and cyclooctane form isomorphous crystals, but the common features causing the benzene and $CCl_4$ complexes to crystallize in this structure type are not clear.

The triclinic hexane complex (Group IV) and the monoclinic cyclononanone complex (Group V) are channel inclusion complexes. The first has the channel axis along [111] (possible disorder not discussed) and the second along [100] (guest disordered over two orientations in a 75:25 ratio).

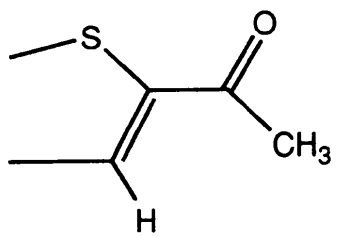
### 3.2. *The structures taken up by the TATM molecule in the various crystallographic structure types*

The crystals included in Table 2 are all racemic [note the correction by Marsh (1994) of some space groups originally reported as $P1$ to $P\bar{1}$] and so absolute optical configurations are not required; nevertheless, meaningful comparison of the geometrical structures taken up by TATM in its various inclusion complexes requires comparison of conformers of the same optical configuration. The enantiomer chosen (arbitrarily) for intercomparison has been drawn (see Fig. 3) so that H1 (attached to C1) is below the plane of the page and the apex C1 of the trigonal pyramid C1C2C8C14 points away from the observer. The torsion angles $\tau_1$, $\tau_2$ and $\tau_3$ are defined (again arbitarily, but consistently) as $\tau_1$ = (H1C1C2C3; C3 linked to S1) and correspondingly for $\tau_2$ and $\tau_3$. The TATM molecule will be achiral only for some special values of the torsion angles $\tau_1$, $\tau_2$ and $\tau_3$; as these were not found, the TATM molecule is chiral. The torsion angle with the smallest absolute value has been taken as $\tau_1$ (it is found that $|\tau_1| \simeq 0°$) and rings 2 and 3 follow in clockwise sequence with the enantiomer oriented as described above. Further distinction among conformers depends on whether the carbonyl oxygens are *syn* (designated *S*) or *anti* (designated *A*) to sulfur in the rings; experimentally it is found that the torsion angles S1—C4—C6—O1 and analogues ($\tau_4$, $\tau_5$ and $\tau_6$) are either ~0 (*syn*) or 180° (*anti*). The values extracted from the results of the crystal structure analyses are summarized in Table 3 and a number of conclusions follow:

(i) Three conformations are found for the TATM molecule, the differences among them being discussed in more detail here. (*a*) Conformation 1, with $\tau_1 \simeq 0$, $\tau_2 \simeq 105$, $\tau_3 \simeq 160°$ and *SSS* for the three acetyl groups. The guests are ethyl acetate, ethanol, cyclohexane (polymorph *A* in Group II) and *n*-hexane. (*b*) Conformation 2, with $\tau_1 \simeq 0$, $\tau_2 \simeq 130$, $\tau_3 \simeq 150°$ and *SSA* for the three acetyl groups. The guests are benzene, $CCl_4$, cyclohexane (polymorph *B* in Group III), cycloheptane and cyclooctane. (*c*) Conformation 3, with $\tau_1 \simeq 0$, $\tau_2 \simeq 100$, $\tau_3 \simeq -15°$ and *SSS* for the three acetyl groups. The guest is cyclononanone.

(ii) When there is more than one molecule in the asymmetric unit (*i.e.* in crystallographic groups III and IV), then analogous torsion angles in the crystallographically independent molecules do not differ by more than ~10°.

(iii) Analogous torsion angles within a group of isomorphous structures (*i.e.* in crystallographic groups II and III) do not differ by more than ~10°.




A search of the Cambridge Crystallographic Data File [Version 5.09, April, 1995 (Allen *et al.*, 1991)] for the fragment produced six hits (apart from those for

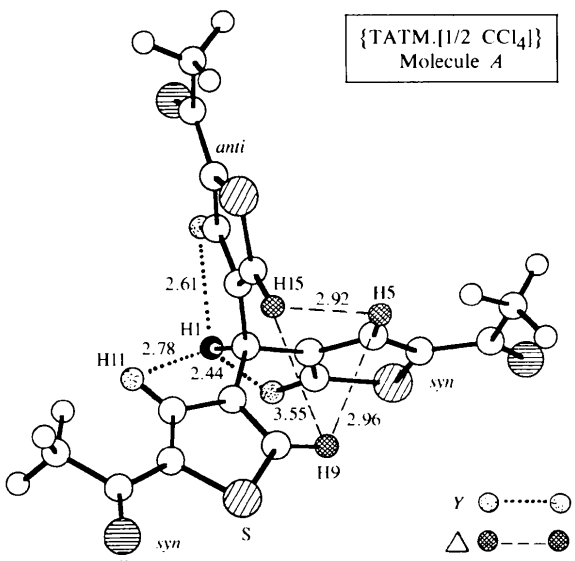



Fig. 2. Ball-and-stick model of TATM molecule as found in its $CCl_4$ complex (only molecule *A* of the two independent molecules in the asymmetric unit is shown). The view is approximately along the methane CH bond, the hydrogen being behind the plane of the page. The *Y*-type and Δ-type H···H distances (Å) shown are also entered into Table 4.

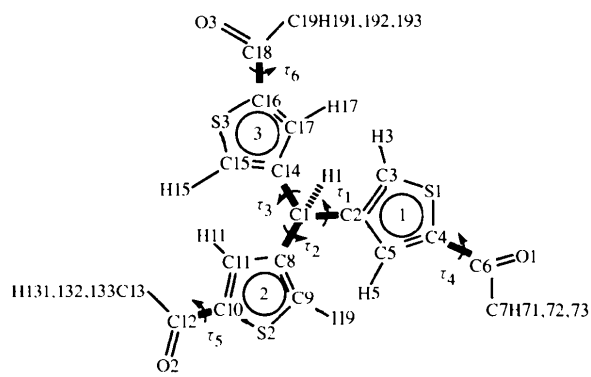



Fig. 3. Formal representation of the TATM molecule, with those bonds emphasized about which torsion can occur. H1 attached to C1 is below the plane of the page and the apex C1 of the trigonal pyramid C1C2C8C14 is pointing away from the observer. The torsion angles S1—C4—C6—O1 and analogues are all ~0 or 180°. The positions of ring hydrogens have been distorted for convenience in drawing. The particular conformation illustrated here and in Figs. 1 and 2 is for molecule *A* in the {TATM.[1/2$CCl_4$]} complex. The line formula of the figure is somewhat misleading as the molecule is not planar, but has the tripod shape shown in Fig. 1. The torsion of five-membered rings about the (H)—C—C bonds ($\tau_1$, $\tau_2$ and $\tau_3$) is one type of conformational variable and the second depends on whether the carbonyl oxygens are *syn* or *anti* to S in the rings ($\tau_4$, $\tau_5$ and $\tau_6$).

Table 3. *Torsion angles (°) in the TATM host molecule as found in some of its inclusion complexes*

The compositions are expressed as {TATM.[*n*(guest)]}. Literature references as in Table 2.

| *n*(guest) | $\tau_1$ | $\tau_2$ | $\tau_3$ | $\tau_4$ | $\tau_5$ | $\tau_6$ | Conformation of carbonyl with respect to ring *S* |
|---|---|---|---|---|---|---|---|
| Group I: channel axis along [100] | | | | | | | |
| 0.5(ethyl acetate) | 7.0 | 102.9 | 157.0 | −2.2 | −1.1 | 0.6 | *SSS* |
| Group II: channel axis along [100] | | | | | | | |
| 0.5(ethanol) | −3.2 | 110.7 | 160.0 | −3.9 | −1.8 | −0.9 | *SSS* |
| 0.5(cyclohexane, polymorph *A* at 220 K | −12.6 | 109.4 | 162.8 | −2.7 | −4.3 | −1.9 | *SSS* |
| Group III: channel axis along [001] | | | | | | | |
| 0.5(benzene), molecule *A* | −16.2 | 126.2 | 148.2 | −3.5 | −1.3 | 178.9 | *SSA* |
| Molecule *B* | −10.1 | 124.2 | 148.7 | −2.6 | −3.9 | 183.0 | *SSA* |
| 0.5($CCl_4$), molecule *A* | −20.0 | 129.0 | 148.3 | −4.9 | −2.0 | 180.0 | *SSA* |
| Molecule *B* | −10.3 | 131.6 | 156.7 | −0.7 | 0.0 | 181.9 | *SSA* |
| 0.5(cyclohexane), polymorph *B* | | | | | | | |
| Molecule *A* | −11.1 | 129.5 | 151.0 | −2.2 | −1.3 | 180.8 | *SSA* |
| Molecule *B* | −18.7 | 128.6 | 149.4 | −4.8 | 0.4 | 178.6 | *SSA* |
| 0.5(cycloheptane) at 220 K | | | | | | | |
| Molecule *A* | −12.2 | 130.4 | 150.2 | −4.8 | −0.3 | 182.2 | *SSA* |
| Molecule *B* | −17.1 | 129.6 | 148.0 | −4.0 | 1.9 | 178.0 | *SSA* |
| 0.5(cyclooctane) at 220 K | | | | | | | |
| Molecule *A* | −16.6 | 130.1 | 146.5 | −3.4 | 2.2 | 179.9 | *SSA* |
| Molecule *B* | −13.9 | 132.2 | 151.9 | −4.2 | 0.1 | 182.2 | *SSA* |
| Group IV: | | | | | | | |
| 1/3(*n*-hexane), molecule *A* | 2.4 | 108.2 | 156.8 | −3.0 | −2.1 | 0.7 | *SSS* |
| Molecule *B* | 0.6 | 110.1 | 157.6 | −0.3 | −1.5 | −4.0 | *SSS* |
| Molecule *C* | 1.6 | 110.5 | 155.4 | −1.1 | −1.5 | −1.5 | *SSS* |
| Group V: | | | | | | | |
| Cyclononanone at 220 K | −7.3 | 101.8 | −15.2 | 0.8 | −10.3 | −4.3 | *SSS* |

the TATM complexes), five for various 4-substituted 5-acetyl-2-(*N*,*N*-disubstituted-amino)thiazoles [including one for a trifluoroacetyl derivative (Caldwell, Meakins, Jones, Kidd & Prout, 1987)] and one for 4-acetyl-2-dicyanomethylene-1,3–dithiole (Komarova, Yufit, Struchkov & Drozd, 1990); three had *syn* sterochemistry and three *anti*. Thus, the *syn* and *anti* conformations of carbonyl O with respect to S appear, from the statistics of occurrence, to be of approximately equal energy, but we do not know what factors govern the appearance of one or other conformation in a particular molecule. This analysis suggests that there are two factors determining the *overall* conformation of the TATM molecule:

(i) The values of the ring torsion angles $\tau_1$, $\tau_2$ and $\tau_3$. This is presumably the major factor affecting the energies of the various conformations. We suggest that the sets of values $\tau_1 \simeq 0$, $\tau_2 \simeq 105$, $\tau_3 \simeq 160°$ and $\tau_1 \simeq 0$, $\tau_2 \simeq 130$, $\tau_3 \simeq 150°$ both belong in the same well of the map of potential energy as a function of $\tau_2$ and $\tau_3$, and in fact refer to one set of ring conformations, from which conformation 3, with $\tau_1 \simeq 0$, $\tau_2 \simeq 100$, $\tau_3 \simeq -15°$, is separated by a substantial potential barrier. We therefore use conformation 1/2 (with either *SSS* or *SSA* appended) instead of the separate denotations used above for conformations 1 and 2.

(ii) The values of the acetyl group torsion angles $\tau_4$, $\tau_5$ and $\tau_6$. Here the evidence suggests that *syn* and *anti* have similar energies and so the combinations *SSS*, *SSA*, *SAS*, *ASS*, *AAA*, *AAS*, *ASA* and *SAA* should be equally frequent. Presently available evidence shows the occurrence of only *SSS* and *SSA*, so either the present sample is unrepresentative or there are other factors, as yet unknown, playing a role.

Thus, we conclude, as a working hypothesis and for simplicity, that there are only three different *overall* conformations of TATM – conformation 1/2–*SSS*, conformation 1/2–*SSA* and conformation 3–*SSS*.

### 3.3. *Steric factors governing the conformations of TATM*

There are two different types of non-bonded H···H interaction which are possibly important in determining the ring conformations in TATM [note that hydrogens have been inserted at calculated positions, with *d*(C—H) = 1.1 Å)]. The first type is between the methane hydrogen H1 and the ring hydrogens H3, H11 and H17 (using the numbering and conformation 1/2 of Fig. 3 and associated diagrams); this is termed the *Y* interaction. The second type is the pairwise interaction between the ring hydrogens H5, H9 and H15; this is termed the $\Delta$ interaction (Fig. 2). The values of the H···H distances are given in Table 4 for one example of each of the three conformational types. It had been expected that H···H repulsions would determine the ring torsion angles, *i.e.* hydrogens would not approach one another more closely than, say, 2.4 Å [note that there is some uncertainty about the appropriate value of the van der Waals diameter of hydrogen as H···H distances shorter than 2.4 Å are often found, for example, the values of 1.98 Å in 18-annulene (Gorter, Rutten-

Table 4. *Values of the H···H distances (Å) found in examples of the three conformational types – conformation 1/2–SSS, conformation 1/2–SSA and conformation 3–SSS*

| Example (guest and overall conformation) | *Y* interactions | | *Δ* interactions | | | |
|---|---|---|---|---|---|---|
| | H1···H3 | H1···H11 | H1···H17 | H5···H9 | H9···H15 | H5···H15 |
| $1/2CCl_4$ (A)<br>Conformation 1/2–*SSS* | 2.44 | 2.78 | 2.61 | 2.96 | 3.55 | 2.92 |
| 1/2 Ethyl acetate<br>Conformation 1/2–*SSA* | 2.44 | 3.03 | 2.51 | 2.87 | 4.16 | 2.74 |
| | H1···H3 | H1···H9 | H1···H17 | H5···H11 | H11···H15 | H5···H15 |
| Cyclononanone<br>Conformation 3–*SSS* | 2.46 | 2.43 | 3.05 | 2.39 | 3.25 | 4.16 |

Keulemans, Krever, Romers & Cruickshank, 1995) and 1.92 Å in kekulene (Staab, Diederich, Krieger & Schweitzer, 1983)]. The limitation of the H···H approach distance appears to hold for conformation 3–*SSS*, but not for conformations 1/2–*SSS* and 1/2–*SSA*. As mentioned above, we do not intend to discuss this (molecular mechanics) aspect of the molecular structure further in this paper.

## 4. Discussion

Until this point our considerations have been based on experimental findings – the crystal structure determinations and the molecular geometries extracted from them. The discussion following is more speculative and is based on the assumptions that the available sample of information is representative of the whole population and that further study, although yielding more detail and examples, will not indicate a situation radically different from that known now. At the least, the discussion provides a strong argument for extension of the information base; at best, it delineates the questions to be asked and possible answers.

### 4.1. *Formation of the inclusion complexes*

The three different *overall* conformations of TATM inferred above will occur in TATM solutions in relative proportions given by the Boltzmann distribution; these proportions will depend, to a first approximation, on temperature but not on the nature of the solvent. In other words, we are assuming the solution to be ideal at higher temperatures, but this no longer holds as the solution becomes supersaturated on cooling and the inclusion complex begins to crystallize. For example, if the solvent is benzene then {TATM.[1/2(benzene)]} will crystallize and the solution will become depleted in molecules with conformation 1/2–*SSA*; the Boltzmann distribution will be continuously re-established by conversion of molecules with conformations 1/2–*SSS* and 3–*SSS* into conformation 1/2–*SSA* and this process will continue until the appropriate amount (determined by its solubility) of crystalline inclusion complex has been formed. What happens with cyclohexane as solvent? Here we presume that nuclei of cyclohexane with the differently shaped conformers, conformation 1/2–*SSS* and conformation 1/2–*SSA*, will be formed and these will give rise to the two polymorphic forms of {TATM.[$1/2C_6H_{12}$]}, designated above as polymorph *A* of Group II and polymorph *B* of Group III. Pang & Brisse (1994*b*) report that polymorph *B* was obtained by relatively rapid cooling ($1\ K\ h^{-1}$) and *A* by slow cooling ($5\ K\ d^{-1}$); this suggests that *B* is metastable with respect to *A*, in accordance with the respective volumes per formula unit ($B$ = 539, $A$ = 527 $Å^3$). Presumably Ostwald's rule of successive reactions (*e.g.* Findlay, Campbell & Smith, 1951) applies to this system, but this has not been explicitly stated.

In terms of this description we can divide the overall process of formation of a crystalline inclusion complex into three stages:

(i) Selection of the appropriate TATM conformer from the ensemble of conformers, requiring recognition between solvent molecule and the appropriate TATM conformer, *i.e.* the determining factor is the host–guest interaction.

(ii) Formation of nuclei from the TATM–solvent aggregates, requiring predominantly host conformer–host conformer recognition.

(iii) Growth of the nuclei to form crystals.

Thus, the formation of crystalline inclusion complexes containing TATM molecules of different conformations (depending on the solvent partner) does not present any conceptual difficulties. This description, with the guest (solvent) molecule plucking out the appropriate TATM conformer from the Boltzmann distribution, is the converse of that given when a rigid host is used in selectivity experiments with a solution of, or containing, a mixture of guests.

This description also provides a possible explanation for the occurrence of an amorphous sublimate; the presence of more than one conformer in the condensing sublimate prevents crystallization.

### 4.2. *Previous examples*

The host–guest complexes of *E,E*-1-(*p*-dimethylaminophenyl)-5-(*o*-hydroxyphenyl)penta-1,4-dien-3-one [the Heilbron complexes (Herbstein, Kapon, Reisner & Rubin, 1984)] are an example of selection by the guest of conformationally distinct states of the host from solution, as shown by the fact that the host molecules have the *s-trans*, *trans* conformation

in some complexes and the *s-cis*, *trans* in others; however, the number of complexes of known crystal structure is limited and generalization is not yet possible. Another example, of somewhat different character, is given by pentaspiro[2,4,2,4,2,4,2,4,2,4]pentatriconta-4,6,11,13,18,20,25,27,32,34-decayne in its 1:1 host–guest complexes with $CH_2Cl_2$ and $CCl_4$ (de Meijere *et al.*, 1995). The crystals of the first of these are monoclinic, space group $C2/c$ ($Z = 4$), and the host molecules are planar. The crystals of the second of these are tetragonal, space group $P4_2/n$ ($Z = 8$), and the host molecules have an envelope conformation (torsion angles around the central ring from the flap: 25.0, 17.0, 2.1, 13.9, 25.2°). The similarity to the TATM examples stems from the different host conformations found in distinctly different host–guest crystals with different guests. The difference is that these host conformations are unlikely to be separated by an appreciable potential barrier, but lie together within a large potential well with an almost flat profile of energy *versus* flap angle.

### 4.3. *Possible hosts analogous to TATM*

TATM is an example of a tripod molecule. Triphenylmethane and analogues are also tripod molecules and have been found by Hartley & Thomas (1906) to form complexes with benzene, thiophene, pyrrole and aniline. These complexes are isomorphous (trigonal, space group $R\bar{3}$, $a \simeq 11$, $c \simeq 27$ Å, $Z = 6$) and {triphenylmethane.[benzene]} has been shown by Allemand & Gerdil (1975) to have a clathrate structure, with the guest molecule in a cavity surrounded by six host molecules; it seems reasonable to infer, on the basis of the TATM results, that the ring conformations are similar in all four complexes. Triphenylcarbinol and triphenylchloromethane (trityl chloride) have been reported by Norris, Rooney, Murphy & Dodge (1916) to form *ca* 1:1 complexes with acetone and $CCl_4$, but structures of the complexes do not appear to have been determined. Triphenylmethane would be expected to have less conformational freedom than TATM because of the greater bulk of six- compared with five-membered rings.

One way of achieving greater conformational freedom in TATM could be by increasing the distances between adjacent five-membered rings. This could be effected conceptually (without considering synthetic problems) by inserting —C≡C— spacers between methane carbon and five-membered rings. Alternatively, methane carbon could be replaced by other Group IV elements, as has been done for the neat compounds $Ph_3MOH$ [$M$ = C (Ferguson, Gallagher, Glidewell, Low & Scrimgeour, 1992), Si (Puff, Braun & Reuter, 1991) and Ge (Ferguson *et al.*, 1992)], but the possible formation of complexes does not yet appear to have been studied.

A referee has suggested that crystallization from a chiral solvent could lead to formation of chiral inclusion complexes. It would also be interesting to see if TATM could act as an acceptor for guests with hydrogen-bonding capabilities.

## 5. Conclusions

Our analysis of published crystallographic data shows that in a particular group of isomorphous host–guest inclusion complexes (with different guests) the TATM molecules all have the same conformation, with numerical values of ring torsion angles not differing by more than ~10° within the group of crystals. The same holds for comparisons between different host molecules in a particular inclusion complex when there is more than one molecule in the crystallographic asymmetric unit. This could be taken to imply that there is a 1:1 correlation between *ring* conformations and crystal structure, but this is an over-simplification. The situation is complicated by the fact that while the ring conformations are the primary factor in determining the energy of the TATM molecule, the conformations of the three acetyl groups (*syn* or *anti* relation of carbonyl oxygen to ring sulfur) are an essential component in determining the overall molecular shape, which is more important than ring conformation in determining the crystal structure of the inclusion complex. Thus, the correlation is between overall molecular conformation (*i.e.* the combination of the conformations of rings and acetyl groups) and crystal structure.

The *syn* and *anti* conformations of the acetyl groups appear to have similar energies from the statistics of their occurrence, but only two of the possible combinations of ring conformation–acetyl group conformation have so far been encountered. It is not clear whether this is because the available sample is unrepresentative of the population as a whole or because other factors contributing to overall molecular energy have not yet been recognized.

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