

Different packing in three polymorphs of 2,4,6-trimethoxy-1,3,5-triazine

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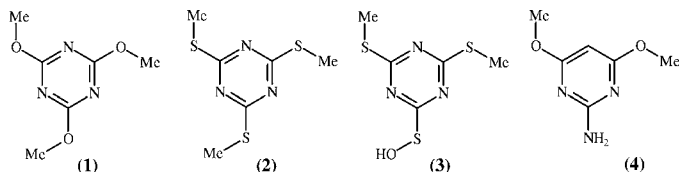
2,4,6-Trimethoxy-1,3,5-triazine was found to exhibit three different polymorphs. The α -polymorph undergoes reversible phase transformation to the β -polymorph at 340 K with an enthalpy of 3.9 kJ mol⁻¹. The heat of fusion of the β -polymorph at 404 K is 18.1 kJ mol⁻¹. The low-temperature phase (α -polymorph) crystallizes in the orthorhombic space group *Pnma*. The high-temperature phase (β -polymorph) can be obtained from the melt and crystallizes in the monoclinic space group *P2*₁. The γ -polymorph is obtained by crystallization from a 1:1 mixture of methanol and methylene chloride from hydrolyzed 2,4-dimethoxy-6-oxybenzophenone-1,3,5-triazine. The γ -polymorph melts at 409 K with an enthalpy of 11.4 kJ mol⁻¹. The γ -polymorph crystallizes in the trigonal space group *R3c*. The molecules occupy a crystallographic threefold axis. Molecules of 2,4,6-trimethoxy-1,3,5-triazine are planar in all three polymorphs. The major difference between the three polymorphs is the mode of packing of the molecules in the crystal.

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1. Introduction

According to McCrone (1965), 'a polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state'. McCrone (1965) also states his own opinion regarding the occurrence of polymorphism, that '...every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound'. An example that justifies this statement is provided in this publication. The crystal structure of the first known polymorph (the α -polymorph) of 2,4,6-trimethoxy-1,3,5-triazine (1) was determined by Głowska & Iwanicka (1989*a,b*) and later refined by Krygowski *et al.* (1997). Later, the crystal structure of a second polymorph of 2,4,6-trimethoxy-1,3,5-triazine was published (Handelsmann-Benory *et al.*, 2000). This polymorph was detected when the thermal behavior of the compound was studied by differential scanning calorimetry (DSC) in connection with the investigation of compounds that might undergo methyl rearrangement in the solid state. Crystals of the new polymorph (β -polymorph) were obtained from the melt. Three years later we have also discovered a third polymorph (γ -polymorph) as a result of an unsuccessful synthesis involving the hydrolysis of 2,4-dimethoxy-6-(3-formylphenoxy)-1,3,5-triazine. Crystals of the γ -polymorph were obtained from a 1:1 mixture of methanol and methylene chloride by slow evaporation of the solvent at room temperature.

Aromatic and other planar rings are usually packed in either stacks or herringbone motifs. Therefore, polymorphism is quite a common feature of this group of compounds. The α -polymorph of 2,4,6-trimethoxy-1,3,5-triazine (1) (Główska & Iwanicka, 1989*a,b*) and 2,4,6-tris(methylthio)-1,3,5-triazine (2) (Greenberg *et al.*, 2000) both adopt the stacking mode. However, 4,6-dimethoxy-1,3,5-triazine-2-sulfenic acid (3) (Triplot *et al.*, 1993) and 2-amino-4,6-dimethoxypyrimidine (4) (Low *et al.*, 2002) adopt the herringbone packing motif.



The differences between the three polymorphs of 2,4,6-trimethoxy-1,3,5-triazine are described with regard to their molecular packing motifs in their unit cells.

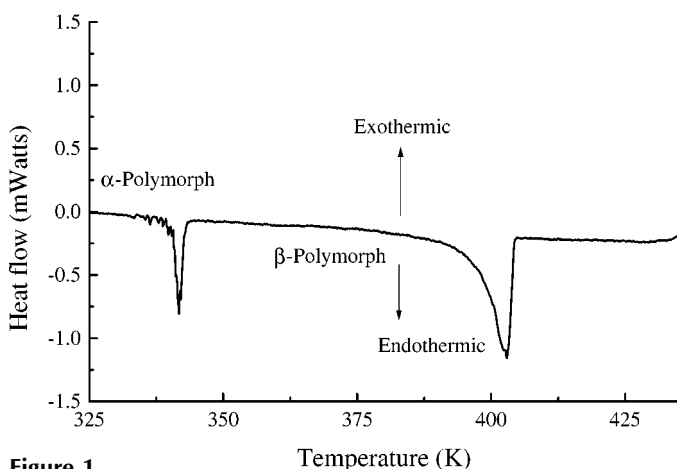


Figure 1
DSC thermograph of the α -polymorph, measured at a heating rate of 1° min^{-1} .

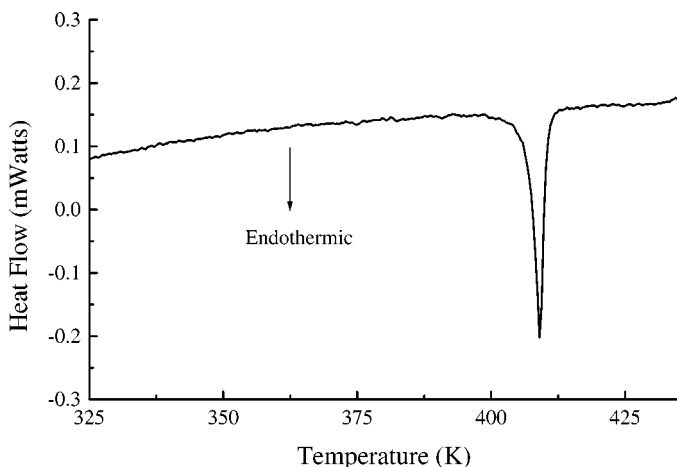


Figure 2
DSC thermograph of the γ -polymorph, measured at a heating rate of 5° min^{-1} .

Table 1
Experimental details.

Crystal data	
Chemical formula	$\text{C}_6\text{H}_9\text{N}_3\text{O}_3$
M_r	171.16
Cell setting, space group	Trigonal, $R3c$
a, b, c (Å)	14.027 (1), 14.027 (1), 7.088 (1)
α (°)	90.00
V (Å ³)	1207.8 (2)
Z	6
D_x (Mg m ⁻³)	1.412
Radiation type	Mo $K\alpha$
No. of reflections for cell parameters	488
θ range (°)	1.8–25.1
μ (mm ⁻¹)	0.12
Temperature (K)	293 (2)
Crystal form, color	Hexagonal rod, colorless
Crystal size (mm)	$0.31 \times 0.24 \times 0.15$
Data collection	
Diffractometer	Nonius KappaCCD
Data collection method	ω scans
Absorption correction	None
No. of measured, independent and observed reflections	439, 238, 204
Criterion for observed reflections	$I > 2\sigma(I)$
R_{int}	0.012
θ_{max} (°)	25.1
Range of h, k, l	$0 \Rightarrow h \Rightarrow 16$ $-13 \Rightarrow k \Rightarrow 0$ $-8 \Rightarrow l \Rightarrow 8$
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.032, 0.082, 1.12
No. of reflections	238
No. of parameters	40
H-atom treatment	Mixture of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0441P)^2 + 0.2582P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\text{max}}$	< 0.0001
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ (e Å ⁻³)	0.09, -0.09
Absolute structure	Flack (1983)
Flack parameter	0 (10)

Computer programs used: COLLECT (Nonius, 2001), DENZO SMN (Otwinowski & Minor, 1997), SHELXS97 (Sheldrick, 1997), SHELXL97 (Sheldrick, 1997), ORTEP3 (Farrugia, 1997).

2. Experimental

2,4,6-Trimethoxy-1,3,5-triazine was synthesized according to a known procedure (Paolini *et al.*, 1968). Crystals of the γ -polymorph of (1) were obtained while attempting to crystallize 2,4-dimethoxy-6-oxybenzophenone-1,3,5-triazine from a 1:1 mixture of methanol and methylene chloride by slow evaporation of the solvent at room temperature; m.p. 409 K, $^1\text{H NMR}$ (CDCl_3) δ 4.0 (9H, s). It turns out that 2,4-dimethoxy-6-oxybenzophenone-1,3,5-triazine hydrolyzes to 2,4,6-trimethoxy-1,3,5-triazine. This procedure was repeated and gave crystals of the same γ -polymorph.

The thermal behavior was studied using a Polymer Laboratory DSC-PL. The DSC thermograms of the α - and γ -polymorphs are shown in Figs. 1 and 2, respectively. NMR spectra were collected on Bruker AC200 and AC400 spectrometers.

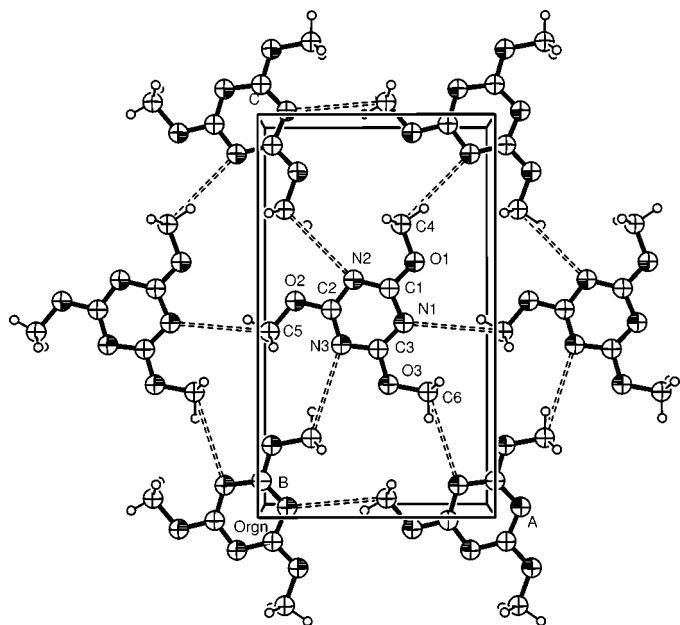


Figure 3
A layer of molecules in the α -polymorph (drawn with a fixed isotropic atomic displacement parameter for non-H atoms).

The X-ray diffraction intensities at 293 K were measured using a Nonius KappaCCD diffractometer. Crystallographic data, and details of the data collection and refinement, are given in Table 1. H atoms were located from difference-Fourier maps and refined using a riding model. The absolute structure could not be determined. Other relevant tables are given as supplementary material.¹ The packing motifs within a layer of each of the three polymorphs are shown in Figs. 3–5.

3. Results and discussion

3.1. Thermal behavior of the α - and the γ -polymorphs

Previously (Główka & Iwanicka, 1989*a,b*; Kaftory & Handelsmann-Benory, 1994; Krygowski *et al.*, 1997; Handelsmann-Benory *et al.*, 2000) it was found that the α -polymorph of 2,4,6-trimethoxy-1,3,5-triazine (1) crystallizes in the orthorhombic space group $Pnma$. Upon heating, the α -polymorph undergoes a phase transformation to the β -polymorph (monoclinic space group $P2_1$), adopting the herringbone packing mode.

The thermal behavior of the α -polymorph is shown by the DSC thermogram in Fig. 1 (Kaftory *et al.*, 2001). The first small endothermic peak, at 340 K, with a measured enthalpy of 3.9 kJ mol^{-1} , is assigned to the phase transition of the β -polymorph. The second endothermic peak, at 404 K ($\Delta H = 18.1 \text{ kJ mol}^{-1}$), is assigned to the melting of the β -polymorph.

The thermal behavior of the γ -polymorph is shown by the DSC thermogram given in Fig. 2. The γ -polymorph melts at 409 K ($\Delta H = 11.4 \text{ kJ mol}^{-1}$). In both cases, the compound

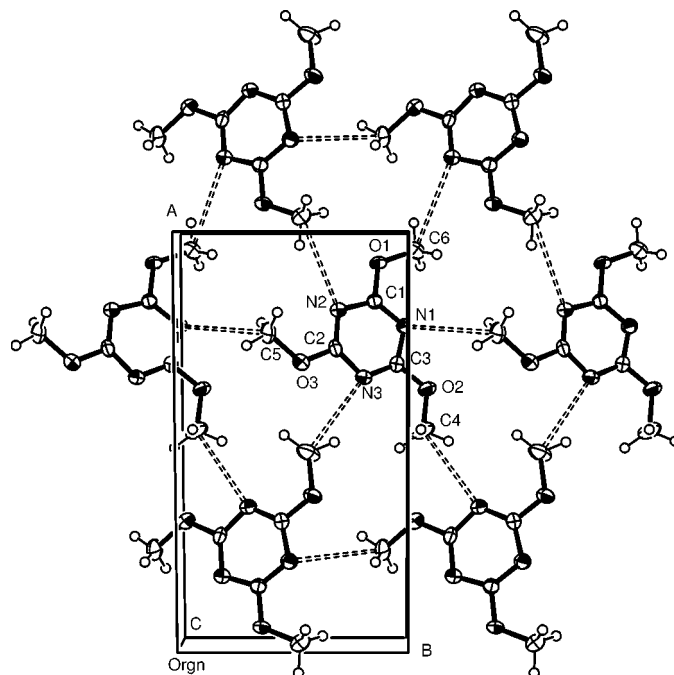


Figure 4
A layer of molecules in the β -polymorph. Ellipsoids of atomic displacement for the non-H atoms are drawn at the 50% probability level.

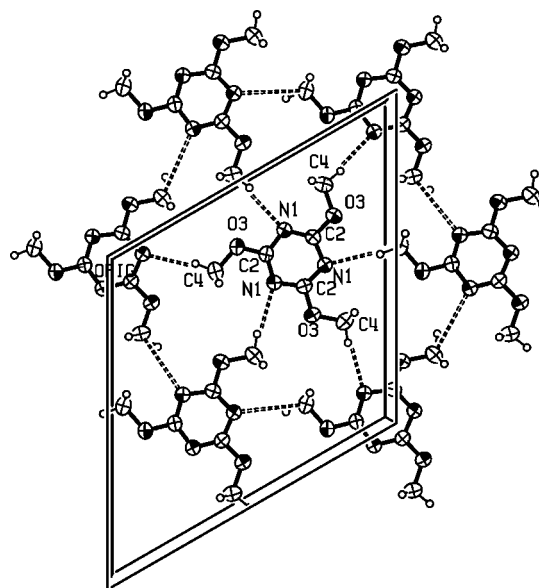


Figure 5
A 'layer' of molecules in the γ -polymorph (viewed down the c axis). Ellipsoids of atomic displacement for the non-H atoms are drawn at the 50% probability level.

sublimes very quickly and the NMR spectrum of the product suggests a mixture of 2,4,6-trimethoxy-1,3,5-triazine and 1,3,5-trimethyl 2,4,6-trioxohexahydro-1,3,5-triazine that can be a result of methyl rearrangements.

3.2. Comparison of the three polymorphs

3.2.1. Crystal data. The phase transition from the α - to the β -polymorph was believed to be irreversible (Kaftory *et al.*,

¹ Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK5003). Services for accessing these data are described at the back of the journal.

Table 2
Comparison of the cell constants of the three polymorphs (at 200 K).

Polymorphs	α	β	γ
a (Å)	8.474 (2)	13.779 (3)	14.027 (1)
b (Å)	6.719 (1)	7.488 (2)	14.027 (1)
c (Å)	14.409 (2)	3.825 (2)	7.088 (1)
α (°)	90	90	90
β (°)	90	98.84 (3)	90
γ (°)	90	90	120
Crystal system, space group	Orthorhombic, $Pnma$	Monoclinic, $P2_1$	Trigonal, $R3c$
Crystal form, color	Needle, colorless	Plate, colorless	Prism, colorless
Z	4	2	6
Volume (Å ³)	820.4 (2)	390.0 (2)	1207.8 (2)
D_x (Mg m ⁻³)	1.386	1.458	1.412

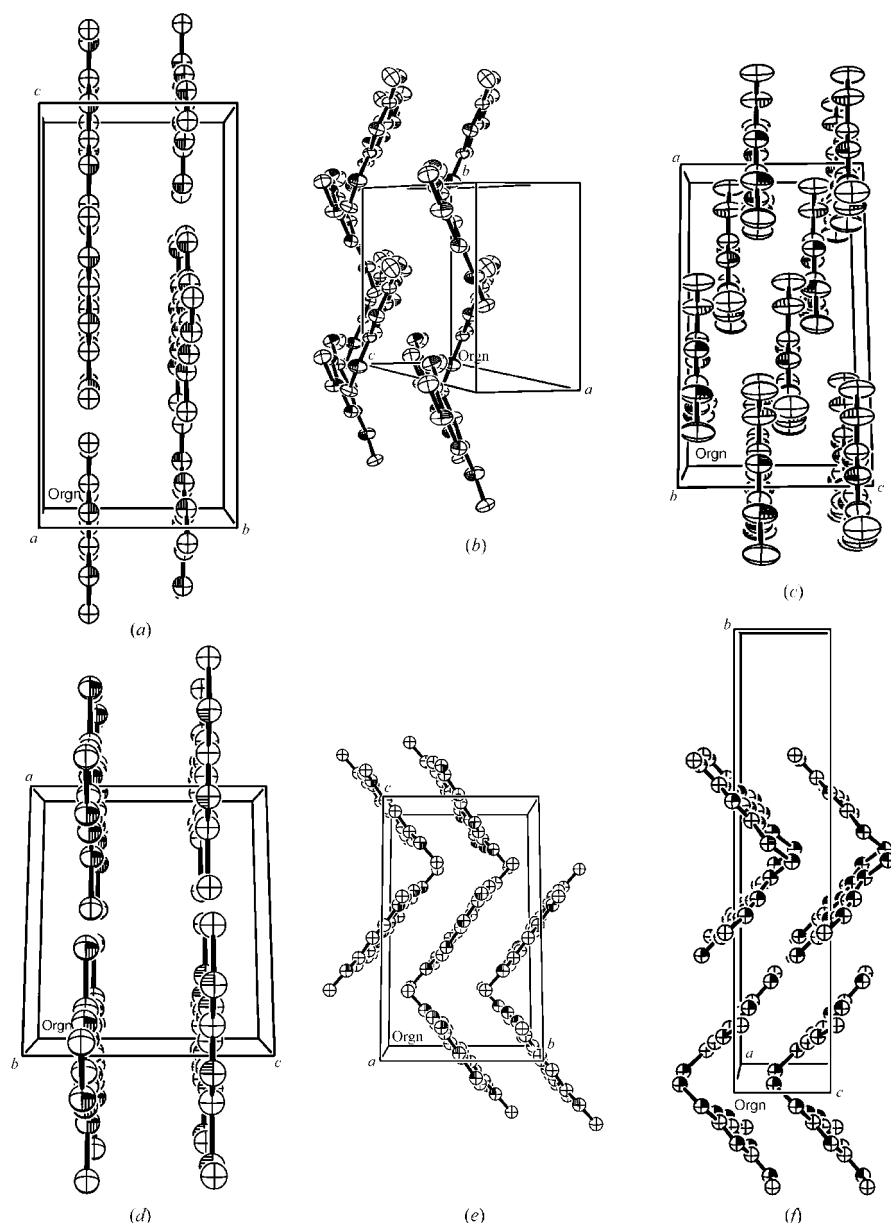


Figure 6
Side view of the α -, β - and γ -polymorphs of (1) (a–c), and (2), (3) and (4) (d–f). Ellipsoids of atomic displacement for the non-H atoms in the β - and γ -polymorphs are drawn at the 50% probability level.

2001); however, it was realized that upon standing at room temperature for a few hours the β -form transformed back to the α -form. Since the α - and β -polymorphs are stable over different ranges of temperature and pressure, these two polymorphs are considered to be enantiotropic. The γ -polymorph is stable over the whole range of temperatures below the melting point and therefore is monotropic with respect to each of the other two polymorphs.

The existence or non-existence of a crystal is determined by the free energy and the energetic manifestation of the arguments of Kitaigorodskii (1961a,b) that the short distances between atoms of adjacent molecules determine the orientation of molecules in a crystal. Therefore, the most stable structure energetically is expected to have the most efficient packing (Bernstein, 2002, and references therein).

The most stable arrangement energetically of molecules in a crystal has the strongest interactions between molecules and hence the highest density. The best possible packing also corresponds to thermodynamic stability. A comparison of cell constants for the three polymorphs is shown in Table 2. These data show that the β -polymorph has the most favorable packing of molecules. From the ‘density rule’ (Burger & Ramberger, 1979) one can conclude that the β -polymorph is the most stable at 0 K. However, the spontaneous transformation of the β - to the α -polymorph suggests that in this case the ‘density rule’ is not obeyed. There are a few examples where the density rule does not hold, such as in resorcinol (Yoshino *et al.*, 1999) and hydroquinone (Naoki *et al.*, 1999). In both cases it was suggested that the formation and breaking of the hydrogen bonds are responsible for the anomaly. Another example is the polymorphism of Neotame studied by Dong *et al.* (2002). Two pairs of the four polymorphs are enantiotropic and one polymorph is monotropic to each of the other four. Also, in one of the pairs, the higher-temperature form is more dense than the low-temperature form.

3.2.2. Packing. A layer of molecules in the unit cell of each of the three polymorphs is shown in Figs. 3–5. The methoxy groups adopt a propeller conformation in all three polymorphs, which is different from the observed conformation in trime-

thoxybenzene (Stults, 1979). The crystal structure of the α -polymorph is made up of layers of planar molecules. The coplanar molecules within a layer form an infinite hexagonal close-packed pattern with short contacts between the methyl groups of one molecule and an N atom of a neighboring molecule, through weak hydrogen bonding ($\text{H}_2\text{CH}\cdots\text{N}$ distances range from 2.71 to 2.78 Å). The distances between the methyl C atoms and the nearest N atoms are 3.536, 3.553 and 3.587 Å, and the $\text{N}\cdots\text{C}-\text{O}$ angles are 118.6, 115.9 and 124.9°, respectively. The crystal structure of the β -polymorph shows that the molecules adopt the herringbone packing mode (Handelsmann-Benory *et al.*, 2000). The distances between the methyl C atoms and the nearest N atoms are 3.463 (6), 3.563 (6) and 3.844 (6) Å, and the $\text{N}\cdots\text{C}-\text{O}$ angles are 139.9 (4), 137.4 (4) and 135.3 (4)°, respectively ($\text{H}_2\text{CH}\cdots\text{N}$ distances range from 2.79 to 3.04 Å).

The γ -polymorph crystallizes in the trigonal space group $R3c$. The molecules occupy a crystallographic threefold axis. It should be noted that Główka & Iwanicka (1989*b*) pointed out that the unit cell of the α -polymorph may be transformed to an approximate trigonal space group by doubling the a axis and

doubling the diagonal of the ac plane. However, the transformation they have shown does not lead to the γ -polymorph.

The arrangement of the molecules within a 'layer', as shown in Figs. 3–5, is rather different. In the α - and β -polymorphs the central molecule is surrounded by six molecules, of which two have propellers of the same rotational sense and the other four adopt a propeller of opposite rotational sense. In the γ -polymorph the central molecule is surrounded by six molecules with the propeller conformation of opposite rotational sense. The molecules in the α -polymorph lie on crystallographic mirror planes 3.260 Å apart; therefore, Fig. 3 represents a genuine layer. The arrangement in a 'layer' of the γ -polymorph shown in Fig. 5 is somewhat misleading. It shows a projection of molecules down the c axis. The 'layer' consists of seven molecules, six of which surround the central molecule in such a way that three of them lie 1/6 of the c axis below and the other three 1/6 of the c axis above the central molecule. Therefore, the 'layer' of molecules shown in Fig. 5 has a thickness of approximately 2.4 Å and consists of three sub-layers.

Fig. 6 shows a side view of the unit-cell packing in 1–4. 2,4,6-

Tris(methylthio)-1,3,5-triazine (2) has a very similar packing to that of the α -polymorph. 4,6-Dimethoxy-1,3,5-triazine-2-sulfenic acid (3) and 2-amino-4,6-dimethoxypyrimidine (4), on the other hand, have a similar packing to that of the β -polymorph. The comparable geometric parameters in the γ -polymorph are $\text{N1}\cdots\text{C4}$ distances of 3.571 (5) and 3.995 (5) Å, and $\text{N1}\cdots\text{C4}-\text{O3}$ bond angles of 114.9 (3) and 119.5 (3)° ($\text{H}_2\text{CH}\cdots\text{N}$ distances are 2.71 Å).

The most striking difference between the three polymorphs is shown by the overlap diagrams of the molecules (Fig. 7). While in the α - and β -polymorphs the overlapping molecules have the same propeller rotational sense with respect to the conformation of the methoxy groups, the two overlapping molecules have opposite propeller rotational sense in the γ -polymorph.

The differences between the overlap diagrams can be expressed by four parameters: the relative rotation between the two six-membered rings, the distances between the centers of the rings, the perpendicular distance between the planes of the rings and the lateral shift of the two molecules given by the distances between the projected centers of the rings' mean plane. The relative rotations of the rings in the three polymorphs α , β ,

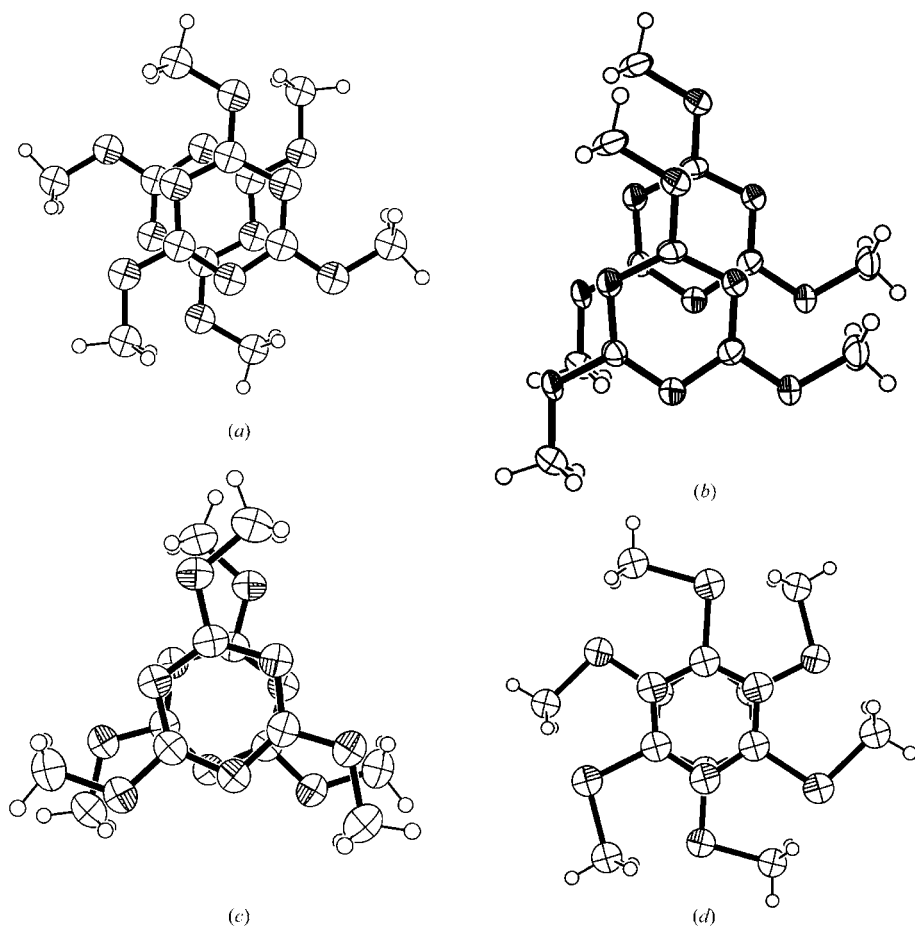


Figure 7

The molecular overlap diagrams of (a) the α -, (b) β -, (c) γ -polymorphs of (1) and (d) overlap diagram of (3). Ellipsoids of atomic displacement for the non-H atoms in the β - and γ -polymorphs are drawn at the 50% probability level.

and γ are 58.0, 0.0 and 20.6 (2)°, respectively.

The distances between the centers of the rings are 3.416, 3.825 and 3.544 (5) Å in the three polymorphs. The perpendicular distances are 3.392, 3.641 and 3.544 (5) Å in the three polymorphs. The shifts of the projection of the centers of the rings are 0.404, 1.170 and 0.0 Å in the three polymorphs. For comparison, the overlap diagram in the crystal structure of 2,4,6-tris(methylthio)-1,3,5-triazine is also shown in Fig. 7. The compound crystallizes in a hexagonal unit cell, space group $P6_3/m$. The overlap diagram shows that the mutual rotation between rings is 60°, with no relative shift of the molecular centers and an interplanar distance of 3.473 (5) Å. In view of the experience we had with the parent oxo compound we would guess that other polymorphs of the thio derivative can be detected if enough time is spent on such experiments.

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