

# The polymorphism of sulphathiazole

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The existence of two species of the low temperature form of sulphathiazole, postulated by Moustafa & Carless (1969) and by Shenouda (1970), has been confirmed. Contrary to the opinions of these workers it is concluded that these are two distinct forms having different lattice structures which give rise to distinguishable X-ray diffraction patterns and infrared spectra. The fact that commercial samples frequently contain both forms casts doubt on the validity of previous solubility measurements and on the use of differential scanning calorimetry as an assay procedure for the low temperature form.

The polymorphism of sulphathiazole has been reported by numerous workers but the relationship between the two generally recognized forms has continued to present problems. Grove & Keenan (1941) obtained two distinct forms, hexagonal prisms which melted on rapid heating at 173-175° and prismatic rods melting at 200-202°. On slow heating the hexagonal form was largely transformed to the rod form below 173°, and little melting was observed below 200°. Miyazaki (1947) reported a third form, making the distinction between the  $\alpha$  form, which underwent a solid-solid conversion at 173-175° to the  $\beta$  form, and the  $\alpha'$  form which melted at 173-175° without conversion. Milosovich (1964), Guillory (1967) and Higuchi, Bernardo & Mehta (1967) all described two forms, the latter workers publishing X-ray diffractograms for the high and low temperature modifications. Kuhnert-Brandstätter & Martinek (1965) compared solubilities of forms I and II, but in a subsequent paper Kuhnert-Brandstätter & Wunsch (1969) mentioned that commercial sulphathiazole sometimes contains a hydrated form, which is converted on heating to the high temperature form. Two additional forms were also noted, which are stabilized by isomorphism in mixed crystals with sulphapyridine.

Carless & Foster (1966) reported that the B.P.C. Authentic Specimen of sulphathiazole contained two or more polymorphs, though it was subsequently suggested (Moustafa & Carless, 1969) that this conclusion, based on differential scanning calorimetry, was in error. Meanwhile, however, Mesley & Houghton (1967) also examined the B.P.C. material and found infrared evidence for the presence of two forms, but this was disputed by Moustafa & Carless (1969). Nevertheless, the latter workers obtained the low temperature form in two varieties having different transition temperatures. This work was repeated by Shenouda (1970), who found that crystallization of sulphathiazole from certain solvents yielded two species, one of which melted at 170-176° while the other underwent a solid-solid transition at 150-166°. This author concluded that it was misleading to call the melting species a third physical form but followed this statement by saying that "it is probable that a third form does exist, although highly unstable on grinding, and this is probably identical to the melting species reported in this investigation". Evidence is here presented for the existence of a second low temperature form which may be distinguished by differences in its infrared absorption spectrum and more noticeably in its

X-ray diffraction pattern. These features clearly indicate a difference in its lattice structure, and therefore justify its description as a separate polymorphic form. The fact that both low temperature forms are present in many commercial samples has an obvious bearing on the various solubility studies which have been carried out, and on the infrared identification test of the B.P.C.

#### MATERIALS AND METHODS

Samples of sulphathiazole used were the B.P.C. Authentic Specimen and a commercial sample (Evans Medical Co.) which had been stored in a screw-top jar for five years after first being opened. Other commercial samples were also examined. Infrared spectroscopy showed that all of these samples were mixtures of two forms, though the proportions varied between individual samples.

Infrared spectra were recorded as mulls in Nujol using Grubb Parsons GS2 and Spectromaster grating spectrometers. Spectra at elevated temperatures were recorded with a Beckman-RIIC VLT-2 cell and TEM-1 temperature controller.

X-ray powder diffraction patterns were recorded photographically using a 9 cm camera and a Philips PW1009 generator with vanadium-filtered chromium  $K\alpha$  radiation. The traces shown in Fig. 3 were obtained with a Joyce recording microdensitometer.

Differential scanning calorimetry was carried out with a Perkin-Elmer DSC-1B apparatus using open pans with aluminium covers (not crimped), nitrogen at 20 ml/min as carrier gas and a heating rate of 8°/min.

#### RESULTS AND DISCUSSION

##### *Preparation of forms*

It was previously stated (Mesley & Houghton, 1967) that the two forms present in the B.P.C. specimen could be isolated by recrystallization from a mixture of chloroform and acetone and from dilute ammonia solution respectively. Shenouda (1970) has since stated that both of these treatments yield a mixture of two species distinguishable by hot-stage microscopy. Moustafa & Carless (1969) also found differences in recrystallization behaviour from Mesley & Houghton, and this variability has now been confirmed. Recrystallization from alcohols containing three or more carbon atoms yields the high temperature form, here designated form I to conform with Kuhnert-Brandstätter & Wunsch (1969)\*. Recrystallization from aqueous ammonia usually, but not invariably, produces the more common of the two low temperature forms (here designated form IIA) and in fact this is also given by recrystallization from water. All other treatments tend to give mixtures of form IIA with varying proportions of the other low temperature form, IIB. All attempts to isolate form IIB during the present investigation, including recrystallization from chloroform-acetone mixtures, have proved unsuccessful.

Both form IIA and the mixture (conveniently called "form II") can be converted wholly to form I by heating in an oven above 180°, from which it must be assumed

\* In most studies of polymorphic systems in which the thermal relationship between the forms is known it is conventional to use Roman numerals to designate individual polymorphs in descending order of melting point, so that additional metastable forms can be added without the necessity of renumbering the stable form. An alternative convention has been used for some enantiotropic dimorphic systems, including sulphathiazole, in which the form stable at room temperature is designated I and the high temperature form II, but this makes no allowance for additional metastable forms.

that any material which melts at  $175^\circ$  subsequently crystallizes as form I. Kuhnert-Brandstätter & Wunsch (1969) stated that form I was enantiotropic with form II; in fact form I normally reverts on long standing to the mixture of forms IIA and IIB, as apparently does form IIA over a period of months. On the other hand, a commercial sample containing the usual mixture was found after five years to have a surface layer containing predominantly form IIB. There seems to be little doubt, however, that the most stable form of sulphathiazole at room temperature is the "form II" mixture.

#### Characterization of forms

The infrared spectra of forms IIA and IIB are remarkably similar, and out of about 40 absorption bands all but seven are indistinguishable. The following distinctions may be noted:

1. The two  $\text{NH}_2$  stretching bands occur at  $3310$  and  $3270\text{ cm}^{-1}$  in form IIA and at  $3345$  and  $3280\text{ cm}^{-1}$  in form IIB (compared with  $3460$  and  $3355\text{ cm}^{-1}$  in form I). The  $3345$  and  $3310\text{ cm}^{-1}$  bands are sufficiently separated to be resolved by a grating spectrometer, and the mixture therefore shows three bands between  $3350$  and  $3250\text{ cm}^{-1}$ .
2. Form IIA has a well-resolved doublet at  $1279$  and  $1265\text{ cm}^{-1}$ , the former being stronger; in form IIB the intensities are reversed and the peaks tend to merge together.
3. Form IIB has a broad band of medium intensity at  $886\text{ cm}^{-1}$  and a very weak peak at  $866\text{ cm}^{-1}$ , both of which are absent from the spectrum of form IIA (see Fig. 1).

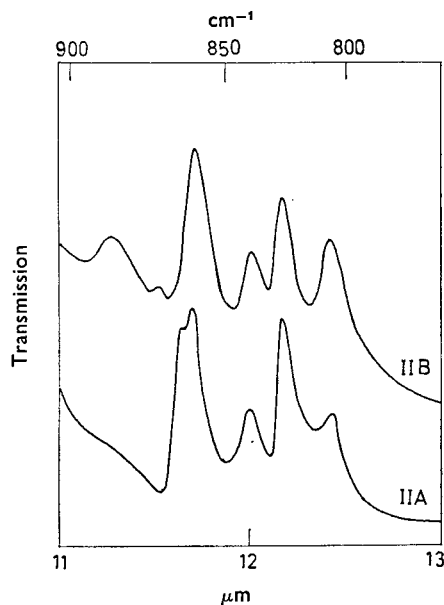


FIG. 1. Infrared spectra of forms IIA and IIB in  $900\text{--}800\text{ cm}^{-1}$  region.

4. A single peak at  $852\text{ cm}^{-1}$  in form IIB is replaced by a close doublet at  $858$  and  $854\text{ cm}^{-1}$  in form IIA, but this difference is detectable only with pure material and a high resolution spectrometer.

5. A well-resolved peak at  $805\text{ cm}^{-1}$  in form IIB is reduced to a shoulder in form IIA, due to filling in of the trough at  $810\text{ cm}^{-1}$ .

6. A weak peak occurs at  $699\text{ cm}^{-1}$  in form IIA and at  $703\text{ cm}^{-1}$  in form IIB. With a grating spectrometer linear in wavelength the mixture gives rise to a doublet (see Fig. 2), but with small instruments having linear wavenumber scales this difference is not detectable.

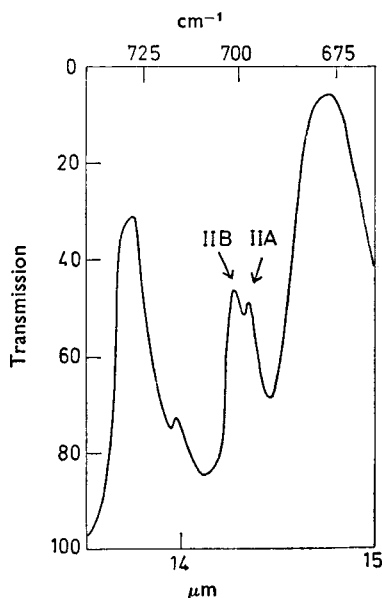


FIG. 2. Infrared spectrum of "form II" mixture, showing doublet near  $700\text{ cm}^{-1}$ .

7. Beyond the rock salt region, a weak band at  $518\text{ cm}^{-1}$  in form IIA is replaced by a stronger absorption at  $524\text{ cm}^{-1}$  in form IIB.

From the criteria above, it appears that the spectrum published by Moustafa & Carless (1969), described as form I, is that of a mixture in which form IIA predominates. Similarly the partial spectrum of form II given by Kuhnert-Brandstätter & Bachleitner-Hofmann (1971) is clearly that of the mixture, although the frequencies quoted are higher than those given here.

X-ray diffraction patterns of the two forms were reproduced by Higuchi & others (1967). Their form I, crystallized from ethanol, appears to correspond to form IIA; this pattern is significantly simpler than that of the B.P.C. specimen (see Fig. 3), and the additional lines in the latter are therefore attributed to form IIB. Unfortunately it has not been possible to prepare form IIB of sufficient purity to record its diffraction pattern. Tabulation of the lines (Table 1) shows three lines, at  $4.48$ ,  $4.13$  and  $3.56\text{ \AA}$ , which are not present in either form IIA or form I.

The results of differential scanning calorimetry need careful interpretation to distinguish between forms IIA and IIB. Moustafa & Carless (1969) observed transitions around  $160^\circ$  and  $176^\circ$  (peak temperatures) for sulphathiazole crystallized from different solvents, and on mixing the two varieties obtained a thermogram showing both transitions. Shenouda (1970) also observed differences depending on the solvent used, and attributed peaks at  $150\text{--}166^\circ$  and at  $170\text{--}176^\circ$  to solid-solid

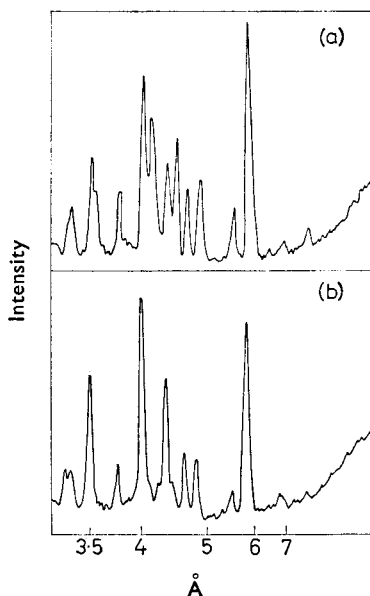


FIG. 3. X-ray diffraction patterns of (a) "form II" mixture (B.P.C. Authentic Specimen), (b) form IIA.

Table 1. X-ray diffraction patterns of sulphathiazole polymorphs. (d-spacings in Å).

Form I	Form IIA	B.P.C. Specimen "Form II" mixture
10.16 w	7.81 w	7.81 w
8.18 m	6.81 w	6.90 w
7.59 vw	5.77 s	5.77 vs
6.94 w	5.47 w	5.47 w-m
6.68 w-m	4.79 m	4.83 m
6.17 w	4.62 m	4.62 m
5.59 s	4.33 m-s	4.48 m-s
5.06 s	4.03 s	4.33 m
4.75 s	3.76 w-m	4.13 s
4.29 m-s	3.51 m-s	4.03 s
4.07 s	3.35 w-m	3.79 m
3.91 w	3.31 w-m	3.56 } m
3.80 w		3.52 } m-s
3.65 m		3.35 } m
3.47 vw		3.31 } w-m
3.30 w		
3.18 m		

transition and to melting respectively. These peaks were highly susceptible to grinding of the sample and to crimping of the sample pans. In the present work form IIA consistently gave a broad endotherm with onset at 157°, while a mixture in which form IIB predominated gave a sharper peak with onset at 170° (results corrected where necessary to give an onset temperature of 202° for the final melting transition). Commercial mixtures such as the B.P.C. Authentic Specimen resembled form IIA, the onset of the broad endotherm being approximately 159°, with a barely detectable peak at about 175° in some thermograms. The absence of the first

transition in the mainly IIB mixture suggests that the behaviour of mixtures tends to be dominated by the major constituent.

Whether the 170° transition of form IIB represented melting, as suggested by Shenouda, was not apparent, as the bulk of the material remained solid. If this endotherm were due to partial melting, it would imply that the remainder of the material had undergone a solid–solid transition without showing any evidence of this in the thermogram. Experience with other polymorphic systems, such as cortisone acetate (Mesley, 1968) and phenobarbitone (Mesley, Clements & others, 1968), suggests that this may be the normal behaviour with organic compounds, and that polymorphic transitions are usually detectable by differential scanning calorimetry only when accompanied by tautomeric changes in molecular structure. However, the apparent constancy of the heat of transition, as mentioned by Moustafa & Carless (1969), would seem to support their statement that both peaks were caused by solid–solid transition. Against this, the higher results obtained by Shenouda (1970) in those instances where both transitions were observed would support the melting hypothesis, since the heat of fusion of a given form must be greater than the heat of transition to another solid form. The discrepancy is possibly explained by the fast heating rate (40°/min) used by Shenouda, which would favour melting before the solid–solid transition had time to occur.

Microscopic examination of behaviour on heating, using a Kofler block, showed about 60% of crystals melting at 170–173° with all samples examined, and the molten portion showed no tendency to recrystallize on further heating. The remaining crystals melted at around 200°. From this observation it appears that both forms IIA and IIB show some tendency to melt, and that the melting point is not diagnostic of either form (though this may not be true of pure form IIB).

#### *Relationship between forms*

Kuhnert-Brandstätter & Wunsch (1969) state that some commercial samples of sulphathiazole contain a hydrate, but they do not indicate how this was identified. In a previous paper (Kuhnert-Brandstätter & Grimm, 1968) solvation was detected by the appearance of bubbles when the solid material was heated on a Kofler block while immersed in silicone oil. When this technique was used with sulphathiazole recrystallized from water (form IIA) and with a mixture in which form IIB predominated, in each case some evolution of bubbles was observed as the material partially melted near 170°, and a more copious evolution accompanied the final melting at about 200°. Since there is no reason to suppose that form I is solvated, the second evolution can only be due to air trapped in the solid particles, and this seems an equally probable explanation for the first evolution. This experiment therefore gave no indication that either form is hydrated. Comparison of the infrared spectra of forms IIA and IIB again shows no evidence for the presence of water in either form, though admittedly there is some interference from NH<sub>2</sub> absorptions in the two regions (near 3300 and 1650 cm<sup>-1</sup>) where water absorptions might be expected. Nevertheless any water present would have to be in less than molar proportion to escape detection.

Assuming the distinction between the two forms is not one of hydration, then the infrared spectra may indicate the nature of the structural differences. The positions of the N–H stretching absorptions indicate the formation of strong intermolecular hydrogen bonds. Comparison with the spectra of deuterated sulphathiazole (forms

I and IIA) shows that the sulphonamide NH group gives rise to a very broad absorption centred near  $2900\text{ cm}^{-1}$ , the corresponding ND band being near  $2200\text{ cm}^{-1}$ . This broad feature is common to all three forms, and is attributed to strong hydrogen bonding to a second nitrogen atom, probably that in the thiazole ring.

The  $\text{NH}_2$  bands in form I occur at  $3460$  and  $3355\text{ cm}^{-1}$ , corresponding to some degree of hydrogen bonding, probably to the oxygen atoms of the  $\text{SO}_2$  group. Using the technique of Novak, Lascombe & Josien (1966) it can be shown from examination of partially deuterated form I that the two N-H bonds are not equivalent, so it appears that only one of the hydrogens is bonded to the  $\text{SO}_2$  group.

The  $\text{NH}_2$  absorptions in forms IIA and IIB have very much lower frequencies, and are indeed lower than those of all the 44 other sulphonamide forms examined by Mesley & Houghton (1967). The very low frequency again suggests bonding to nitrogen, rather than to the  $\text{SO}_2$  group. There is no evidence to support the suggestion by Kuhnert-Brandstätter & Bachleitner-Hofmann (1971) that the difference between form I and "form II" is due to amide-imide tautomerism; this conclusion is apparently based on the erroneous assignment of the  $\text{NH}_2$  absorptions in "form II" to the two highest frequency bands, which in fact arise from the two different forms IIA and IIB, and of the sulphonamide NH absorption to that at  $3280\text{ cm}^{-1}$  instead of the broad band near  $2900\text{ cm}^{-1}$ . Form IIB is the only one of the three forms in which the  $\text{NH}_2$  frequencies conform to the relationship suggested by Bellamy & Williams (1957) as a test for equivalence of the two hydrogens, so in this form it appears that both hydrogens are strongly bound to nitrogen. In form IIA the frequencies are even lower, suggesting that one of the hydrogens is bound more strongly to nitrogen while the other may form a weaker hydrogen bond. Deuteration of form IIA has shown that the distinctive bands at  $1266$ ,  $810$  and  $518\text{ cm}^{-1}$  are all associated with NH or  $\text{NH}_2$  groups, so it may be supposed that virtually all the differences between forms IIA and IIB are attributable to the relative strengths of the hydrogen bonds.

Clearly the very strong intermolecular hydrogen bonds in both components of "form II" are sufficient to account for the lower solubility of the normal material relative to that of form I, as noted by Kuhnert-Brandstätter & Martinek (1965) and by Higuchi & others (1967). The energy required to break these bonds on conversion to form I explains the appearance of the endothermic peak in the  $150$ – $175^\circ$  region in DSC and DTA thermograms. It seems probable that the transitions with onset temperatures of  $157^\circ$  and  $170^\circ$ , which apparently correspond to those of Moustafa & Carless (1969), are both attributable to solid-solid transitions, in which case the apparent constancy of the heats of transition noted by these workers implies a marked similarity in structure. The melting transition, when it occurs, is probably very close to the  $170^\circ$  transition of form IIB and would not normally be resolved from it. From the microscopic results it appears that the melting transition is not restricted to form IIB, and at least one thermogram of pure form IIA shows a very small endothermic peak at  $175^\circ$ . The similarity in melting point suggests that neither of these forms corresponds to form III or form IV, for which melting points of  $162^\circ$  and  $158^\circ$  were given by Kuhnert-Brandstätter & Wunsch (1969). Infrared spectra of the B.P.C. specimen recorded at elevated temperatures show no apparent tendency for interconversion between forms IIA and IIB; up to  $120^\circ$  the proportions were apparently unchanged, the only spectral difference being due to the appearance of some form I, and after 15 min at  $160^\circ$  the material was entirely form I.

## CONCLUSIONS

Moustafa & Carless (1969) claimed that the heat of transition could be used to assay the low temperature form in sulphathiazole mixtures. The work of Shenouda (1970) has shown that this heat of transition may vary considerably unless all samples are ground and crimped. In view of the fact that commercial samples are frequently mixtures, this assay method is of doubtful validity (the effect of grinding a mixture of form I and "form II" could well alter the relative proportions).

The solubility measurements of Higuchi & others (1967), apparently carried out on pure form IIA, may also be invalid for normal commercial samples for the same reason. There is obviously a need for solubility data on both of the low temperature forms, though there is little doubt that both are significantly less soluble than the high temperature form. It is probable that the crystal growth studies of Carless & Foster (1966) resulted in different forms under different conditions, though the possibility of polymorphism was admitted by these authors.

The differences in infrared spectra, though slight, could affect the infrared identification test of the B.P.C. Conversion to the high temperature form (form I), either by heating as recommended by Moustafa & Carless (1969) or by recrystallization from n-propanol (Mesley & Houghton, 1967), is therefore recommended for this purpose.

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