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# Influence of polymorphism on the Young's modulus and yield stress of carbmazepine, sulfathiazole and sulfanilamide

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**Abstract**

The mechanical properties of Young's modulus and yield stress have been found to vary between polymorphic pairs depending on the structural differences in the packing motifs. Carbamazepine and sulfanilamide enantiotropic pairs show the largest differences in crystal structure and these differences are reflected in their mechanical properties. In the case of sulfathiazole the hydrogen bonding patterns and strength of the intermolecular interactions are similar in both forms and therefore the mechanical properties are similar.

*Keywords:* Young's modulus of elasticity; Yield stress; Polymorphism

## 1. Introduction

Polymorphism is the ability of an organic molecule to crystallise into more than one distinct crystal architecture and is associated with different packing arrangements of molecules. As a result polymorphs may differ substantially in terms of the physicochemical and mechanical properties both of which will affect their compaction behaviour in a punch and die.

Bernstein (1993) considered that the existence of polymorphs provides a unique opportunity to examine crystal structure-property relationships, because of the constancy of chemical composition, which limits variability amongst forms to structural factors. Few studies comparing the mechanical property behaviour of pharmaceutical polymorphs have been carried out. Of note is the work of Summers et al. (1977) who showed differences in the tensile strength of compacts for different polymorphs of sulfathiazole and barbital, and Ragnarsson and Sjogren (1984) and Kopp-Kubel et al. (1992) who measured the yield pressures of two forms of metoprolol tartrate and three forms of phenobarbital, respectively. In all cases it has always been found that the less stable polymorph is the more easily deformed, has the lower yield pressure and produces weaker compacts.

A critical mechanical property in powder compaction not previously studied with respect to polymorphism is Young's modulus, $E$, which de-

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Table 1
The molecular weight, $M_W$, true density ($\rho$, molar volume ($V$) of the various forms total ($\delta$), dispersive component ($\delta_d$), polar component ($\delta_\rho$) and hydrogen bonding component ($\delta_h$) solubility parameters respectively

| Drug | Form | $M_W$ (g mol$^{-1}$) | $\rho$ (g cm$^{-3}$) | $V$ (cm$^3$ mol$^{-1}$) | $\delta$ (MPa$^{1/2}$) | $\delta_d$ (MPa$^{1/2}$) | $\delta_\rho$ (MPa$^{1/2}$) | $\delta_h$ (MPa$^{1/2}$) |
|---|---|---|---|---|---|---|---|---|
| Carbamazepine | III | 236.26 | 1.34 | 175.92 | 24.7 | 21.5 | 7.8 | 9.4 |
| Carbamazepine | I | 236.26 | 1.24 | 191.30 | 23.7 | 20.7 | 7.5 | 9.0 |
| Sulfathiazole | III | 255.32 | 1.57 | 162.62 | 26.3 | 22.2 | 7.6 | 11.8 |
| Sulfathiazole | I | 255.32 | 1.50 | 170.21 | 25.7 | 21.7 | 7.4 | 11.5 |
| Sulfanilamide | $\beta$ | 171.21 | 1.51 | 113.75 | 27.4 | 21.6 | 9.1 | 14.2 |
| Sulfanilamide | $\gamma$ | 171.21 | 1.49 | 115.89 | 27.2 | 21.4 | 9.0 | 14.0 |

scribes the elasticity or stiffness of the material. In this study the influence of polymorphism on both the Young's modulus and yield pressure of carbamazepine, sulfanilamide and sulfathiazole has been studied using three-point beam bending (Roberts et al., 1991) and Heckel analysis (Heckel, 1961a; Heckel, 1961b), respectively, and related to the differences in crystal structure.

## 2. Material and methods

### 2.1. Polymorph preparation

Carbamazepine (Form III, nomenclature as Behme and Brooke, 1991) was obtained from Aldrich (Aldrich Chemical Company, Dorset) Carbamazepine (Form I, nomenclature as Behme and Brooke, 1991) was prepared by heating Form III at 140°C for 4 h (as described by Behme and Brooke, 1991).

Sulfathiazole (Form III) was obtained from Sigma (Sigma-Aldrich Chemical Company Ltd, Dorset). Form I was prepared by heating Form III at 170°C for 1 h (as described by Shakhtshneider and Boldyrev, 1993).

$\beta$-Sulfanilamide (nomenclature, Lin and Guillory, 1970) was obtained from Aldrich (Aldrich Chemical Company, Dorset). The $\gamma$-Form was prepared by heating the $\beta$-Form at 140°C for 1 h (as described by Sheridan, 1994).

All the samples were carefully ground in a mortar and pestle prior to characterisation and mechanical property measurement. The true densities of the materials were determined by helium pycnometry (Beckmann model 930). This was carried out in triplicate and the mean determined (Table 1). Molar volumes were calculated from molecular weight and true density and solubility parameters were calculated using group molar attraction constants (see Roberts et al., 1991; Roberts et al., 1994); these are shown in Table 1.

### 2.2. Crystal structure generation

The structures of the three molecules are shown in Fig. 1. Crystal structures for the various forms were generated using crystal structure parameters and atomic coordinates from the various references listed below. Desktop Molecular Modeller (Oxford University Press, 1991) was used to visualise crystal structures which had been previously generated by the Symmetry Operator Program (Oxford University Press, 1992). This program uses space group information to translate the atomic coordinates into crystal packing diagrams.

### 2.3. Polymorph characterisation

#### 2.3.1. Differential scanning calorimetry (DSC)

The sample (1–2 mg) was heated at a rate of 10°C min$^{-1}$ over a temperature range of −10–300°C using a Mettler DSC 30 (Mettler Instruments AG, Greifensee, Switzerland)

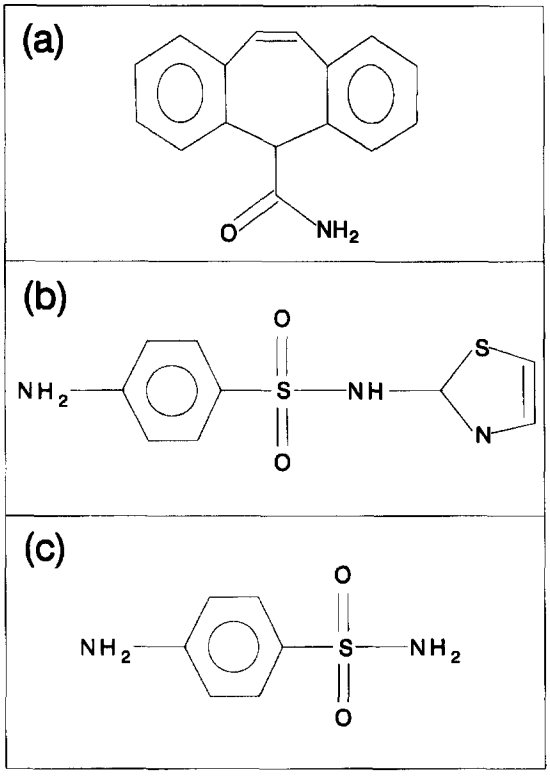



Fig. 1. The molecular structures of (a) carbamazepine, (b) sulfathiazole and (c) sulfanilamide.

in sealed pans. The instrument was calibrated with indium having a melting point of 156.6°C and a heat of fusion of 28.45 J $g^{-1}$ at 10°C $min^{-1}$.

DSC data for the various polymorphs are shown in Table 2 and Table 3. There is excellent agreement between the data and literature data in terms of transition temperatures, melting points, heats of transition and fusion. The small differences seen are likely to be due differences in preparation. In particular the transition temperature for unground carbamazepine is higher than that for ground material (data of Behme and Brooke, 1991). Furthermore Lagas and Lerk (1981) showed that for sulfathiazole, depending on the source of the material or whether it was pre-ground, had a transition temperatures in the range of 140–170°C. These data (Tables 2 and 3) therefore confirm the designation of the various forms.

*2.3.2. Solution calorimetry of the various polymorphic forms*

Immersion calorimetry was performed to confirm/assess the relative thermodynamic stability of each of the two forms of the three drugs. This was carried out using the Tronac solution calorimeter (isoperibol calorimeter, model 458, Tronac Inc., UT, USA). This consists of a large thermostatted insulated water bath that holds the reaction vessel (a 50-ml silvered glass vacuum Dewar flask) to which was added 50 ml of 95% ethanol (a solvent in which all the forms are soluble). A glass ampoule was filled with a known weight of polymorph (approximately 100 mg), secured with a rubber bung and sealed with wax to prevent any leakages. The ampoule was placed into the rotating holder with the spring loaded hammer placed above to allow breakage of the ampoule. The Dewer flask was placed around the holder, thermistor and calibration heater, clamped in place and lowered into the water bath which had previously allowed to reach an equilibrium temperature of 25°C. The experiment was controlled and data logged using an IBM XT PC linked via an interface to the calorimeter. The experiment was carried out in triplicate.

The enthalpy of solution, is related to the lattice energy of the various polymorphs and therefore determines the stability of the various forms at room temperature. The difference in the heats of solution, for the transition ($\Delta H$) will be equal to the difference in the lattice energy of two forms,

$$\Delta H_t = \Delta H_s^A - \Delta H_s^B$$

where $\Delta H_s^A$ is the enthalpy of solution of the Form A (most stable or highest enthalpy) and $\Delta H_s^B$ is the enthalpy of solution of the Form B (least stable or lowest enthalpy). This equation is valid provided the solvent used allows rapid dissolution of the material.

The results from the experiment are presented in Table 4. Both the heat of transition and heat

Table 2
Comparison between the transition temperatures ($T_t$) and melting points (MPT) of the various forms from this work and with literature data

| Drug | Form | $T_t$ (°C; this work ) | $T_t$ (°C; lit. data) | MPT (°C, onset; this work) | MPT (°C; lit. data) | References |
|---|---|---|---|---|---|---|
| Carbamazepine | III | 152.2 (III > I) | 146 (III > I)[a] | 187.9 (mpt I) | 190 (mpt I) | Lefebvre et al., (1986) |
| | | | 174 (III > I) | | 189 (mpt I) | Behme and Brooke (1991) |
| Carbamazepine | I | - | - | 188.2 | 189 | Behme and Brooke (1991) |
| Sulfathiazole | III | 172.5 (III > I) | 140–170 (III > I) | 200.6 (mpt I) | 201 (mpt I) | Lagas and Lerk (1981) |
| Sulfathiazole | I | - | - | 200.5 | 201 | Lagas and Lerk (1981) |
| Sulfanilamide | $\beta$ | 127.3 ($\beta$ > $\gamma$) | 131–141 ($\beta$ > $\gamma$) | 163.9 (mpt $\gamma$) | 166 (mpt $\gamma$) | Lin and Guillory (1970) |
| Sulfanilamide | $\gamma$ | - | - | 163.7 | 166 | Lin and Guillory (1970) |

[a]Data for ground material comparable with sample used in study.

Table 3
Comparison between heat of transition ($\Delta H_t$) and heat of fusion ($\Delta H_f$) from this work with literature data

| Drug | Form | $\Delta H_t$ (kJ mol$^{-1}$; this work) | $\Delta H_t$ (kJ mol$^{-1}$; lit.) | $\Delta H_f$ ((kJ mol$^{-1}$; this work) | $\Delta H_f$ (kJ mol$^{-1}$; lit.) | References |
|---|---|---|---|---|---|---|
| Carbamazepine | III | 2.79 | 3.19 | - | 29.39 | Behme and Brooke (1991) |
| Carbamazepine | I | - | - | 23.72 | 26.20 | Behme and Brooke (1991) |
| Sulfathiazole | III | 7.07 | 6.87 | - | 29.47 | Lagas and Lerk (1981) |
| Sulfathiazole | I | - | - | 27.22 | 27.75 | Lagas and Lerk (1981) |
| Sulfanilamide | $\beta$ | 1.63 | 1.45 | - | 22.26 | Lin and Guillory (1970) |
| Sulfanilamide | $\gamma$ | - | - | 22.58 | 20.81 | Lin and Guillory (1970) |

Table 4
The enthalpy of solution, $\Delta H_s$, and heat of transition, $\Delta H_t$, of the various polymorphic forms

| Drug | Form | Enthalpy of solution, $\Delta H_s$ (kJ mol$^{-1}$) | Heat of transition, $\Delta H_t$ (kJ mol$^{-1}$) |
|---|---|---|---|
| Carbamazepine | III | 24.15 | 3.10 |
| Carbamazepine | I | 21.05 | |
| Sulfathiazole | III | 25.53 | 3.34 |
| Sulfathiazole | I | 22.19 | |
| Sulfanilamide | $\beta$ | 19.61 | 2.29 |
| Sulfanilamide | $\gamma$ | 17.32 | |

of solution show the same trends as found from DSC measurements, i.e., the metastable form has the lower heat of solution.

*2.3.3. Powder X-ray diffraction (PXRD)*

Approximately 1 g of the sample was measured on a Siemens model D5000 X-ray diffractometer (Siemens AG, Karlsruhe, Germany) using monochromatic Cu K $\alpha$-radiation at a scanning rate of 0.020° $2\Theta$ min$^{-1}$ over the range 4–40° $2\Theta$. Samples were spun horizontally at 30 rpm in an attempt to minimise the possibility of preferred orientation and to improve counting statistics.

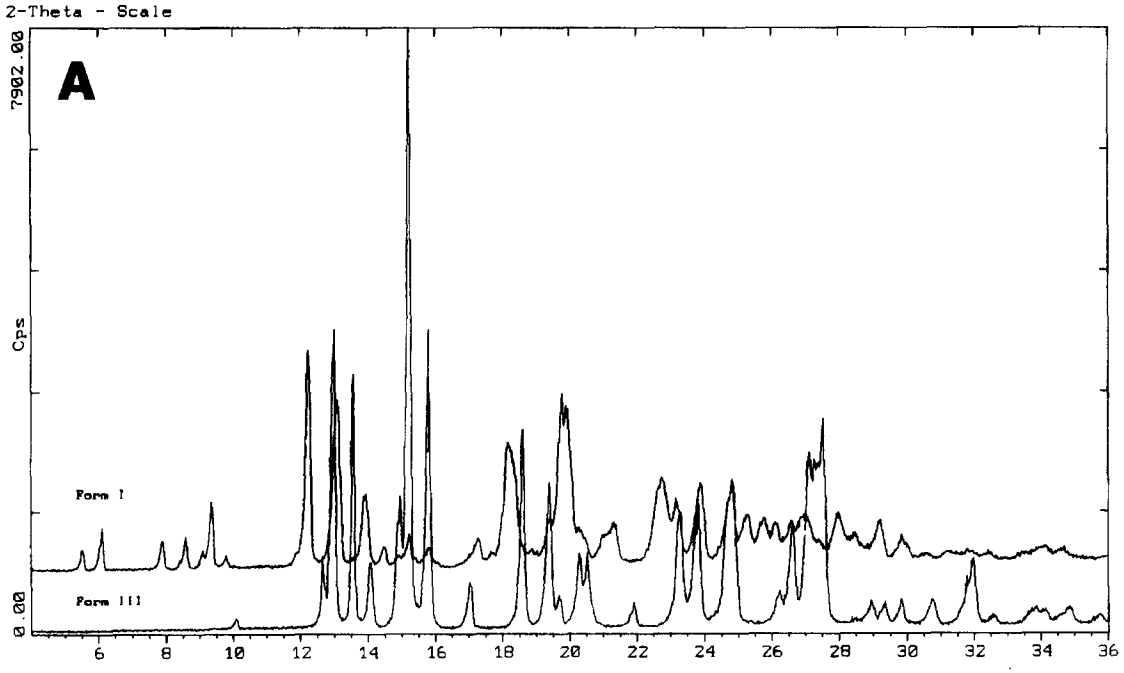
The XRD data for the polymorphs under examination are shown in Fig. 2a–c. All the molecules and forms examined compare well with the patterns from other workers; Lowes et al. (1987) for carbamazepine, Anwar et al. (1989) for sulfathiazole and Sheridan (1994) for sulfanilamide. Furthermore, it is evident from the comparisons of the three polymorphic pairs that grinding in a mortar and pestle does not induce phase transformations and therefore the materials are pure polymorphs before mechanical measurement.

*2.4. Mechanical property measurement*

*2.4.1. Young's modulus of elasticity*

Young's moduli of the polymorphs were determined using three-point beam bending as reported by Roberts et al. (1991). Beams were prepared by compacting 200–270 mg of the powders in a rectangular die 20 mm in length and 7 mm in breadth. The die was lubricated prior to compaction by applying a solution of magnesium stearate in methanol. Compaction was carried out using either a 150-kN hydraulic press (Specac address) or a 30-kN tensometer (M30K, J.J. Lloyd Instruments). Ejection of the beams from the die were carried out in a controlled manner by first relieving die wall stresses and then ejecting the compact using the tensometer at a rate of 5 mm min$^{-1}$. This minimised the effects of structural failures such as visible cracks and flaws which can lead to lamination of the beam specimens, as were evident with carbamazepine Form III and $\beta$-sulfanilamide. In these two cases the materials were left under load for extended periods (30–60 min) to allow plastic deformation and stress relaxation to take place. Care was also taken during the unloading after the extended dwell period. Porosities of the beams were determined from their weight, dimensions and true densities of the powders.

Despite showing that no phase transformations had occurred during grinding in a mortar and pestle it was also important to demonstrate that there were no compaction-induced transformations, since typical pressures of between 50 and 200 MPa were applied to prepare the beams. XRD data on compacted specimens compressed to 200 MPa showed that for carbamazepine and sulfathiazole no conversion had taken place during the testing period. This confirms the findings of Lefebvre et al. (1986) for the compaction of the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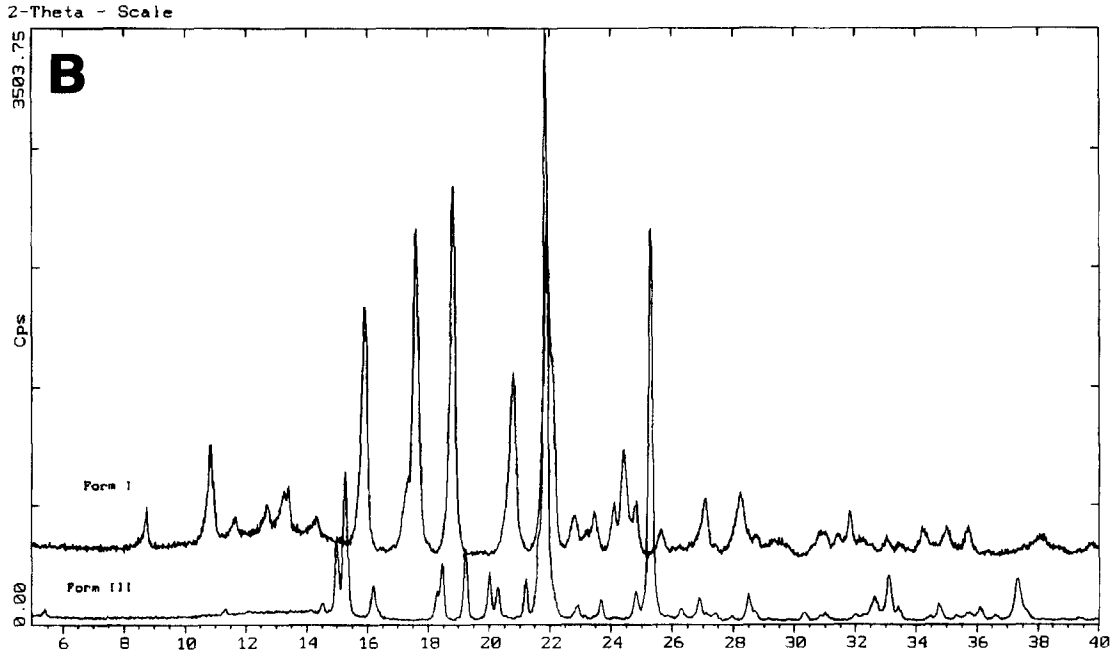
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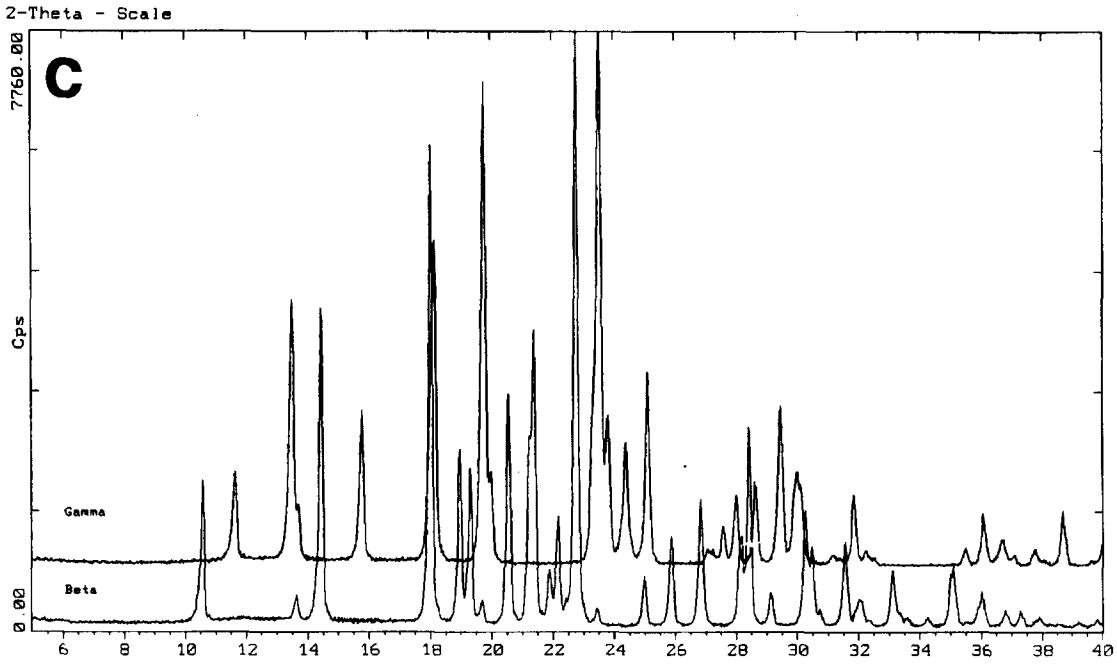


Fig. 2. The PXRD patterns of (a) carbamazepine Form III and Form I, (b) sulfathiazole Form III and Form I and (c) $\beta$- and $\gamma$-sulfanilamide.

metastable form of carbamazepine upto 400 MPa, and Kala et al. (1987) who showed that conversion of Form I to III was 9, 28 and 80% for compaction loads of 20, 50 and 100 kN after 50 days, indicating very slow conversion. Kala et al. (1982) also examined the conversion of sulfathiazole Form I to III but at pressures in excess of these used here (1052 MPa) and showed 100% conversion. In the case of sulfanilamide a small amount of conversion of the $\gamma$-Form to the $\beta$-Form had taken place after 40 min when compressed to 200 MPa, although the amount was not quantified. This confirms the findings of Sheridan (1994) who found that only 4% conversion had taken place after 30 min for a compression pressure of 280 MPa.

Mechanical property measurements were therefore made within 30 min after compaction of the beam to ensure that no conversion from the metastable form to the stable form occurred during the experiment. The beams were tested using a three-point bend rig attached to a Thermal Mechanical Analyser (Mettler TMA40) by applying a static load of 0.3 N with an additional dynamic load of 0.25 N at a frequency of 0.17 Hz. Twenty measurements of specimen displacement were performed on each beam to an accuracy of $\pm 0.005$ $\mu$m and a mean determined. A calibration run was performed to eliminate mechanical distortion, Young's modulus was determined using:

$$E_s = \frac{Fl^3}{4(s-d)t^3w}$$

where $E_s$ is the Young's modulus of the beam specimen, $F$ is the applied dynamic load, $l$ is the distance between the supports (17 mm), $t$ is the thickness of the beam, $w$ is the width of the beam (7 mm), $s$ is the displacement of the beam and $d$ is the distortion.

Young's modulus at zero porosity, $E_0$, was determined by extrapolating the measured modulus, $E_s$, at a known porosity, $P$, using the relationship (Spriggs, 1961),

$$E_s = E_0 \exp^{(-bP)}$$

where $b$ is a constant.

Fig. 3 shows an extrapolation to zero porosity for both forms of carbamazepine, indicating that as the pores are reduced in size by increasing the compaction pressure to form the beam, Young's modulus increases. Furthermore there is a differ-

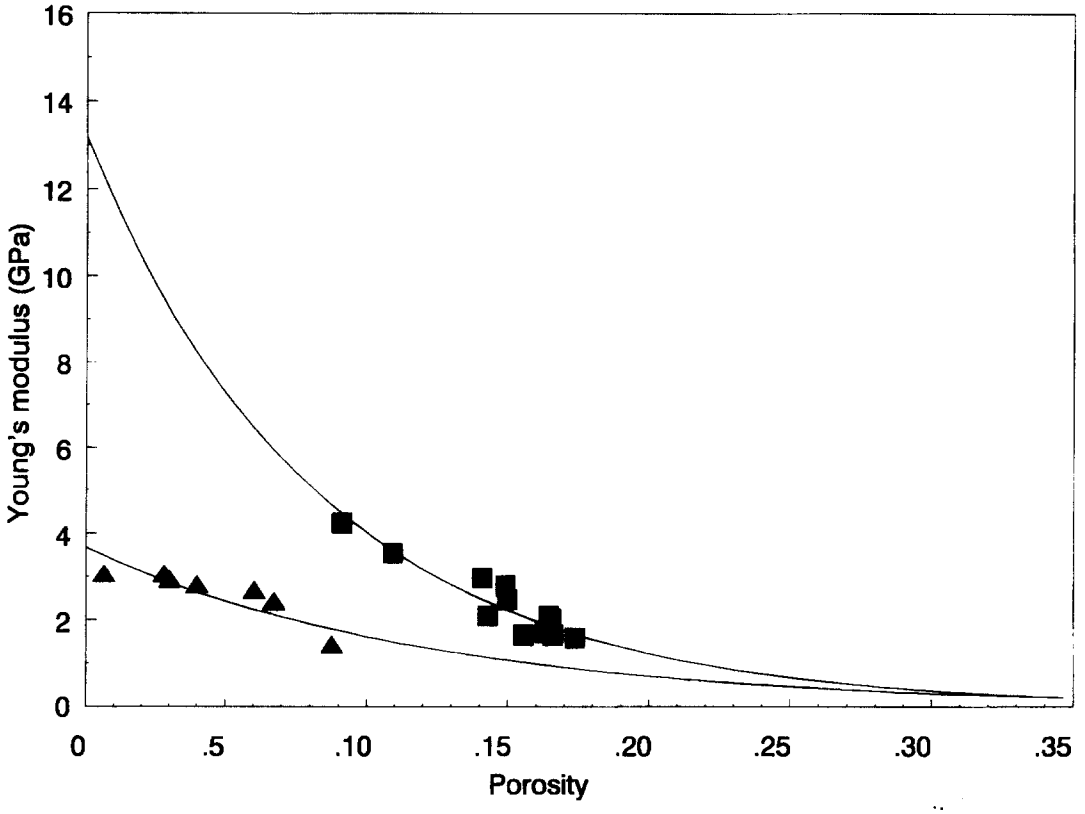


Fig. 3. The Youngs modulus versus porosity for carbamazepine: (■) Form III and (▲) Form I.

ence in the strength of bonds formed at equivalent porosities with Form I being clearly weaker. All the data for the linear regression analysis for the extrapolation to zero porosity are shown in Table 5. All the polymorphs have excellent correlation coefficients and standard errors, the higher standard errors for the most stable forms reflects the more variation in the specimen integrity indicative of the difficulty in forming beams from these forms.

*2.4.2. Yield pressure determination*

The Compression Simulator (Roberts and Rowe, 1985; Roberts and Rowe, 1986; Roberts et al., 1989) was used to compress all the materials at a punch velocity of 0.033 mm $s^{-1}$ to a pressure of between 400–500 MPa. This was carried out using 10-mm flat faced punches utilising a saw-tooth displacement/time profile for the upper punch, whilst the lower punch remained stationary. The die and punches were cleaned after each compression and lubricated with a suspension of 2% w/w magnesium stearate in methanol applied with a fine brush. Material equivalent to a 3.5-mm thick compact at zero porosity (calculated from each of the polymorphs true densities, see Table 1) was weighed and poured into the die ensuring even distribution in the die cavity. Displacement/force data were collected during each compression event, capturing readings every 0.25 s (500–1000 points). Data analysis, making use of the Heckel relationship (Heckel, 1961a; Heckel, 1961b) was carried out in triplicate as detailed in previous studies (Roberts and Rowe, 1985; Roberts and Rowe, 1986; Roberts et al., 1989).

Typical data of $\ln(1/1-D)$ versus compression pressure are shown in Fig. 4 for the two forms of carbamazepine. It is apparent that the metastable Form I densifies more easily than Form III requiring 64 MPa to produce a compact of 5%

Table 5
The Young's modulus, constant $b$, standard errors (SE for 95% confidence limits of the intercept) and the correlation coefficient (CC)

| Drug | Form | Young's modulus (GPa) | $b$ | SE | CC |
|---|---|---|---|---|---|
| Carbamazepine | III | 13.19 | 11.9032 | 1.31 | 0.8994 |
| Carbamazepine | I | 3.67 | 8.2483 | 1.12 | 0.8510 |
| Sulfathiazole | III | 14.59 | 9.1268 | 1.56 | 0.8046 |
| Sulfathiazole | I | 10.55 | 10.1178 | 1.24 | 0.9662 |
| Sulfanilamide | $\beta$ | 10.66 | 7.9928 | 1.21 | 0.8574 |
| Sulfanilamide | $\gamma$ | 6.34 | 5.8465 | 1.12 | 0.9467 |

porosity (under load) compared with a pressure of 184 MPa for Form III. The same trend is also reflected in the sulfanilamide enantiotropic pair.

## 3. Results and discussion

All the forms of the three molecules are enantiotropic pairs and therefore the most stable form at room temperature has the highest lattice energy as is evident from the heat of fusion, heat of solution data and a higher true densities. This is consistent with the thermodynamic rules of Burger (1982) for enantiotropic systems.

As might be expected the most stable form of each molecule has the higher Young's modulus, yield stress and as a result (from porosity pressure data) is the most difficult to compact. Furthermore the magnitude of the thermodynamic quantities from heat of fusion are unrelated to the values of Young's modulus for all six crystal structures. This is not surprising since it might be expected that bulk energetic properties will not reflect the subtle variations in crystal packing motifs, which for low symmetry systems tend to be anisotropic in nature.

It is interesting to note that the general relationship between Young's modulus and CED (Roberts et al., 1991) only holds in the case of the most stable polymorphic form with calculations for carbamazepine, sulfathiazole and sulfanilamide being 8, 9 and 10 GPa, respectively. For carbamazepine and sulfanilamide there were large differences in Young's modulus between enantiotropic pairs. Data by Sheridan (1994) confirms this trend for sulfanilamide, finding that the bulk modulus ($K$) at higher stresses $> 350$ MPa was 18 and 12.4 GPa for $\beta$- and $\gamma$-Forms respectively (note, $E = 1.3\ K$ if Poisson's ratio $= 0.3$). Although the values are somewhat higher than the values in this work the ratio of the bulk moduli of the two Forms $\beta/\gamma$ is 1.5, similar to that for the ratio of Young's moduli of the two forms, $\beta/\gamma = 1.7$.

For sulfathiazole, both forms had values of Young's modulus and yield stress that were close and therefore the forms must be structurally similar. Yield stress data by Summers et al. (1976) showed a similar trend with values of 114 and 102 MPa for the stable and metastable forms of sulfathiazole respectively.

To summarise, the most stable form has the higher Young's modulus, yield stress, true density, is the least compressible (Heckel plots) and would seem to more difficult to form compacts (dwell time is needed to allow sufficient plastic flow and bond formation to occur). Similar findings have been reported for phenobarbital (Kopp-Kubel et al., 1992) and metoprolol tartrate (Ragnarsson and Sjogren, 1984). For phenobarbital, Kopp-Kubel et al. (1992) found that the most stable form (III) had the highest yield stress, the lowest elastic recovery (e.g., equivalent to the higher modulus), was less compressible but gave the largest tensile strength. Similarly Ragnarsson and Sjogren (1984) found that Form II (most stable form) had the greater true density, higher yield stress (76 compared with 50 MPa for Form I), lowest elastic recovery and larger tensile strength. The latter is not surprising since the most stable form will have a larger lattice energy and recently Roberts et al. (1995) have shown that for organic

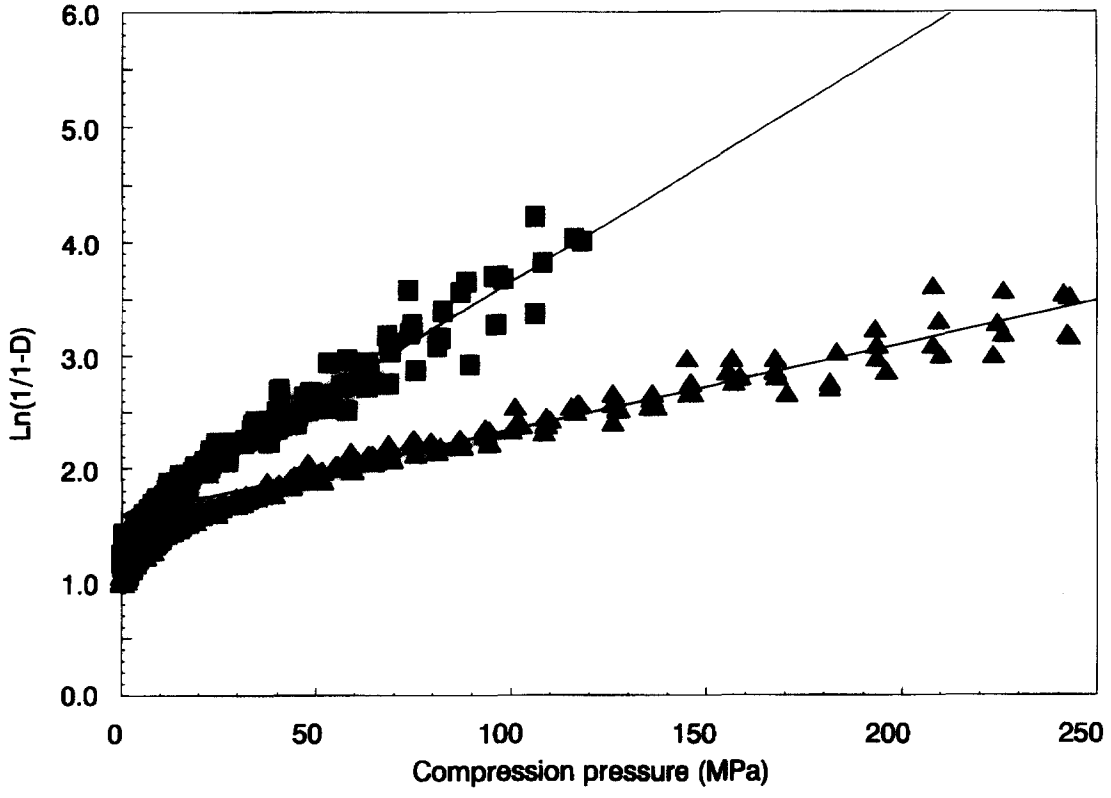


Fig. 4. The Heckel plot for carbamazepine: (■) Form I and (▲) Form III.

solids tensile strength increases with an increase in cohesive energy density.

In order to understand the reasons for the differences in mechanical properties for carbamazepine and sulfanilamide forms and the similarities for the sulfathiazole forms, the crystal structures and hence the molecular packing of each form requires detailed examination.

Crystal data for Form III (Reboul et al., 1981) and Form I (Lowes et al., 1987) of carbamazepine indicate that they form monoclinic (space group $P2_1/c$, with four molecules in the unit cell) and trigonal (space group $R\bar{3}$, with 18 molecules in the unit cell) crystal classes, respectively. The molecular conformations of the two forms are very similar and both form centrosymmetric dimers via intermolecular hydrogen bonding between the carboxamide groups. However the lengths of the hydrogen bonds between $O\cdots H{-}N$ are longer in Form III (2.11 Å) compared with Form I (1.97 Å). Furthermore the angles between the $O\cdots H{-}N$ bonds are 174° and 160° for forms III and I, respectively, indicating that other intermolecular interactions are also important in the structure of Form III which can modify the strength of the hydrogen bonded dimer. The differences in the intermolecular interactions between the two forms is manifested in the crystal structures (Fig. 5 and Fig. 6). Form I consists of a very open structure with sheets of carbamazepine molecules stabilised by hydrogen bonded dimers and van der Waals interactions stacked in layers along the $c$-axis. These sheets are stabilised by short H···H intermolecular interactions (2.70 Å) formed by three dimers forming a triangular structure with three phenyl groups pointing inwards to the centre of the triangle. Furthermore longer H···H bonds (3.14 Å) are

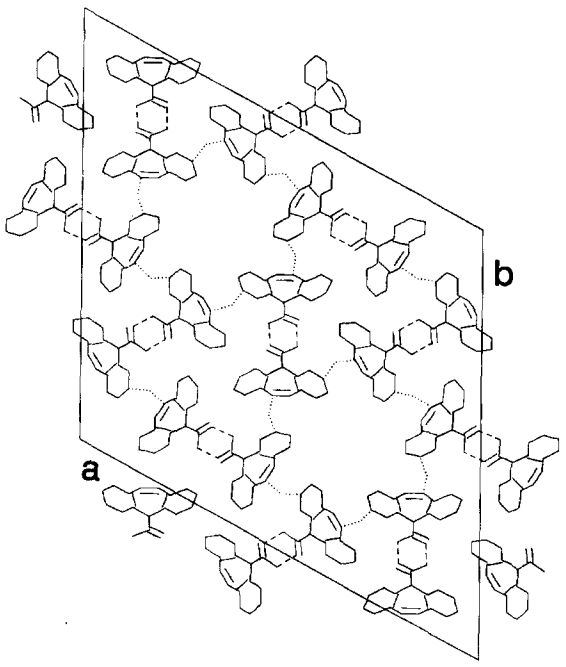


Fig. 5. The crystal structure of carbamazepine Form I viewed in the $c$-direction [001] (some of the H atoms are omitted for clarity). The dashed lines represent hydrogen bonding and the dotted line, short contacts between hydrogens.

evident forming the periphery of the triangle, this formation leaving significant hexagonal voids (see Fig. 5), whereas in Form III it is obvious that the molecules are packed into a more compact structure with dimers formed along the $b$-axis (Fig. 6). Chains are formed by the dimers and are connected to short H· · ·H contacts between the phenyl hydrogens and those of the azepine rings. These chains form a zig-zag pattern throughout the structure with chains stacked above one another.

These differences in crystal structure reflect the lower true density (Table 1), Young's modulus and yield stress (Tables 4 and 5) of Form I when compared with that of Form III. It is clear that Form III is a rigid structure (similar to corrugated sheets) and therefore will be more difficult to deform than the open sheet structure of Form I. In terms of yielding it is clear that slip in Form I will occur very easily via the [100] and [010] directions since the (001) plane is clearly the weakest (see Roberts et al., 1994 for discussion of identification of slip directions and yielding). This is in contrast to Form III where slip is most likely on the (011) plane. This will involve shearing the zig-zag chains of molecules which is likely to be restricted.

Sulfathiazole crystallises into four forms (Anwar et al., 1989), Form III and Form I are monoclinic (space group $P2_1/c$) with eight molecules in the unit cell of which there are two independent molecules (Kruger and Gafner, 1972) and are conformationally similar. The hydrogen bonding patterns are described in detail by Kruger and Gafner (1972) being very different for the two forms and hence are not reproduced here. In Form I centrosymmetric dimers are formed via symmetrical hydrogen bonds between the imide nitrogen and the hydrogen attached to the nitrogen on the thiazole ring, with further hydrogen bonds between the amine group attached to the benzene ring and the sulphoxide oxygen. Only symmetry related molecules are hydrogen bonded to each other, i.e., no hydrogen bonds exist between the independent molecules in the unit cell.

Table 6
Yield ($\sigma_y$), standard deviation of the results (SD), relative density of the intercept ($D_A$) and relative density at zero pressure ($D_0$) from the Heckel analysis

| Drug | Form | $\sigma_y$ (MPa) | SD (MPa) | $D_A$ | $D_0$ |
|---|---|---|---|---|---|
| Carbamazepine | III | 122.9 | 3.4 | 0.784 | 0.612 |
| Carbamazepine | I | 37.1 | 5.3 | 0.788 | 0.689 |
| Sulfathiazole | III | 89.6 | 3.4 | 0.695 | 0.586 |
| Sulfathiazole | I | 86.9 | 5.9 | 0.658 | 0.514 |
| Sulfanilamide | $\beta$ | 138.3 | 2.9 | 0.721 | 0.636 |
| Sulfanilamide | $\gamma$ | 119.4 | 4.9 | 0.677 | 0.505 |

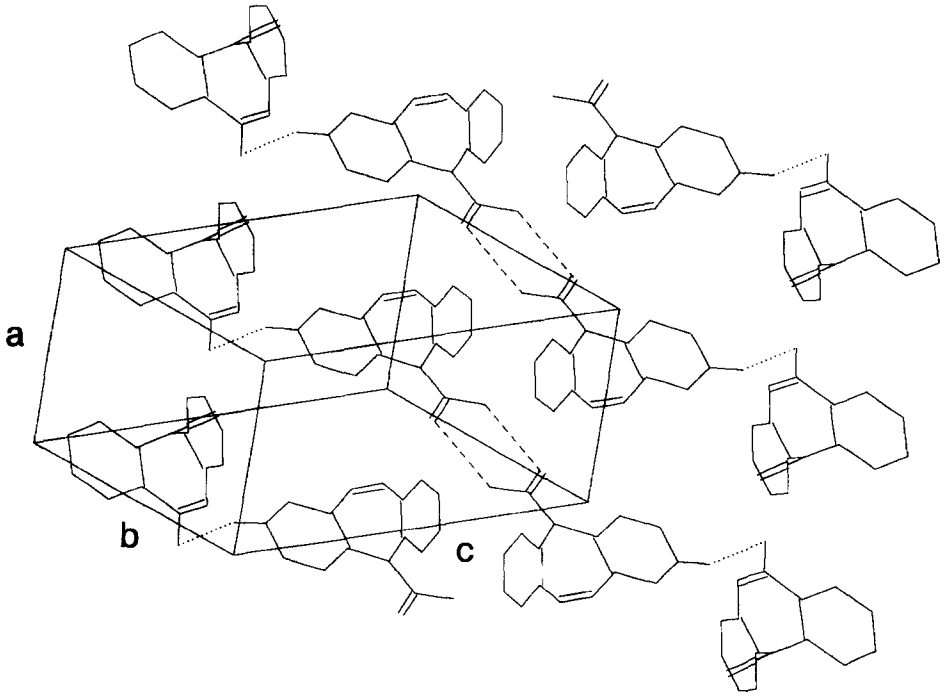


Fig. 6. The H-bonding pattern and packing of carbamazepine Form III (some of the H atoms are omitted for clarity). The dashed lines represent hydrogen bonding and the dotted line, short contacts between hydrogens.

This means there are two intermeshed but independent hydrogen bonded networks running throughout the crystal. In Form III the imide nitrogen does not participate in any hydrogen bonding. Two independent hydrogen bonding networks are integrated into irregular sheets of molecules that are parallel to the (001) plane. Neighbouring molecules are hydrogen bonded through the amine hydrogens (attached to phenyl group) and the oxygen of the sulphoxide group of two other molecules. The nitrogen of amine on phenyl group is hydrogen bonded to the hydrogen attached to the nitrogen of the thiazole ring.

Despite the differences in hydrogen bonding motifs in both forms the number of hydrogen bonds per molecule is the same and their strengths (bond lengths) are very similar (Kruger and Gafner, 1972). These similarities are reflected in the closeness of both true densities (Table 1), Young's moduli (Table 5) and yield stresses (Table 6). Furthermore, since the structures involve intermeshed hydrogen bonding motifs it might be expected that sulfathiazole would have the highest Young's modulus amongst the three molecules as indeed is shown in Table 5.

Sulfanilamide $\beta$ (Alleaume and Decap, 1965a) and $\gamma$ (Alleaume and Decap, 1965b) are both monoclinic (space group $P2_1/c$ with four molecules per unit cell) with four hydrogen bonds per molecule. In the $\beta$-Form a hydrogen of the amine attached to the phenyl group forms a hydrogen bond to the oxygen of the sulphoxide group to form a zig-zag chain along the $b$-axis with this motif being repeated along the $c$-axis (see Fig. 7). Additionally the chains are interconnected by a buckled sheet of molecules which extend down the $a$-axis (Fig. 7, as molecules A, B, C and D). This hydrogen bond motif is shown in Fig. 8 and involves the other oxygen of the sulphoxide group which forms a short hydrogen bond (2.36 Å) to the amine group (attached to sulphoxide) on another sulfanilamide group. Additionally there is an interaction between the nitrogen of the phenyl amine to one of the

hydrogens of the amine (attached to sulphoxide) which is 2.93 Å. Although there are no hydrogen bonds between molecules A,B and C,D the closeness of the phenyl rings suggests a $\pi\cdots\pi$ interaction between molecules A$\cdots$C and B$\cdots$D (Fig. 8). Five interactions are responsible for the stability of the pair of phenyl rings stack, 4 $\pi\cdots\sigma$interactions between two carbons of the phenyl group to the two amide hydrogens (amide group attached to phenyl) having distances of 2.93 and 3.33 Å and a $C\cdots C$ interaction of 3.37 Å of the phenyl ring. This net favourable $\pi\cdots\pi$ interaction[1] as a result of $\pi\cdots\sigma$ attractions that overcome the $\pi\cdots\pi$ repulsions and has been used to explain the nature and geometrical requirements of such systems (Hunter and Sanders, 1990). This type of interaction is very common feature of simple organic structures and in biological systems but can vary in its geometrical arrangement (Hunter, 1994; Hunter and Sanders, 1990).

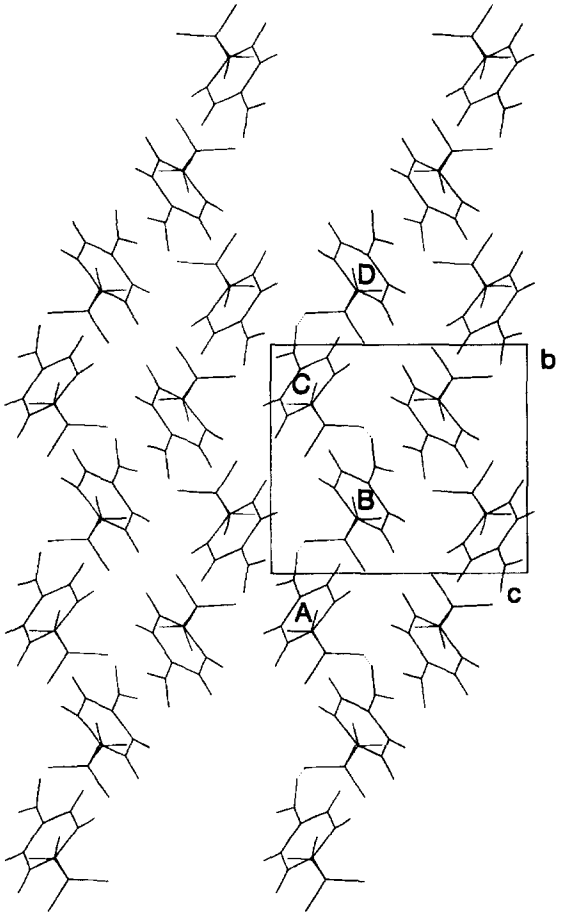


Fig. 7. The H-bonding pattern between $\beta$-sulfanilamide molecules, A, B, C and D, viewed down the $a$-axis [100] direction with the dotted lines representing hydrogen bonding.

In the $\gamma$-Form the hydrogens of the amide group (connected to sulphoxide) are hydrogen bonded to a sulphoxide oxygen from two different sulfanilamide molecules which are above and below the central molecule, forming a chair-shaped eight-membered ring. It should be noted that only one of the sulphoxide oxygen atoms is involved in hydrogen bonding. A further short contact between the phenyl amide hydrogen and the nitrogen (attached to sulphoxide) connects sulfanilamide molecules in a chain along the $a$-axis in the [100] direction (Fig. 9). This forms a buckled H-bonded sheet which stack above and below the (011) plane (Fig. 10) with the shortest distance between successive sheets of approximately 5 Å. The better packing and the three-dimensional nature of the packing motif of the $\beta$-Form is consistent with its higher Young's modulus. Furthermore the large gap between successive sheets in the $\gamma$-Form when compared to the three-dimensional H-bond network of the $\beta$-Form manifests itself in the differences in yield stress between the two polymorphs, e.g., $\gamma$-Form has the lower yield stress.

## 4. Conclusions

This paper has shown the potential of investigating structure-property relationships in organic crystals by studying polymorphic pairs since the variability between the forms is only related to variations in their crystal structure and not molecular structure. Future work will examine the effect on mechanical properties on polymorphic pairs which have conformational differences.

[1] Pure $\pi\cdots\pi$ interactions result in repulsion of the negative charge of the delocalised ring system, whereas $\pi\cdots\sigma$ interactions result in attraction since the charges on the phenyl delocalised ring and hydrogen or carbon are negative and positive repectively.

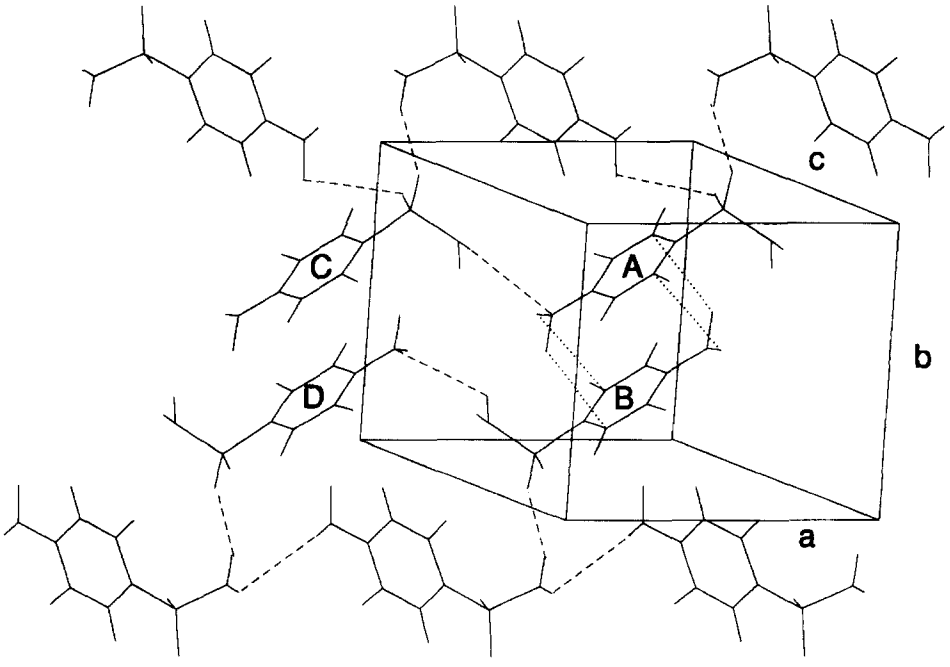


Fig. 8. A section of hydrogen bonding pattern of $\beta$-sulfanilamide. The dashed lines represent hydrogen bonding and the dotted line, short contacts between hydrogens and the delocalised pi-electron cloud.

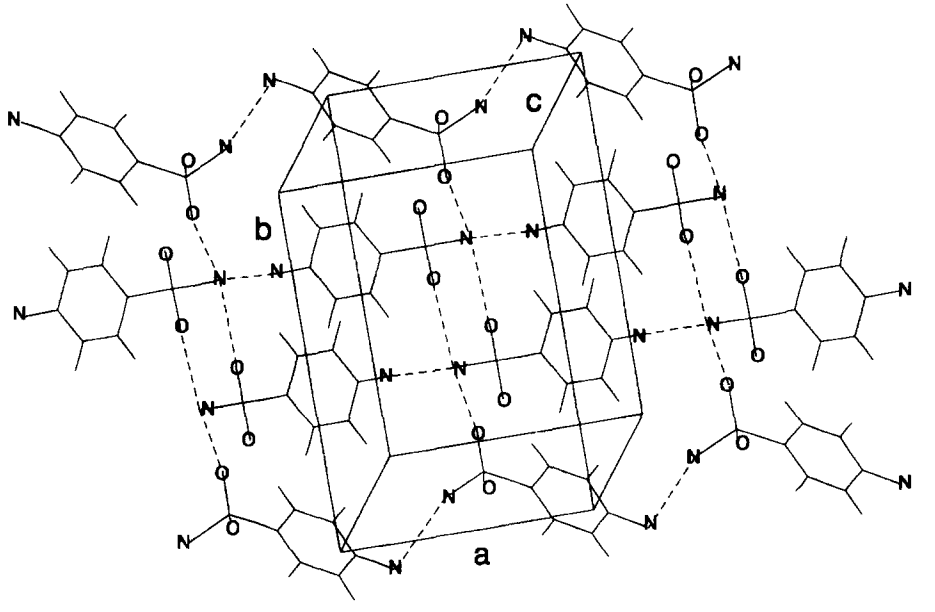


Fig. 9. The hydrogen bonding pattern of one of the sheets of $\gamma$-sulfanilamide (O indicates oxygen, and N nitrogen atoms; the H atoms are omitted for clarity). The dashed lines represent hydrogen bonding.

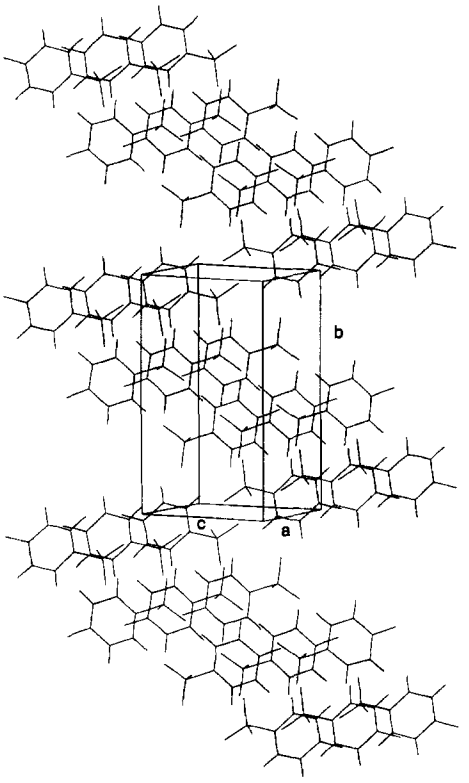


Fig. 10. The relationship between the sheets in the crystal structure of $\gamma$-sulfanilamide, showing the wide gap between successive sheets of molecules.

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