Physical Properties of Four Polymorphic Forms of Sulfanilamide I: Densities, Refractive Indexes, and X-Ray Diffraction Measurements

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Abstract □ Densities, refractive indexes, and X-ray crystallographic data are tabulated for four crystalline forms of sulfanilamide. These data suggest that three of the forms have very similar structures.

Keyphrases □ Sulfanilamide—densities, refractive indexes, and X-ray diffraction data for four polymorphic forms □ Polymorphs—sulfanilamide, physical properties □ X-ray diffraction—four polymorphic forms of sulfanilamide

In a previous article (1), IR spectra, heats of transition, and differential thermal analysis (DTA) thermograms were reported for four polymorphic forms of sulfanilamide. The properties of these crystalline species differed somewhat from those previously reported in the literature. Consequently, it was deemed essential to obtain additional information for characterizing the polymorphs.

EXPERIMENTAL

Crystal Structures—The Weissenberg camera and Precession camera were employed for taking single-crystal diffraction pictures. One end of a fine fiber of glass was fixed on a goniometer head using Canada balsam. A selected crystal was mounted on the other end of the glass fiber. The goniometer head holding the crystal was then transferred to the Weissenberg or Precession camera. Adjustments were made on the goniometer so that the chosen axis of the crystal was coincident with the axis of rotation of the goniometer. The Weissenberg zero-layer-line and first-layer-line pictures and Precession pictures were taken after the crystal was well aligned. Cell dimensions and monoclinic angles were determined by careful measurements on these pictures for each crystal sample. In addition, cell dimensions and errors for the α- and γ-forms were calculated by a least-squares computer program of back-reflection Weissenberg single-crystal diagrams. The errors of cell dimensions for the β- and δ-forms were then determined by comparing the values of cell dimensions and errors for the α- and γ-forms obtained by direct measurements and computer calculations. The number of molecules per unit cell for each crystal form was calculated according to Eq. 1:

$$Z = \frac{\text{unit cell volume} \times \text{density} \times \text{Avogadro's number}}{\text{molecular weight}} \quad \text{(Eq. 1)}$$

The calculation and interpretation of X-ray pictures were performed according to procedures described by Buerger (2) and McLachlan (3).

Refractive Indexes—Refractive indexes were determined with a Zeiss polarizing microscope. The microscope used for examination of the crystals was equipped with polarizing prisms below and above a rotating, graduated, circular stage, and with accessories including a Bertrand lens and first-order red and quartz wedge compensators. Crystals were immersed in a series of liquids of known refractive indexes and were examined between crossed polars under the microscope. One of the component vibrations of light of the crystal was selected, and the Becke test was applied for the refractive index determinations. A crystal has the same refractive index as the medium in which shadow boundaries are at a minimum. This operation and test were repeated after rotating the stage 90°, and a second refractive index of the substance was obtained. The precision of each determination of refractive index was within ±0.004.

RESULTS AND DISCUSSION

Data obtained from the X-ray crystallographic study of sulfanilamide polymorphs are reproduced in Table I. These data indicate that the δ-, β-, and γ-forms in this study correspond to the α-, β-, and γ-forms reported by Watanabe (4). The α-form in this investigation is a form that was not reported previously (1).

The unit cell volumes of these polymorphs are calculated to be 768.7, 758.8, 769.2, and 1544.7 Å^3 for the α-, β-, γ-, and δ-forms, respectively. The similarity in cell dimensions and monoclinic angles in the α- and β-forms indicates that the structures of these two forms are similar. This conclusion is further supported by the observation that they have very nearly the same heat of transition (1). The slightly greater unit cell volume of the α-form suggests that the packing of this form is less compact and its structure is more easily broken down. Therefore, the α-form undergoes a phase transition to the γ-form at a lower temperature than does the β-form.

Data obtained from optical crystallographic studies of sulfanilamide and sulfanilamide-d_4 polymorphs are listed in Table II. The data for the refractive indexes of the δ-, β-, and γ-forms are in agreement with data on the α-, β-, and γ-forms reported previously (5, 6). A careful comparison of refractive indexes between the α- and β-forms in this study reveals that the α-form has lower refractive indexes on the average than the β-form. These results imply that light passes through a crystal of the α-form at a slightly higher speed. In other words, the α-form is less compact in terms of molecular packing. The slightly lower refractive indexes of sulfanilamide-d_4 polymorphs compared to the corresponding undeuterated forms can be interpreted to mean that substitution of deuterium for hydrogen in sulfanilamide increases the hydrogen bond distances. Therefore, the molecular packings are less compact in sulfanilamide-d_4 crystals.

The crystal densities of sulfanilamide polymorphs were determined to be 1.505, 1.523, 1.510, and 1.499 g/cm^3 for the α-, β-, γ-, and δ-forms, respectively. The lower value of the density for the α-form, as well as observations obtained from solubility and dissolution studies (7), indicates that there is a correlation between these physical measurements and the results of the X-ray diffraction studies. Both groups of data provide evidence that the α-form is less compact and less stable as compared with the β-form. The small differences in crystal structures between the α- and β-forms apparently have a substantial influence on their physical properties.

Significant changes in physical characteristics resulting from minor differences in crystal structure were reported previously. Katayama (8) studied the structures of two polymorphic forms of chloroacetamide. In spite of very small variations in the cell's dimensions and in the monoclinic angles of the α-and β-chloroacetamide polymorphs, their solubility behaviors are quite different.

The α-, β-, and γ-forms of sulfanilamide are monoclinic and contain four molecules in each unit cell. Transformations from the α- and β-forms to the γ-form at transition temperatures probably involve only bond bending and bond dilation within a cluster. The δ-form, on the other hand, is orthorhombic and contains eight molecules in each unit cell. The transformation from the δ-form to the γ-form may, therefore, be expected to involve a molecular reconstructive process. Such processes, as a rule, involve more work, and more energy has to be absorbed during the phase

Table I—X-Ray Crystallographic Data for Sulfanilamide Polymorphs

Polymorphic Forms	Crystal Systems	Cell Dimensions, Å	Unit Cell Numbers	Monoclinic Angles
α-Form	Monoclinic	$a = 9.042 \pm 0.003$ $b = 9.034 \pm 0.002$ $c = 10.06 \pm 0.02$	4	110°42′
β-Form	Monoclinic	$a = 8.95 \pm 0.02$ $b = 9.06 \pm 0.02$ $c = 9.96 \pm 0.02$	4	110°
γ-Form	Monoclinic	$a = 7.783 \pm 0.006$ $b = 12.944 \pm 0.003$ $c = 7.95 \pm 0.02$	4	106°1′
δ-Form	Orthorhombic	$a = 14.81 \pm 0.02$ $b = 5.65 \pm 0.02$ $c = 18.46 \pm 0.02$	8	—

Table II—Optical Crystallographic Data for Sulfanilamide and Sulfanilamide-d_4 Polymorphs

	Polymorphic Forms	Refractive Indexes α	β	γ
Sulfanilamide polymorphs	α-Form	1.580	1.644	—
	β-Form	1.560	1.680	—
	γ-Form	—	1.676	>1.800
	δ-Form	1.548	1.624	
Sulfanilamide-d_4 polymorphs	α-Form	1.576	1.640	—
	β-Form	1.556	1.672	—
	γ-Form	—	1.664	>1.800
	δ-Form	1.540	1.620	—

transformation. Consequently, the transformation energy is higher for the δ-form as compared with the α- and β-forms.

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Effect of Multiple Doses of Cadmium on Glucose Metabolism in the Rat

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Abstract □ The effect of multiple doses of cadmium on carbohydrate metabolism in rats was studied. The treated groups received two dose levels, 0.25 and 0.50 mg cadmium/kg ip every 2nd day for 20 doses. Plasma glucose, immunoresponsive insulin levels, and body weights were determined before treatment and after 10 and 20 doses of cadmium. After the last dosage, D-glucose-^{14}C (uniformly labeled) was administered to a randomly chosen subgroup and a carbon dioxide radiorespirometry experiment was performed. Statistically significant differences in blood glucose and insulin levels were not detected at any time, indicating no effect of cadmium on the pancreatic secretory activity. There was no effect on body weights. However, cadmium increased the evolution of respiratory $^{14}CO_2$. It is postulated that cadmium affects the rate of glucose metabolism *in vivo* by affecting mechanisms such as glycolysis and the tricarboxylic acid cycle.

Keyphrases □ Cadmium—effect of multiple doses on glucose metabolism, rat □ Glucose metabolism—effect of multiple doses of cadmium, rat □ Glycolysis—possible effect of multiple doses of cadmium on glucose metabolism, rat

In the last 15 years, the role of metals in the structure and function of proteins became a new field for investigation. Unfortunately, there is limited information concerning the nature of the metal-binding sites in metalloproteins. Although different metallic ions may have similar chemical properties, they may