

Research Papers

THE POLYMORPHISM OF SULPHATHIAZOLE

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(Received October 8th, 1980)

(Revised version received December 5th, 1980)

(Accepted December 17th, 1980)

SUMMARY

Three crystalline modifications and one amorphous form of sulphathiazole have been characterized using differential scanning calorimetry, X-ray diffraction and infrared spectroscopy. The melting points of polymorphs I, II and III are 201.0°C, 196.5°C and 173.6°C, respectively. Complete melting of the polymorphs I and II was only observed if the crystalline modifications were very pure. Methods for the preparation of these very pure substances are described. The amorphous form shows a glass transition at 62°C. Dissolution studies have shown that the polymorphs I and II are very unstable in water and are rapidly converted into polymorph III of sulphathiazole.

INTRODUCTION

The polymorphism of sulphathiazole has been studied extensively by numerous workers, but there are conflicting reports about the number of polymorphic forms and there is confusion about the characterization of some of these forms.

Grove and Keenan (1941) described two distinct forms: hexagonal prisms and prismatic rods, with melting points of 173–175°C and 200–202°C, respectively. On slow heating, however, most of the hexagonal prisms turned white or opaque below 173°C and little melting was observed below 200°C. Miyazaki (1947), Mesley and Houghton (1967) and Mesley (1971) reported 3 crystalline modifications of sulphathiazole. These forms were symbolized as α , A and I or IIA, which underwent transition below 173–175°C and melted at 200–204°C; β , B, II or I which melted at 200–204°C and α' , C or IIB which melted at 173–175°C¹. Milosovich (1964), Higuchi et al. (1967) and Kanke and Seki-

¹ Today in most studies on polymorphism it is conventional to use Roman numerals to designate the different polymorphs in descending order of melting point. An alternative convention has been used for some dimorphic systems in which the stable form at room temperature was symbolized as I or α and the metastable form as II or β .

guchi (1973) all described two polymorphic forms of sulphathiazole: a low temperature form which melted at 174–175°C and a high temperature form which melted at about 200°C. Moustafa and Carless (1969) also reported two polymorphic forms: however, the low temperature form underwent solid–solid transition at 140–180°C into the high temperature form and the high temperature form melted at about 207°C. Even at a rather fast heating rate, the authors did not observe any melting below 200°C. In contrast, Shenouda (1970) has shown that in all cases where the low temperature form was produced, two species could be obtained, one which underwent solid–solid transition at 150–166°C and the other one which melted at 176–179°C. The melting form, however, appeared to be highly unstable on grinding.

Since sulphathiazole has been used extensively as the model drug in research work in recent years (Carless and Jordan, 1974a and b; Summers et al., 1976; Jordan and Carless, 1976; Niazi, 1976; Summers et al., 1976; Hüttenrauch and Keiner, 1977; Badawi and El-Sayed, 1980) the purpose of this investigation was to elucidate the polymorphism of sulphathiazole.

MATERIALS AND METHODS

Materials

Sulphathiazole was Ph. Eur. grade and was supplied by Interpharm, 's-Hertogenbosch, The Netherlands and by O.P.G., Utrecht, The Netherlands.

Different polymorphic forms were prepared by crystallization from water, acetone, ethanol, *n*-propanol, 2-propanol, *n*-butanol, isobutanol, *n*-pentanol, and from an ethanol–water mixture (1 : 1) and a chloroform–acetone mixture (1 : 3). All solvents were of analytical grade.

Polymorph I was obtained by crystallization from *n*-propanol at 80°C.

Polymorph II was prepared by boiling a supersaturated solution of sulphathiazole in water (boiling temperature about 100°C) until all the solvent was evaporated. The procedure was carried out in a conical flask on a hot-plate. During the evaporation the solution was stirred with a magnetic stirrer. To avoid further heating of the dry material, as soon as all the solvent was evaporated, the flask was removed from the hot-plate.

Polymorph III was obtained by very slow crystallization from either water, ethanol, the water–ethanol mixture or the chloroform–acetone mixture. Almost saturated solutions of sulphathiazole in the different solvents at temperatures corresponding to their boiling points, were cooled at a rate of about 5°C/h to room temperature.

The amorphous form of sulphathiazole was prepared by cooling the melt.

Polymorph characterization

Differential scanning calorimetry (DSC) and thermogravimetry (TG)

The DSC profiles of the different polymorphic forms were recorded on a DuPont 990 thermal analyzer equipped with a DSC cell 910 (DuPont de Nemours, Wilmington, U.S.A.) and calibrated with indium. The thermal behaviour was studied under normal conditions with open crucibles at a nitrogen gas flow of 10 ml/min. Phase transition temperatures were corrected for the non-linear response of the chromel–alumel thermo-

couple. The thermogravimetric curves were recorded on a Linseis L 81 simultaneous DTA/TG/DTG/T system under normal conditions without an inert gas atmosphere.

X-ray diffraction

X-ray diffraction patterns were obtained with a Guinier-Hägg camera (XDC-700, Jungner instrument, Stockholm, Sweden) using CuK_{α_1} radiation. The diagrams were calibrated with silicon. For a better interpretation of the DSC profiles, X-ray diffraction diagrams were recorded as a function of the temperature with a Guinier-Simon camera (Enraf Nonius, Delft, The Netherlands) using CuK_{α_1} radiation. The heating rate was $10^\circ\text{C}/\text{min}$.

Infrared spectroscopy

For the characterization of polymorphic forms by means of infrared spectroscopy both the KBr disc method and the nujol mull technique are only suitable if no polymorphic changes take place during sample preparations. Because, as will be shown in a subsequent publication, two of the polymorphic forms of sulphathiazole are highly unstable on grinding, attenuated total reflectance was employed to obtain the infrared spectra. The spectra were recorded on a Perkin-Elmer Model 577 grating infrared spectrophotometer equipped with a Beckman Multi-ATR unit TR-25 with a 45° KRS-5 (thallous

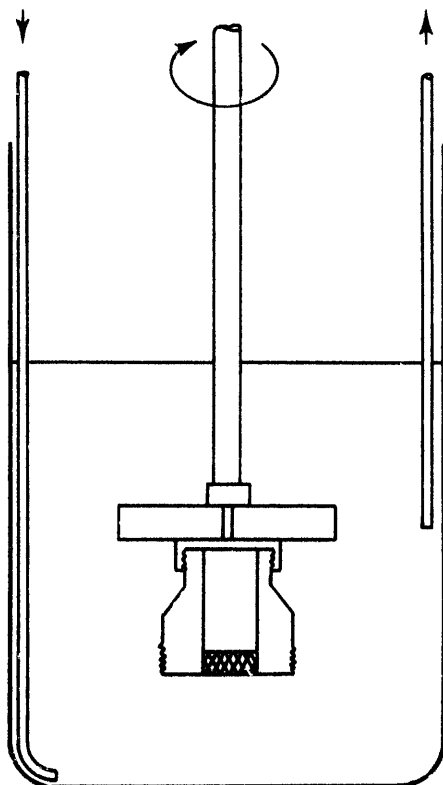


Fig. 1. Apparatus for dissolution rate measurement.

bromide–iodide) reflection plate. An adhesive tape technique was used for preparing the samples for IR analyses.

Dissolution studies

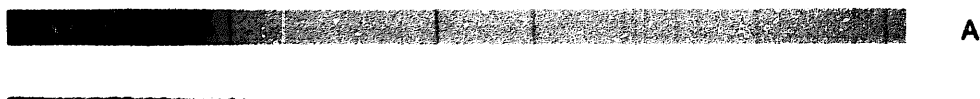
Dissolution studies of the different polymorphic forms were performed in water. Non-disintegrating discs, 13 mm in diameter, were prepared by compressing 300 mg of the crystalline material at a load of 1500 N in a die and punch assembly for 5 min. The die served as disc holder and allowed only one surface to be exposed to the dissolution medium. The disc holder was attached to a shaft and was rotated at 100 rpm in the centre of a water-jacketed beaker containing 750 ml of water. To achieve adequate mixing a straight 4-bladed impeller, 5 cm in diameter with a blade width of 1 cm, was attached to the shaft above the disc holder (see Fig. 1). The concentration in the beaker was continuously monitored by circulation of the dissolution medium at a rate of 5 ml/min through a flow-cell in a recording spectrophotometer (Model 25 Beckman Instruments, Fullerton, Calif., U.S.A.) and returning it into the vessel. The absorbance was measured at 283 nm.

RESULTS AND DISCUSSION

Fig. 2 shows the Guinier-Hägg photographs of the different crystalline modifications and of the amorphous form of sulphathiazole. The diffraction patterns of polymorphs I and III are nearly identical to those published by Higuchi et al. (1967), representing the high and low temperature forms, respectively. The diffraction pattern of form II has not yet been described in the literature.

The infrared spectra of polymorphs I, II and III and that of the amorphous form of sulphathiazole are depicted in Fig. 3. The differences observed in the infrared spectra and X-ray patterns are sufficiently distinct to characterize the various crystalline modifications.

In Fig. 4 (top) the DSC profile (heating rate 10°C/min) of the amorphous form of



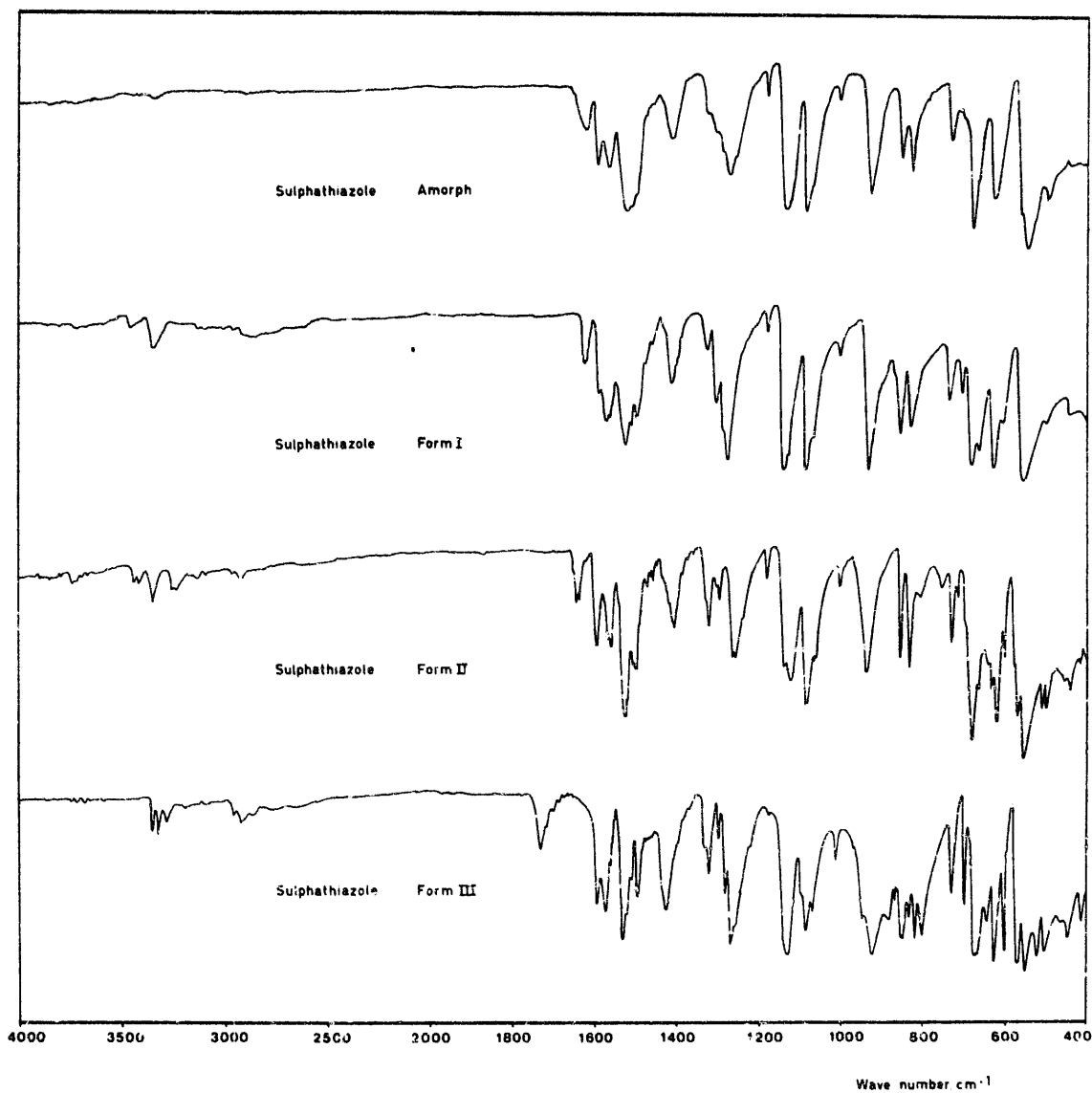


Fig. 3. Infrared spectra of the different polymorphic forms of sulphathiazole.

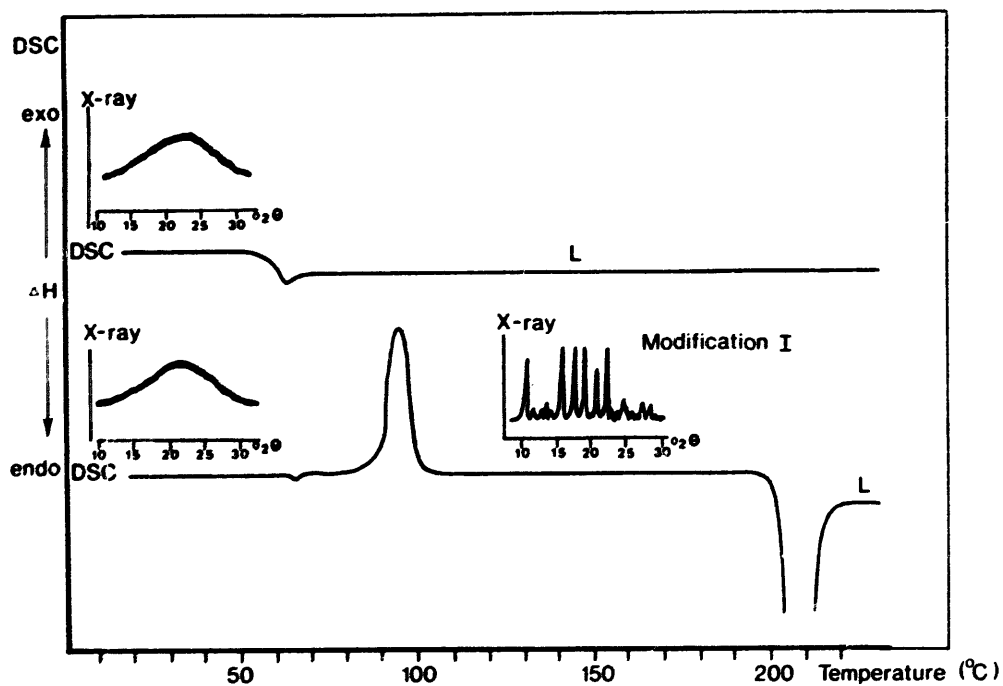


Fig. 4. DSC profiles (heating rate $10^{\circ}\text{C}/\text{min}$) and X-ray diffraction patterns of the amorphous form of sulphathiazole.

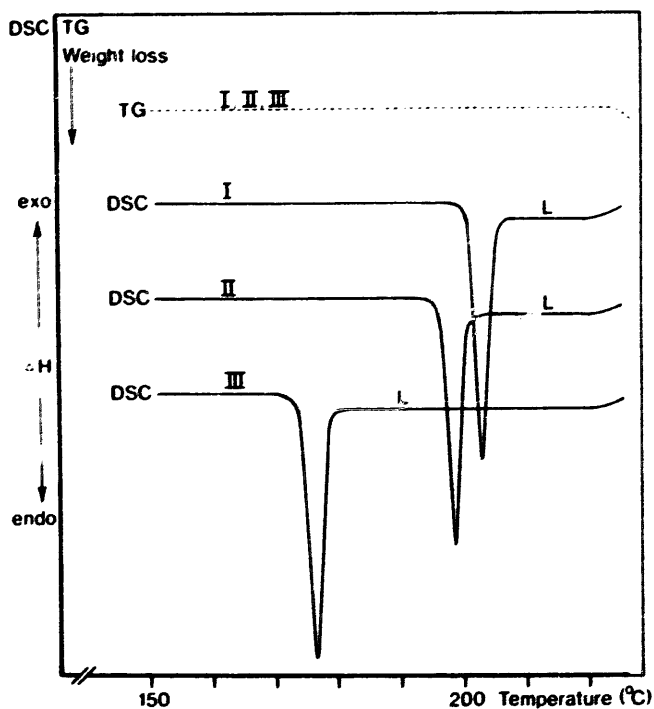


Fig. 5. TG and DSC curves of polymorphs I, II and III of sulphathiazole, recorded at a heating rate of $5^{\circ}\text{C}/\text{min}$ (TG curve) and $10^{\circ}\text{C}/\text{min}$ (DSC curve), respectively.

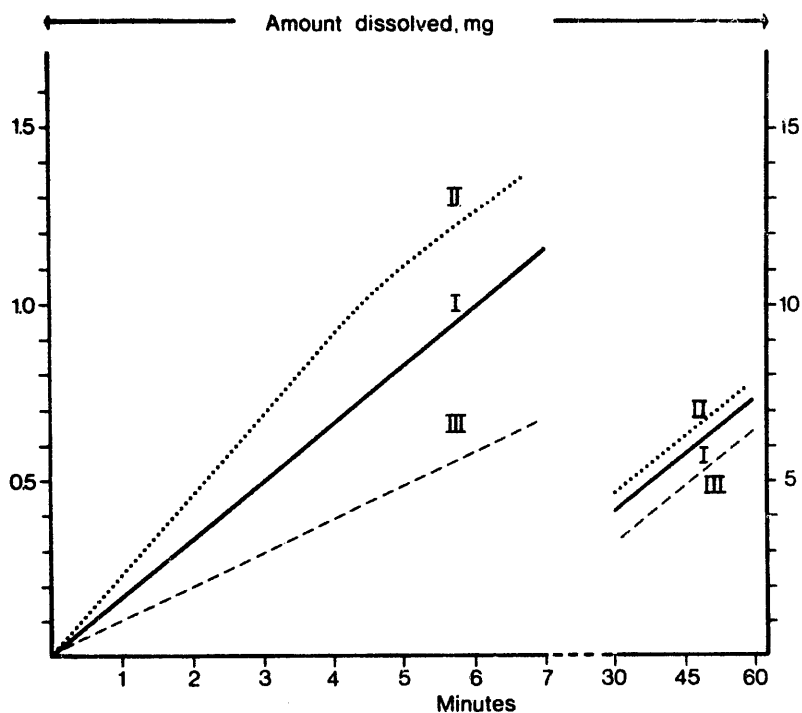


Fig. 6. Dissolution rates of form I, II and III, respectively, of sulphathiazole in water at 37°C.

diffraction pattern of the crystalline material was characteristic for polymorph I of sulphathiazole.

The DSC and TG profiles of the 3 crystalline modifications of sulphathiazole are depicted in Fig. 5. The thermogravimetric curve was recorded at a heating rate of 5°C/min and shows that under the experimental conditions the decomposition starts at about 220°C. The various endotherms of the different DSC profiles all represent melting of the corresponding crystalline modifications, as was verified by hot-stage microscopic examination as well as by visual observation in the open pan while scanning. At a heating rate of 10°C/min, melting points of 201.0°C, 196.5°C and 173.6°C were obtained for polymorphs I, II and III, respectively.

The dissolution rates of the different polymorphic forms of sulphathiazole at $37 \pm 0.5^\circ\text{C}$ are shown in Fig. 6. Only the dissolution rate of polymorph III was constant during the entire run, indicating that this form was stable under the experimental conditions. This was verified by rotating a suspension of polymorph III in water for two weeks at a temperature of 37°C. After this period the infrared spectrum as well as the X-ray diffraction pattern of the solid particles were characteristic for form III of sulphathiazole. For polymorphs I and II, only the initial dissolution rates were constant, but decreased after 7 and 4 min, respectively, and approached those for form III. The polymorphs I and II must be metastable under the experimental conditions and converted rapidly to the more stable form III. This was verified by the aging of a suspension of the polymorphs I and II respectively, in water for two weeks: after this period both the infrared spectra and the

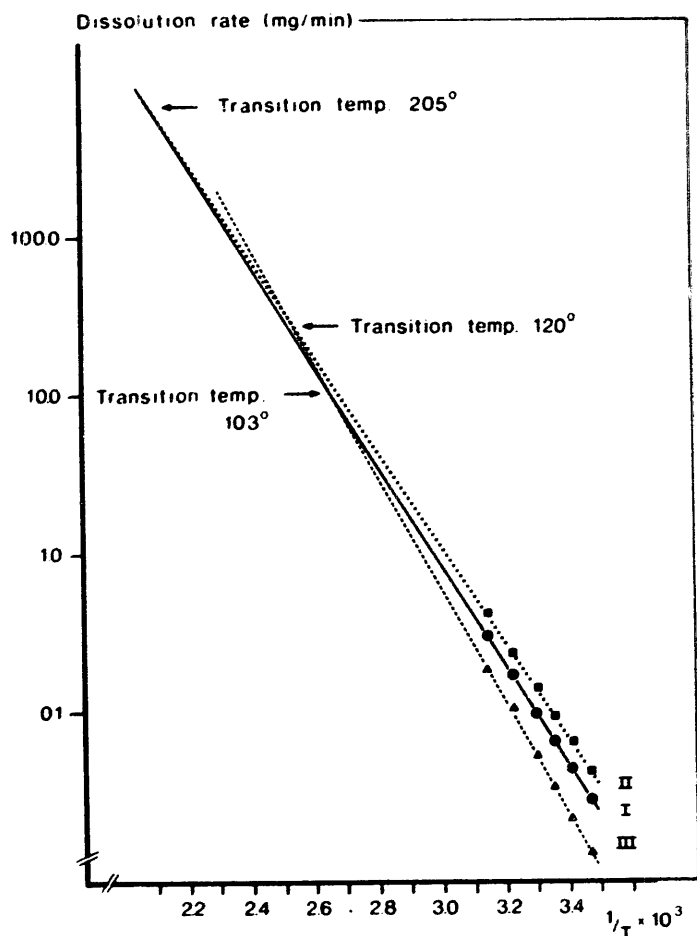
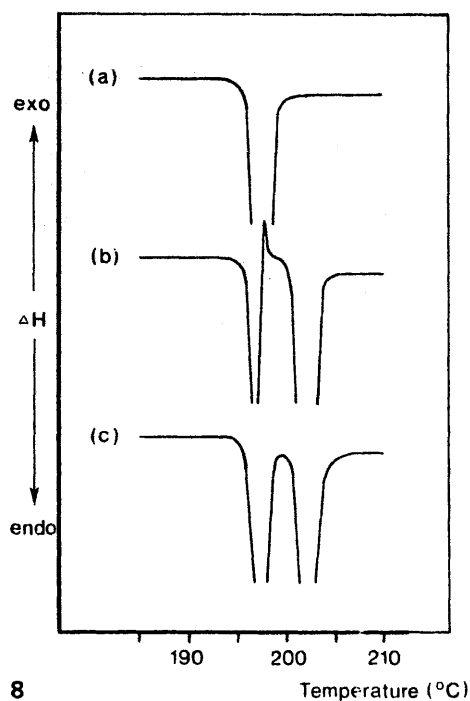


Fig. 7. Arrhenius plot of the initial dissolution rates of polymorphs I, II and III of sulphathiazole.

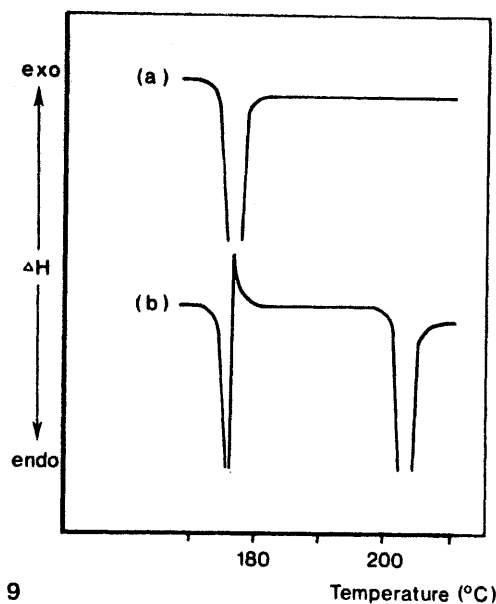
X-ray diffractions patterns were characteristic for polymorph III of sulphathiazole. The ratios of the initial dissolution rates of the polymorphs II and I, to that of form III were 2.33 and 1.60, respectively, at $37 \pm 0.5^\circ\text{C}$. The latter value is in very good agreement with those reported by Milosovich et al. (1964), Higuchi et al. (1967) and Kanke and Sekiguchi (1973) (1.55, 1.70 and 1.57, respectively). The initial dissolution rate of the amorphous form of sulphathiazole was identical to that of form III, indicating that the conversion must be extremely rapid in water.

In Fig. 7 the initial dissolution rates of the different crystalline modifications of sulphathiazole are plotted against the reciprocal of the absolute temperature. The transition temperatures, indicated by the intersections of the different curves, were about 103°C , 120°C and 205°C for the polymorphs I and III, II and III, and I and II, respectively. The transition energies, calculated from the differences in slopes, were $6.90 \text{ kJ} \cdot \text{mol}^{-1}$, $9.50 \text{ kJ} \cdot \text{mol}^{-1}$ and $2.60 \text{ kJ} \cdot \text{mol}^{-1}$ for the polymorphs I and III, II and III, and I and II, respectively.

Complete melting of the crystalline modification II of sulphathiazole at a temperature



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Fig. 8. DSC curves of polymorph II of sulphathiazole: (a) pure form II, heating rate 5°C/min; (b) form II, contaminated with a small amount of form I, heating rate 5°C/min; and (c) as in (b) with a heating rate of 10°C/min.

Fig. 9. DSC curve of polymorph III of sulphathiazole: (a) pure form III, heating rate 10°C/min; and (b) form III, contaminated with an extremely small amount of form I, heating rate 10°C/min.

of 196.5°C, as illustrated in the DSC profile of Fig. 8a, was only observed if this form was very pure. If at the start of the experiment, only the slightest amount of form I was present, polymorph I crystallized during the melting process. As can be seen in Fig. 8b the endothermic melting peak is immediately followed by an exothermic crystallization peak. With further heating the crystals melted at 201°C. Because the crystallization process overlaps the melting process, the area under the melting peak is much smaller than when no crystallization takes place. At a heating rate of over 10°C/min the exotherm will not be observed in the DSC profile, because there is insufficient time for crystallization.

Analogous behaviour was observed for polymorph III of sulphathiazole: only the very pure form melted at 174°C on condition that the heating rate was at least 5°C/min (see Fig. 9). If the modification was contaminated with form I, a melting and crystallization process was noticed (see lower curve of Fig. 9) after which the crystals melted at 201°C.

According to Fig. 7, it is to be expected that form III undergoes a solid–solid transition at 103°C into form I. As shown in Fig. 5 the crystals of polymorph III melted at 173.6°C on condition that freshly prepared crystals were tested and that the heating rate was at least 5°C/min. This discrepancy is due to the relatively high energy of activation of the solid–solid transition (235 kJ · mol⁻¹) as reported by Shami et al. (1972). At a very

low heating rate (e.g. $0.2^{\circ}\text{C}/\text{min}$) or if the crystals were previously ground in a mortar for only a short time, the partial transition of form III into form I took place. Thermal or mechanical activation was probably enough to pass the energy barrier. The X-ray diffraction pattern and the infrared spectrum of the milled crystals were completely identical to those of the unmilled substance. Of particular interest is the observation that if freshly prepared crystals of form III were placed at a temperature of about 160°C and subsequently one of the crystals was touched with a needle, the solid–solid transition in this particular crystal immediately took place and this was followed by identical processes in the other crystals, which occurred through their points of contact. By heating up, the completely isolated crystals melted at 173.6°C and the other crystals at 201°C . The transition temperature of the mechanically activated crystals was found to be strongly dependent upon the heating rate and the degree of activation; between the heating rate and the transition temperature a non-linear positive correlation and between the degree of activation and the transition temperature a negative correlation was found. If the not-activated crystals of polymorph III were stored at room temperature for two weeks, complete melting was no longer observed, and instead the DSC profile of Fig. 9b was obtained. At a temperature just under the melting point of form III, some crystals imperceptibly underwent a solid–solid transition into form I and these crystals acted as seeding material during the melting process.

In Fig. 10 the DSC curves of two commercial samples of sulphathiazole are shown. In both cases the infrared spectra and X-ray diffraction patterns were characteristic for polymorph III. The upper curve indicates that the solid partially underwent a solid–solid transition at about 152°C , followed by a melting and crystallization process at about 174°C and that polymorph I finally melted at 201°C . The DSC curve of the other commercial sample (middle curve) shows an analogous profile with the exception of the small

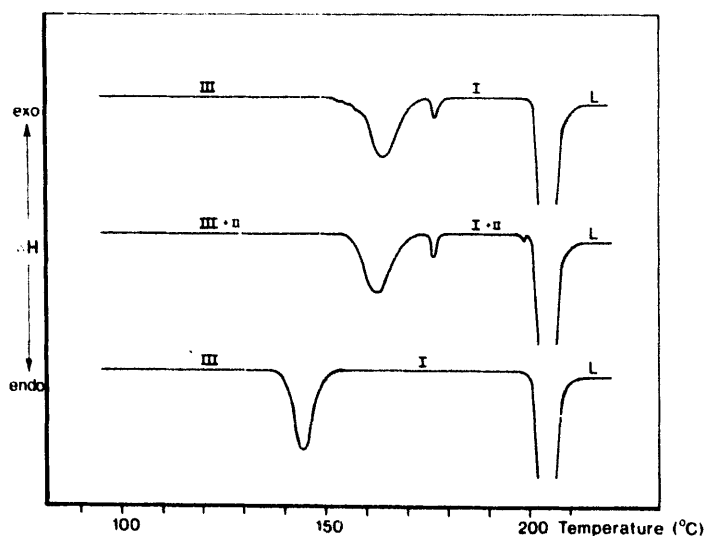


Fig. 10. DSC curves of two commercial samples of sulphathiazole. Upper curve: commercial sample form III. Middle curve: commercial sample form III contaminated with a small amount of form II. Lower curve: like sample in upper curve, after milling for a short time in a mortar.

TABLE 1

TRANSITION TEMPERATURES AND ENTHALPIES OF THE DIFFERENT CRYSTALLINE MODIFICATIONS OF SULPHATHIAZOLE

Transition	Temperature (°C)	ΔH^a (kJ · mol ⁻¹)
III → I	105–170	6.87 ± 0.13
III → L	173.6	29.47 ± 0.33
II → L	196.5	25.07 ± 0.27
I → L	201.0	27.75 ± 0.42

^a Mean of 7 determinations.

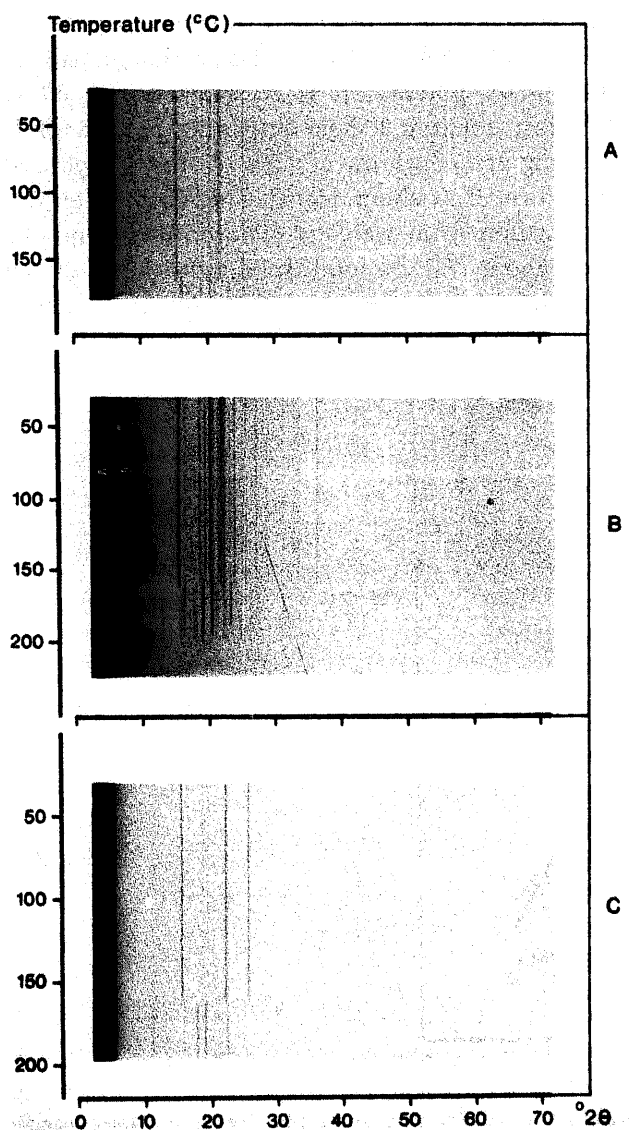


Fig. 11. X-ray diffraction patterns of polymorph III of sulphathiazole as a function of the temperature. A: form III prepared by fast crystallization from water. B: form III obtained by slow crystallization from water. C: form III prepared by very slow crystallization from water.

peak near 196.5°C, which indicates that a small amount of polymorph II was present. This amount was too small to be detected in the infrared spectrum or the X-ray pattern. The lower curve is the result of grinding the former commercial sample in a mortar for a short time.

In Table 1 the transition enthalpy of form III into form I and the melting enthalpies of the 3 crystalline modifications, as estimated by means of the DSC, are summarized. The value of the transition enthalpy of form III into form I is in very good agreement with the value calculated from the initial dissolution rates. As can be seen from the different DSC profiles, the specific heat of the molten substances was significantly higher than those of the crystalline modifications.

The influence of the method of preparation on the purity of polymorph III is demonstrated by using temperature-dependent X-ray patterns (see Fig. 11). The upper photograph shows the X-ray pattern of polymorph III of sulphathiazole which was prepared by very fast crystallization from water, immediately followed by isolating the crystals by filtration. During the cooling procedure firstly polymorph II crystallized and subsequently polymorph III. As a result of the fast isolation a slight amount of polymorph II remained in the material. During the heating procedure the crystals of form II induced the solid–solid transition of form III into form II at about 160°C. The X-ray pattern of polymorph III obtained by slow crystallization from water is pictured in the middle photograph of Fig. 11. At a temperature of about 160°C a solid–solid transition is shown of form III into form I and form II. At subsequent heating up polymorph II melted at

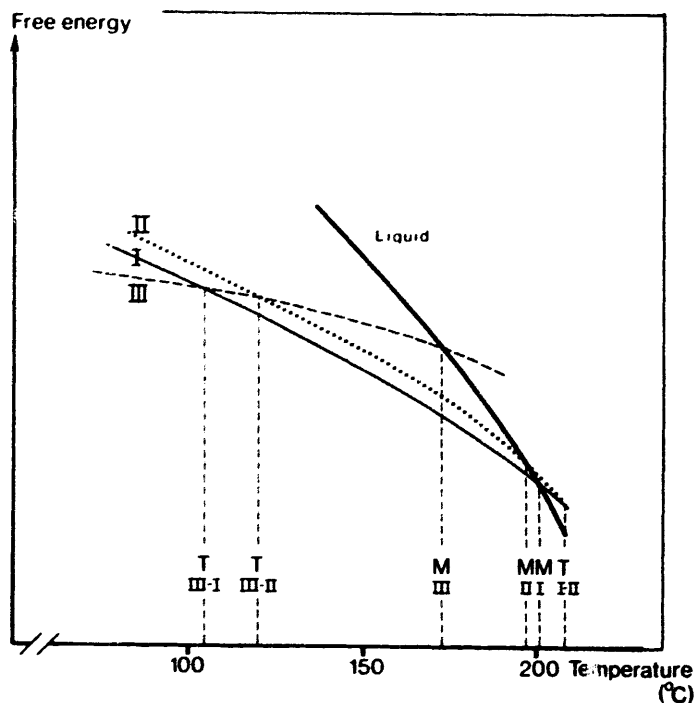


Fig. 12. Temperature course of the free energies of the different polymorphic forms of sulphathiazole as a function of the temperature. M = melting point, T = transition point.

196°C, which can be seen from the disappearance of the X-ray pattern of this modification. The diffraction pattern of form I remains visible until about 200°C. Polymorph III corresponding with the lower X-ray pattern was prepared by very slow crystallization from water. At about 160°C this modification underwent a solid–solid transition into form I of sulphathiazole, which indicates that this form was very pure.

Based on the preceding results, it was possible to draw the temperature course of the free energies of the different modifications of sulphathiazole. The transitions of the polymorphs I and II and of the polymorphs II and III are enantiotropic; the transition of polymorph II into polymorph I is monotropic.

In conclusion 3 crystalline modifications and an amorphous form of sulphathiazole were characterized by means of X-ray diffraction, thermoanalysis and infrared spectroscopy. The melting points of polymorphs I, II and III are 201.0°C, 196.5°C and 173.6°C, respectively. Complete melting of the polymorphs II and III was only observed if these modifications were very pure. Based on dissolution studies solid–solid transition temperatures of about 103°C for forms I and III, 120°C for forms II and III and 205°C for forms I and II were calculated. The transitions of polymorphs I and III and of II and III are enantiotropic; the transition of the polymorph II into polymorph I is monotropic.

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