

Various Species of Sulfathiazole Form I

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Abstract □ Sulfathiazole crystallized from ethanol, a mixture of ethanol and benzene, a mixture of chloroform and acetone, isopropyl alcohol, or 10% and 1% ammonia solutions gives Form I, which consists of varying proportions of a melting species and another species which undergoes solid-solid transition. This was confirmed both microscopically and by differential scanning calorimetry. Crimping of the samples crystallized from ammonia solutions causes the separation of the peaks representing these species and gives a thermogram identical to that obtained from samples crystallized from alcohol. Grinding appears to destroy the melting species and to have a significant effect on the transition temperature but not on the heat of transition. The calculated average heat of transition, for ground samples crystallized from both ammonia solutions and from alcohol, is 1652 ± 56 cal./mole. IR spectra and X-ray diffraction patterns of the powder did not show any major differences between samples crystallized from either solvent.

Keyphrases □ Sulfathiazole species—Form I □ Grinding, crimping effect—sulfathiazole crystals □ Melting range—sulfathiazole Form I crystals □ Differential scanning calorimetry—identity □ IR spectrophotometry—identity □ X-ray diffractometry—identity

There are conflicting reports as to whether sulfathiazole exists in two or three crystalline forms. Grove and Keenan (1) reported two forms: Forms I and II for which melting points are 175 – 176° and 201 – 202.5° , respectively. Milosovich (2), using the solubility method, stated that the transition temperature of Form I is $94.5 \pm 2.7^\circ$ with a heat of transition of 1744 cal./mole. On the other hand, Guillory (3), using differential thermal analysis, reported a transition temperature of 161° and a heat of transition of 1420 ± 40 cal./mole for Form I. Three crystalline forms of sulfathiazole were reported by Miyazaki (4) and Mesley and Houghton (5). These forms are symbolized as α or A (I),¹ β or B (II),¹ and a third form α' or C. These investigators claimed that the third form of sulfathiazole can only be prepared by crystallization from dilute ammonia solution. Form I can be prepared by crystallization from warm alcohol or a mixture of chloroform and acetone, and Form II by crystallization from *n*-propanol at 80° , *sec*-butanol, or by heating Form I at 180° .

Since sulfathiazole has been used extensively as a model drug in research work in recent years, it was found necessary to conduct a further investigation of the sulfathiazole polymorphic system to see whether or not this drug exists in more than two crystalline polymorphs.

EXPERIMENTAL

Materials and Apparatus—Sulfathiazole NF (Mallinckrodt) was used in this investigation. Group I solvents consists of ethanol USP, a mixture of benzene and ethanol (3:1), a mixture of chloroform and acetone (1:3), isopropyl alcohol, and 1% and 10% am-

Table I—Thermal Data of Sulfathiazole Form I Crystallized from Different Solvents Using DSC

Treatment	Solid-Solid Transition Peak		Melting Species Peak, Temp.	ΔH , cal./mole
	Transition Temp.	Maximum Temp.		
Hot Alcohol in Ice Bath				
Uncrimped and unground	161	170	179	1792 ± 249
Crimped and unground	161	170	177	2058 ± 137
Ground and crimped	141	Broad	—	1637 ± 83
10% Ammonia in Crystallizing Dish				
Uncrimped and unground	169	178	—	1899 ± 131
Crimped and unground	167	174.5	177	1984 ± 82
Ground and crimped	154	164.5	—	1647 ± 49
1% Ammonia in Beaker without Stirring				
Uncrimped and unground	—	—	176.5	2265 ± 369
Crimped and unground	159.5	171	176	1671 ± 236
Ground and crimped	157.0	167.5	—	1673 ± 22

monia solutions. Group II consists of *n*-propanol and *sec*-butanol. Unless otherwise specified, all these solvents were reagent grade.

A DSC-1B (Perkin-Elmer) was employed. Nitrogen, as an effluent gas, was used at a rate of 20 ml./min. Indium and tin were used for calibration of the temperature scale. In this investigation, the former was used as the main calibrant for calculating the heat of fusions and transitions since its heat of fusion is known to be 6.8 cal./g. (3, 6). Since a known weight of indium used in this investigation was supplied by the manufacturer, it was found necessary to check it against a substance whose heat of fusion is well documented. Form II of silver nitrate was used for this purpose. The heat of fusion of Form II of this compound is 2760 cal./mole (7). Areas under the peaks were measured with a planimeter. IR spectra were obtained using both KBr disks and mineral oil mulls. X-ray diffraction patterns, using 200-mesh powder, were obtained using a Siemens X-ray diffraction instrument.² Microscopic examinations were done employing a Zeiss polarizing research microscope equipped with a Kofler hot stage.

² The patterns were obtained through the courtesy of Dr. S. C. Mehta at the University of Michigan College of Pharmacy, Ann Arbor, Mich.

¹ Nomenclature used by other investigators.

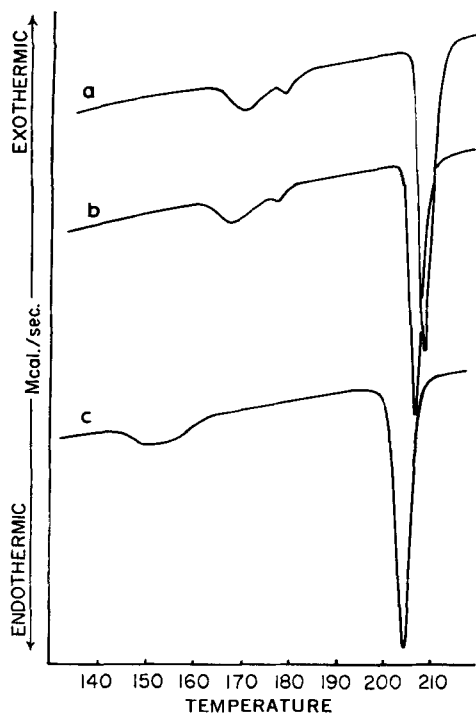


Figure 1—Thermograms of samples crystallized from alcohol in an ice bath. Key: a, uncrimped and unground; b, crimped and unground; c, ground and crimped; scan speed 40°/min. Peaks appearing below 200° represent the species of Form I and the peak appearing above this temperature represents Form II.

Preparation of Samples—Sulfathiazole was crystallized from a saturated solution in the various solvents. Sulfathiazole was crystallized from 10% ammonia solution on a watch glass. On the other hand, crystallization from 1% ammonia solution was performed in a beaker without stirring; the scaly crystals were filtered and dried at 100° for 30 min. under vacuum and scanned immediately.

Differential Scanning Calorimetry (DSC)—Samples weighing 1–6 mg. were used. A semimicro balance with a sensitivity of 0.01 mg. was used to weigh all samples. A scanning speed of 40°/min. was employed throughout this study, because a scanning speed of 10°/min. gave broad and irregular transition peaks. Using indium as the calibrant, the calculated heat of fusion of Form II of silver nitrate is 2812 ± 46 cal. mole. This value is comparable to the value reported (7).

Since sulfathiazole does not sublime on heating, it was thought at first to run the crystalline material prepared from different solvents without subjecting them to any stress or strain, *i.e.*, without crimping or grinding. The results obtained were compared with experiments performed on the crimped unground and crimped ground samples. Grinding was done using a mortar and pestle.

RESULTS AND DISCUSSION

Microscopic examination of sulfathiazole crystallized from Group I solvents revealed that these samples consist of two species in various proportions. One species undergoes solid–solid transition in a temperature range of 150–166°, depending on the solvent of crystallization. The second species melts between 170–176° with immediate partial crystallization. On further heating of the samples, complete melting was observed at 198–203°. The latter temperature range is the same melting range for sulfathiazole Form II crystallized from Group II solvents or from warm alcohol and heated to 180°. Crystallization of sulfathiazole from the solvents which yield Form I was done on a glass slide. On microscopic examination of the crystals on a hot stage, it was observed that complete melting occurred at 170–176° without crystallization in all cases. The absence of crystallization from the melt is due to the absence of seed material, as was demonstrated when the two species were present.

Since the two species of sulfathiazole Form I are present regardless of solvent system used and since sulfathiazole crystallized from am-

monia presents the point of controversy, it was decided to limit quantitative determination to crystals obtained from 10% and 1% ammonia solutions and to those crystallized from hot alcohol in an ice bath. The DSC results on those samples, subjected to various treatments, are summarized in Table I and their thermograms are shown in Figs. 1–3. Examination of the table and various thermograms in the figures shows that in the region of 140–180°, there are one or two peaks present, depending on the solvent of crystallization and the treatment of the sample. For example, the thermogram for sulfathiazole crystallized from alcohol consists of two peaks regardless of crimping. The first peak represents solid–solid transition and the second represents the melting species. Under the present conditions, *i.e.*, at a scanning speed of 40°/min., it was difficult to calculate the areas under the peak of each species. Slow scanning speed of 10°/min. caused the separation of two peaks, but the peaks were broad and very hard to differentiate from the base line. The total area under the two peaks was measured for a scanning rate of 40°/min., and ΔH was calculated. A large value of ΔH with a very large standard deviation was obtained for both crimped and uncrimped, unground samples. This is an indication of the nonuniformity of samples or, in other words, the samples taken consist of various proportions of the melting species which contribute to this great variation. However, after grinding and crimping the sample, it was found that the peak of the melting species completely disappeared, and only one peak was observed. The calculated heat of transition was found to be 1637 ± 83 cal./mole. On the other hand, uncrimped and unground samples crystallized from ammonia gave one peak on scanning. An exotherm was observed in samples crystallized from 1% ammonia and, in some instances, in samples crystallized from 10% ammonia, indicating some crystallization of the melt. This was confirmed by the microscopic examination, as well as by visual observation in the open pan while scanning. The exotherm was not noticed when the crystallized sample was run after a few days.

After crimping the unground sample, two peaks were obtained similar to those obtained in the case of sulfathiazole crystallized from alcohol. The appearance of two peaks, the first representing solid–solid transition and the second representing melting, may be due to crimping. In the case of samples crystallized from ammonia solutions, crimping caused the separation of the two peaks repre-

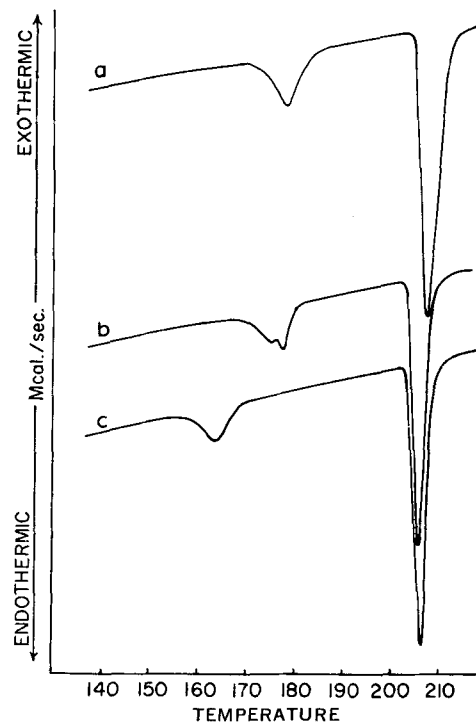


Figure 2—Thermograms of samples crystallized from 10% ammonia solution in a crystallizing dish. Key: a, uncrimped and unground; b, crimped and unground; c, ground and crimped; scan speed 40°/min. Peaks appearing below 200° represent the species of Form I and the peak appearing above this temperature represents Form II

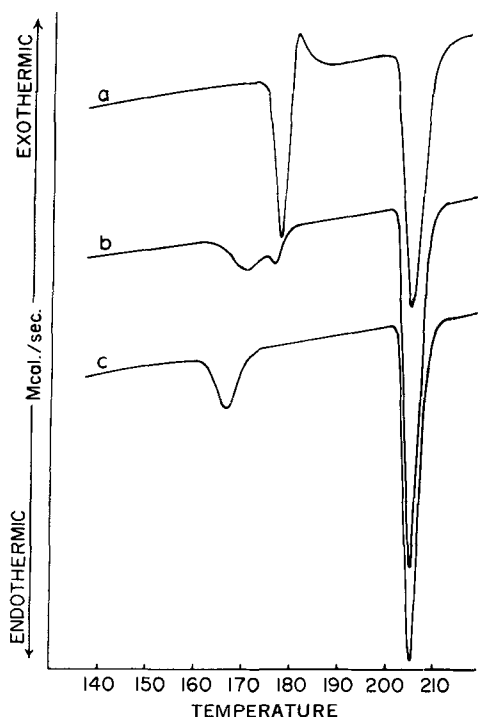


Figure 3—Thermograms of samples crystallized from 1% ammonia solution in a beaker without stirring. Key: a, uncrimped and unground; b, crimped and unground; c, ground and crimped; scan speed 40°/min. Peaks appearing below 200° represent the species of Form I and the peak appearing above this temperature represents Form II.

senting the two species. Upon grinding and crimping, the system was apparently stabilized and only one peak was observed. The calculated heats of transition are 1647 ± 49 and 1673 ± 22 cal./mole for both sulfathiazole crystallized from 10% and 1% ammonia, respectively. These values are not significantly different, within experimental errors, from the value obtained when alcohol was used as a crystallizing medium. The values for ΔH obtained from 18 runs gave a calculated average of 1652 ± 56 cal./mole. It appears, therefore, that crimping and grinding have an effect on the thermal behavior of sulfathiazole Form I. Furthermore, grinding caused a shift in transition temperature of about 15 and 20° in the case of sulfathiazole crystallized from ammonia and alcohol, respectively, although the calculated heats of transition are almost the same. This shift in transition temperatures might be due to differences in particle size and change in thermal conductivity of the sample as reported by Guillory (3) and Moustafa and Carless (8). The findings reported here are not different from those reported recently (8). In their report, Moustafa and Carless stated that in no case was melting observed below 200°. The present results, both microscopically and calorimetrically, suggest the presence of a melting species and another that undergoes solid-solid transition. This phenomenon was observed in all cases where Form I was produced and not only in the case of sulfathiazole crystallized from 95% alcohol as reported (8). The same authors reported that vibration milling of Form I crystallized from 95% ethanol resulted in the transition temperature being lowered by 5°. This finding is in agreement with the present observa-

tion, although a more dramatic effect was noticed with grinding. Mesley and Houghton (5) reported differences in the IR spectra of sulfathiazole crystallized from dilute ammonia and from alcohol, although no spectra were presented in their report. In the present study, there were no major differences in either IR spectra or X-ray diffraction patterns of both samples when those patterns were compared with already published ones (8, 9). Since grinding is a prerequisite for the preparation of samples tested by these techniques, and since it has been shown to destroy the melting species in this study, differences in the mentioned patterns were not observed.

It is rather misleading to call the melting species of sulfathiazole a third physical form, since the techniques employed in this investigation did not confirm its presence as a separate and pure entity with great differences in physical characteristics. However, the present results do not preclude the existence of a third form of sulfathiazole. 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.

The peaks representing Form II in all runs performed in this study were evaluated and compared to those obtained from samples crystallized from Group II solvents and from warm alcohol heated at 180°. Large variation was observed in the case of uncrimped and crimped, unground samples. This is probably due to incomplete crystallization of the melting species. However, grinding the sample resulted in a heat of fusion which compares well with that obtained from pure Form II. The calculated average heat of fusion for this form, whether the starting sample was crystallized from ammonia or alcohol, is 6893 ± 185 cal./mole. This value is comparable to the one reported by Moustafa and Carless (8)—*viz.*, 6615 ± 235 cal./mole. The scanning rate was found to have little or no effect on the value of ΔH of Form II. In this study, it was found that there is a difference of about 2% in the value of ΔH of Form II scanned at 10°/min. and 40°/min. This is the same difference observed when the calibrant was scanned at both rates.

REFERENCES

- (1) D. C. Grove and G. L. Keenan, *J. Amer. Chem. Soc.*, **63**, 97(1941).
- (2) G. Milosovich, *J. Pharm. Sci.*, **53**, 484(1964).
- (3) J. K. Guillory, *ibid.*, **56**, 72(1967).
- (4) H. Miyazaki, *Jap. J. Pharm. Chem.*, **19**, 133(1947); through *Chem. Abstr.*, **45**, 3559(1951).
- (5) R. J. Mesley and E. E. Houghton, *J. Pharm. Pharmacol.*, **19**, 295(1966).
- (6) J. Tsau and D. F. R. Gilson, *J. Phys. Chem.*, **72**, 4082(1968).
- (7) F. D. Rossini, D. D. Wagman, W. H. Evans, S. Levine, and I. Jaffe, *Nat. Bur. Stand. (U. S.) Circ.*, **500**, 679(1952).
- (8) M. A. Moustafa and J. E. Carless, *J. Pharm. Pharmacol.*, **21**, 359(1969).
- (9) W. I. Higuchi, P. D. Bernardo, and S. C. Mehta, *J. Pharm. Sci.*, **56**, 200(1967).

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