Thermodynamic Study of Sulfanilamide Polymorphism: (I) Monotropy of the α-Variety

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Purpose. Sulfanilamide was chosen as a model compound in order to gain insights on the stability hierarchy of drug polymorphs from structural and thermodynamic criteria. Despite numerous studies, disagreements remained on the reported enthalpies associated with the mutual interconvertions of the α-, β-, and γ-forms of sulfanilamide. Therefore, the unambiguous determination of these enthalpies was the purpose of this work.
Methods. Samples, free of solvent inclusions and made of only one form, were prepared, and analyzed combining X-ray powder diffraction and Differential Scanning Calorimetry (DSC).
Results. The enthalpy values associated with the α- to γ- and β- to γ-transitions were found to be + 10.2 and + 10.9 J g^{-1}, respectively. The calculated enthalpy of the β- to α-transition is consistent with the experimental one (+ 1 J g^{-1}).
Conclusions. The monotropy of the α-form was ascertained over the explored temperature range at ordinary pressure.

KEY WORDS: sulfanilamide polymorphism; monotropy; solid-solid transitions; solvent inclusions.

INTRODUCTION

Polymorphism can affect drug bioavailability (1). Hence, one needs to determine the thermodynamic stability hierarchy of the polymorphs of a drug because metastable forms frequently yield the highest plasma levels. As a contribution to pressure-temperature descriptions of polymorphism (2, 3), sulfanilamide was chosen as a model compound. Indeed, it is not known whether one of its polymorphs (the α-form) is monotropic or enantiotropic.

At room temperature, sulfanilamide crystallizes at least in three forms, the so-called α-, β- and γ-forms (4, 5). The crystal structures have been determined: the α-form is orthorhombic (6) while the β- (7) and γ-forms (8, 9) are monoclinic. A fourth form has been identified (10–13), but its crystal structure remains unknown. A comparative analysis of enthalpy changes at the β→γ and α→γ transitions, $\Delta H_{\beta\to\gamma}$ and $\Delta H_{\alpha\to\gamma}$ respectively, is required to apply the Ostwald lowest vapour pressure criterion in order to establish a stability hierarchy among the α-, β-, and γ-forms. Since the literature shows discrepancies among the $\Delta H_{\beta\to\gamma}$ and the $\Delta H_{\alpha\to\gamma}$ values (11, 12, 14–16), we performed DSC measurements on these forms. In order to get unambiguous results, a particular attention was paid in the preparation and characterization of batches containing one kind of polymorph.

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MATERIALS AND METHODS

Material

Sulfanilamide (purity >99%) was used as received from Aldrich Chemie (FGR). Radiocrystallographic controls only revealed Bragg reflections of the β-form.

DSC Measurements

Temperatures and heats of transition and fusion were determined at a heating rate of 10 K · min^{-1} with a TA Instruments (USA) DSC10 Differential Scanning Calorimeter equipped with a TA Instruments 9900/2100/2000 computer-analyzer system. Accuracy on fusion heats was estimated to be about 5% and reproducibility was better than 2%. Most measurements were performed under static air. During low-temperature scans (from 100 K) a nitrogen purge was maintained in the standard cell in order to prevent moisture condensation.

The mass of each sample (3–15 mg) was determined using a H51 Mettler (Switzerland) microbalance whose uncertainty was less than 0.5% and reproducibility better than 0.03 mg.

X-Ray Measurements

Ideal X-ray diffraction profiles for α-, β- and γ-forms (Figures 1a–c) were calculated using the Lazy™ software. Experimental X-ray diffraction spectra were obtained at room temperature with an Enraf-Nonius (Netherlands) Guinier camera (114.59 mm diameter) or with a CGR (France) diffractometer ($CuK\alpha_1$ radiation (154.05 pm) in both cases).

Preparation of Samples

α-Form

Transparent needles were obtained by two methods. According to method A, α-crystals were grown by cooling a hot filtered saturated solution in n-butanol kept ten minutes at 373 K. DSC curves showed the presence of a small amount of γ-form. The X-ray diffraction spectrum (Figure 2) confirmed this result as well as the presence of residual β-crystals.

Method B consisted in preparing a solution in n-butanol at 353 K according to the solubility data for the less soluble β-form (17). The quantity corresponding to the saturation limit at 353 K was heated and stirred in 20 ml of n-butanol until β-sulfanilamide was dissolved. Then, the solution was rapidly cooled at room temperature. α-crystals began to grow at about 343 K. Once separated, DSC and diffractometry measurements did not reveal any other form.

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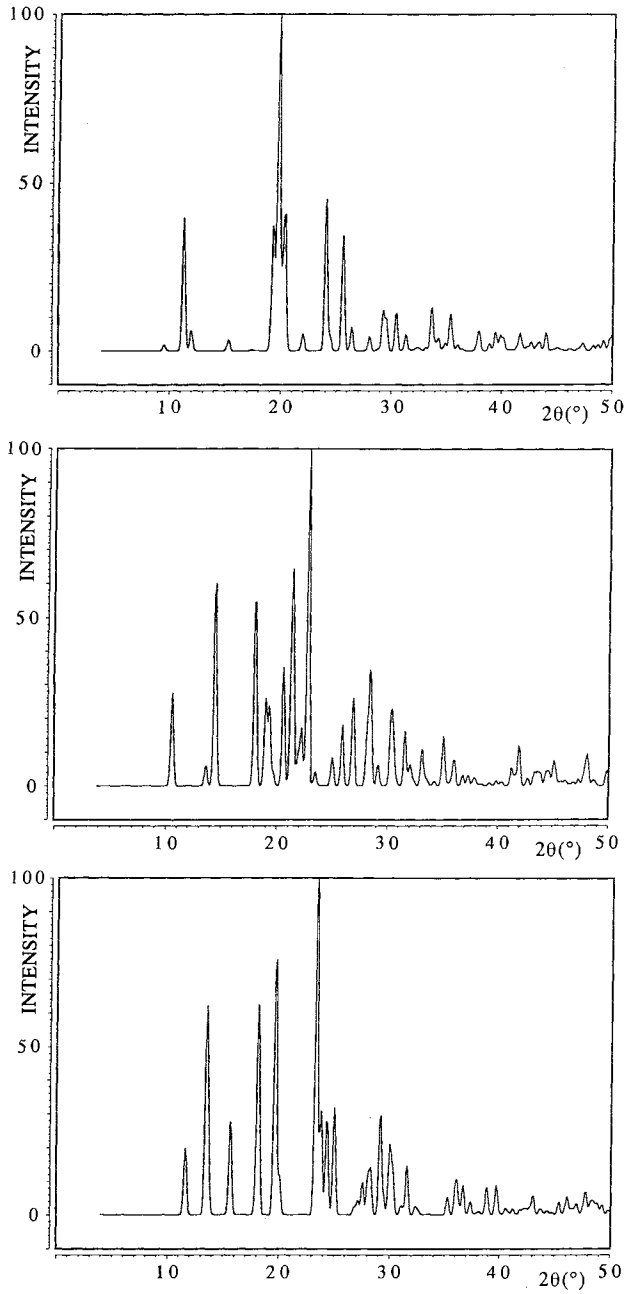

Fig. 1. Ideal X-ray diffraction profiles for the α-, β- and γ-forms (1a, 1b and 1c, respectively), from crystal structure data.

β-*Form*

This form always appeared whichever solvents we used (water, acetone, ethanol, n-propanol and n-butanol).

Transparent prismatic crystals were obtained by slowly evaporating an acetone solution at room temperature. Visual examination under microscope showed in-crystal cavities which were accounted for solvent inclusions which appeared during the crystal growth.

By hot crystallization in n-propanol, very small transparent crystals were obtained with the method used to prepare the α-form.

Opaque crystals were prepared by fast crystallization in acetone, and by slow crystallization in ethanol, n-propanol, n-butanol or water and, at high temperature, by slowly cooling a 15%-in-mass sulfanilamide aqueous solution.

γ-*Form*

This polymorph was prepared by evaporating a n-butanol solution at 373 K. Needle-shaped crystals were obtained. They were slightly opaque and shorter than the α-needles.

RESULTS

α-*Form*

Seven DSC experiments performed on the A samples showed an endothermal peak (onset at 379.6–380.2 K) related to the α→γ transition ($\Delta H_{\alpha\rightarrow\gamma} = +9.0\ J \cdot g^{-1}$). Four out of seven thermograms showed a very small endothermal peak at about 426 K. This was assigned to the fusion of some remaining α-crystals, in agreement with reference (12), which describes the metastable fusion of the α-form at 424 K. Melting of the γ-form, obtained from the α→γ transition, occurred at 437.5–438.0 K ($\Delta H_{fus}(\gamma) = +126.2 \pm 5.2\ J \cdot g^{-1}$). The sharpness of the fusion peak suggests that some residual α-crystals have no effect on the fusion temperature of the γ-form.

These experiments were carried out in punctured pans. When a sealed pan was used, a smaller $\Delta H_{\alpha\rightarrow\gamma}$ value was found ($+6.4\ J \cdot g^{-1}$).

As for experiments carried out in closed pans on the B samples, no thermogram showed the α-form fusion. The transition temperature $T_{\alpha\rightarrow\gamma}$ varied between 378.6 and 381.2 K ($\Delta H_{\alpha\rightarrow\gamma} = +10.2 \pm 0.5\ J \cdot g^{-1}$). The mean $\Delta H_{fus}(\gamma)$ value was $+134.5 \pm 2.0\ J \cdot g^{-1}$.

β-*Form*

The thermal behavior of this polymorph was investigated with samples obtained from different solvents. Both $T_{\beta\rightarrow\gamma}$ and $\Delta H_{\beta\rightarrow\gamma}$ values depend on the sample origin as

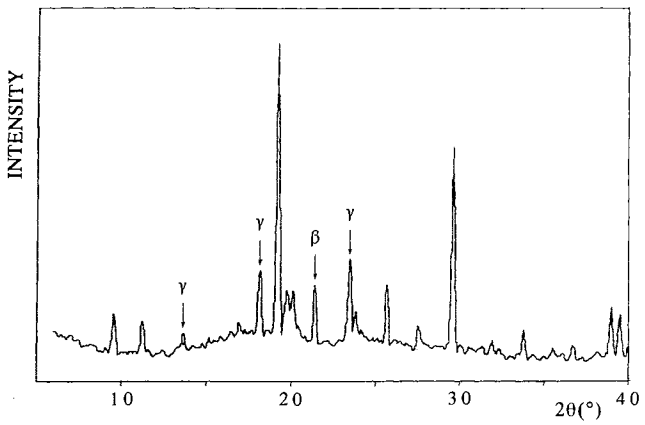

Fig. 2. X-ray diffraction spectrum of α-sulfanilamide crystallized in n-butanol (method A); some peaks of the γ-form and one of the main peaks of the β-form are present.

shown in Table I. When the same solvent was used, other parameters (such as the crystallization rate or the sample morphology) could influence the experimental results. For instance, let us consider the case of sulfanilamide crystallized in acetone. With a single crystal, $T_{\beta\rightarrow\gamma}$ and ΔH_{fus} values are lower than those obtained with a powder: this could be due to mechanical constrains and to solvent inclusions which introduce some uncertainty on the sample mass. This effect on $\Delta H_{\beta\rightarrow\gamma}$ could be balanced by a slight increase due to endothermal solvent-loss as can be noticed in Table I.

The broadening of the melting peak in Figure 3B can be replaced by a small endothermal peak at about 430 K followed by the narrow melting endotherm of phase γ, as in Figure 3A. These two observations can be understood in terms of the melting of some residual β-form. Therefore, the transformation β→γ is never observed as complete when form β is the starting material.

γ-Form

This form was obtained by evaporating a solution in n-butanol or by recrystallization from melt after supercooling (about 30 K) and could be kept for months at room temperature, without transformation.

The γ-form did not undergo any transition on heating before fusion (Figure 3C).

Although the occurrence of the γ→β transition was never observed on cooling, we consider that the γ-form is the stable one only between $T_{\beta\rightarrow\gamma}$ and $T_{fus}(\gamma)$.

In fact, as $T_{\alpha\rightarrow\gamma} < T_{\beta\rightarrow\gamma}$, it turns out that the Ostwald least vapor pressure criterion is satisfied for both the β- (for $T < T_{\beta\rightarrow\gamma}$) and the γ-forms (for $T > T_{\beta\rightarrow\gamma}$ up to $T_{fus}(\gamma)$), if one takes into account that:

a) β-v and γ-v solid-vapour equilibrium curves cross at $T_{\beta\rightarrow\gamma}$ and are described by linear (Ln(p) vs T) equations, whose slopes are equal to the sublimation heats;

b) $\Delta H_{\beta\rightarrow\gamma}$ is positive and roughly equal to the difference between the β- and γ- sublimation heats,

Thus, the enantiotropic character and, consequently, the stability of the β-γ equilibrium are unambiguously demonstrated.

Table I. DSC Results on β-Sulfanilamide Obtained by Crystallization in Different Solvents

	$T_{\beta\rightarrow\gamma}$ (K)	$\Delta H_{\beta\rightarrow\gamma}$ (J · g^{-1})	$T_{fus}(\gamma)$ (K)	$\Delta H_{fus}(\gamma)$ (J · g^{-1})
Water[a]	384.4	10.0	437.1	133.2
Water[b]	382.1	10.9	437.7	130.1
Ethanol	391.6	10.2	437.7	133.9
n-propanol	401.8[c]	9.3	437.7	128.4
n-butanol	395.6[c]	9.4	436.1	129.5
Acetone[d]	393.9	9.9	437.9	126.0
Acetone[e]	401.1	9.8	437.8	129.5
DSC results on commercial β-sulfanilamide				
Ground sample	381.9	9.9	436.8	129.6
Ground sample[f]	389.0	10.1	437.4	131.9
Original sample	384.6	9.4	434.8	123.2

[a] Complete evaporation of the solvent.
[b] Sulfanilamide obtained by filtration of a saturated aqueous solution.
[c] The DSC base line deflection actually started at about 383 K.
[d] Crystalline sample.
[e] Ground sample.
[f] Sample kept 10 months in sealed pans before being submitted to DSC analysis.

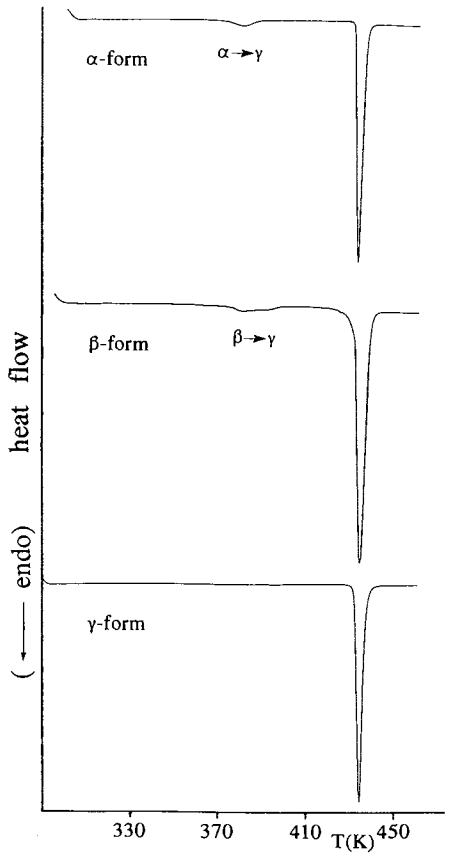

Fig. 3. DSC curves of A) α-form, B) β-form and C) γ-form.

Low Temperature Studies

Since there were no results on these polymorphs at low temperature, we studied their thermal behavior from 100 K up to 298 K. We also wanted to check the prediction according to which a reversible α→β transition occurs at 154 K (12).

Samples of the β-form crystallized in n-propanol and in water, were analyzed. The thermogram of the former sample, as well as those of the α- and γ-samples, did not exhibit any low-temperature transition peak, while the latter form thermogram showed a weak endothermal peak (+ 0.8 J · g^{-1}) at about 274 K. X-ray analysis performed on this sample cooled at 100 K and heated up to 298 K in the DSC cell, yielded the β-form spectrum. However, this result could not eliminate the possibility of a reversible conversion of the β-variety into another one on cooling.

DISCUSSION

Solvent inclusions in β- crystals were ascertained only during experiments on single crystals slowly crystallized from acetone solutions. However, we could not exclude the formation of inclusions with other solvents. This might ex-

plain the discrepancies among the reported values of $T_{\beta\rightarrow\gamma}$ and $\Delta H_{\beta\rightarrow\gamma}$.

Five crystallographic studies (5, 7, 8, 10, 13) showed that the α-form possesses the greatest specific volume. This result was used (13) to explain why $T_{\alpha\rightarrow\gamma}$ must be lower than $T_{\beta\rightarrow\gamma}$. Thus, the energy needed to transform into the γ-form will be higher for the β-form than for the α-one. Therefore, the α-form would be monotropic, as already found by Bürger (15). However, according to the $\Delta H_{\alpha\rightarrow\gamma}$ and $\Delta H_{\beta\rightarrow\gamma}$ values he reported, $\Delta H_{\alpha\rightarrow\beta}$ would be positive on heating. Albérola (14) agreed on the monotropy of the α-form because of the experimental irreversibility of the α→γ transition. However, the $\Delta H_{\alpha\rightarrow\gamma}$ mean value that he reported is smaller than the other values of the literature.

Considering their finding that $\Delta H_{\alpha\rightarrow\gamma} > \Delta H_{\beta\rightarrow\gamma}$, Sekiguchi *et al.* (12) concluded that the α form is enantiotropic at low temperature. However, they did not draw any thermodynamic conclusion as to the incompleteness of the β→γ transition as it appeared from their DSC thermograms of the β-form (which also showed the β-fusion peak at around 425 K). Besides, the existence of a α→β transition at 154 K was not proved experimentally.

Since the β→γ transition is incomplete, contrary to the α→γ one, this implies that the actual $\Delta H_{\beta\rightarrow\gamma}$ value should be higher than those we have determined. Hence, we have retained the highest value ($+ 10.9\ J \cdot g^{-1}$) for the sake of comparison with $\Delta H_{\alpha\rightarrow\gamma}$ ($+ 10.2\ J \cdot g^{-1}$). Therefore, it yields $\Delta H_{\alpha\rightarrow\beta} = - 0.7\ J \cdot g^{-1}$. The associated transition (if it does occur) will be observed from β to α on heating because, according to the Le Chatelier principle, it evolves endothermically. Thus, the α-form should not be the stable form at low temperature.

Despite the experimental uncertainty is larger than this $\Delta H_{\alpha\rightarrow\beta}$ value, the sign of this enthalpy has been determined from a DSC experiment on a B sample of the α-form, taking an equal amount of the β-form as the reference sample. By integrating the peak areas representing the difference $\Delta H_{\beta\rightarrow\gamma} - \Delta H_{\alpha\rightarrow\gamma}$, we obtained $+ 1\ J \cdot g^{-1}$, which is the $\Delta H_{\beta\rightarrow\alpha}$ value in agreement with the result reported above.

In conclusion, our measurements revealed a monotropic behavior of the α-form over all the temperature domain. In fact, only an α→γ transition was detected. Neither the opposite one nor the α- and β- transformations into each other were ever observed. However, according to the definition of the overall monotropy given in a previous paper (3), these results cannot exclude the existence of a high pressure stability domain for the α-form.

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