# Demonstration of the Terms Enantiotropy and Monotropy in Polymorphism Research Exemplified by Flurbiprofen

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Received May 5, 1998. Accepted for publication October 8, 1998.

**Abstract** □ The thermodynamic terms enantiotropy and monotropy are demonstrated by means of solid-state analytical results of polymorphous flurbiprofen (FBP). Vibrational spectra, differential scanning calorimetry (DSC), and thermomicroscopy investigations as well as X-ray powder patterns for three modifications of FBP are described. The melting points are mod. I 113–114 °C (enthalpy of fusion 27.9 ± 0.2 kJ $mol^{-1}$) for modification I (mod. I), 92 °C for mod. II, and 87 °C for mod. III. The true densities of mod. I (1.279 ± 0.001 g $cm^{-3}$) and mod. II (1.231 ± 0.002 g $cm^{-3}$) were measured at 25 °C. Modification I (commercial product) is the thermodynamically stable crystal form from absolute zero to its melting point. Modification II was crystallized on a gram scale from a warm saturated solution of FBP in *n*-heptane and rapid cooling of the solution to –18 °C. Modification I is monotropically related to mod. II and mod. III, due to application of the density rule and the entropy-of-fusion rule. The thermodynamic relationships between the three modifications are demonstrated by a semischematic energy/temperature diagram. Theoretical vapor pressure/temperature diagrams and energy/temperature diagrams are compared and briefly discussed.

## Introduction

Compared with mineralogy and metallography, pharmacy was relatively slow to deal with the terms enantiotropy and monotropy, which are very important in crystal polymorphism research. Even today, some authors working in this area seem to have great trouble with these terms, as has been shown by recent publications in respected journals on chloramphenicol palmitate[1] and flurbiprofen.[2] Two pharmaceutically relevant modifications, mod. I (A) and mod. II (B), are of particular interest in the case of chloramphenicol palmitate. The lower melting form II is pharmacologically active and is used in suspensions, whereas form I is inactive as an antibiotic.[3] The reason for the loss of activity of suspensions of the drug substance is that mod. II is thermodynamically unstable under ambient conditions and, due to its better solubility, this crystal form slowly recrystallizes into mod. I in suspensions.

From the many papers about the polymorphism of chloramphenicol palmitate only the one published by Burger[4] will be mentioned here because it also contains a critical review of earlier contributions. Due to the differences in solubility (thermodynamically unstable modifications exhibit better solubility than the thermodynamically stable one at a given temperature) and the differences in the enthalpy of fusion (unstable modifications show a lower enthalpy of fusion than the stable one in a monotropically related system) it is obvious, that mod. II is thermodynamically unstable in relation to mod. I from absolute zero up to its melting point (mp); that is, mod. I and mod. II are monotropically related. This fact was denied by the cited authors[1] and they postulated enantiotropy in this case because they succeeded in obtaining mod. II by quenching and recrystallizing the melt of mod. I. This mistake obviously happened because these authors[1] are unaware of the fact that the terms enantiotropy and monotropy are related to the direct transition between two crystalline phases; that is, that solid−solid transitions occur and intervening melting processes are excluded. The term "enantiotropy" was chosen by Lehmann[5] because it refers to a reversible process in the solid state, whereas the converse "monotropy" implies that the transition can occur in one direction only. Furthermore, it seems that the authors[1] are not familiar with the fact that for more than 100 years, one of the most common methods to obtain polymorphic modifications is crystallization of supercooled melts. Of course, nature has used this method thousands of years ago to create polymorphic modifications of minerals and chemical elements. It is a matter of fact that the method of crystallizing mod. II out of the melt of mod. I using differential scanning calorimetry (DSC) has been successfully tested on numerous drugs.[6] Because the authors of the second paper[2] just mentioned were not quite sure whether the two modifications of flurbiprofen described by them are enantiotropic or monotropic ("probable enantiotropic transition of form II into form I"), we decided to check the polymorphism and found a third modification as well. With this new result it is possible to explain most of the apparent discrepancies.

It is a general question in pharmacy whether polymorphic modifications can transform reversibly (enantiotropy) or irreversibly (monotropy) at atmospheric pressure, because polymorphic crystal forms of a specific chemical compound have different physical properties caused by different arrangements of the molecules in the crystal lattice. These different characteristics often lead to considerable differences in grinding and compression behavior as well as in hygroscopicity, solubility, and bioavailability, etc. All these properties are of great importance for the production of pharmaceutical formulations. Using a thermodynamically unstable modification in the production of tablets, creams, suspensions, solutions, etc. is sometimes the reason why unwanted changes take place in such formulations after a time of storage, caused by transition into the room temperature, thermodynamically stable modification. In the worst case, as shown by the case of chloramphenicol palmitate, this transition may lead to a complete loss of activity of the drug substance. On the other hand it is possible, to apply thermodynamically unstable modifications intentionally, to take advantage of very special properties. There are thermodynamically unstable modifications known, which turned out to have a consider-

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10.1021/js9801945 CCC: $18.00
Published on Web 12/05/1998

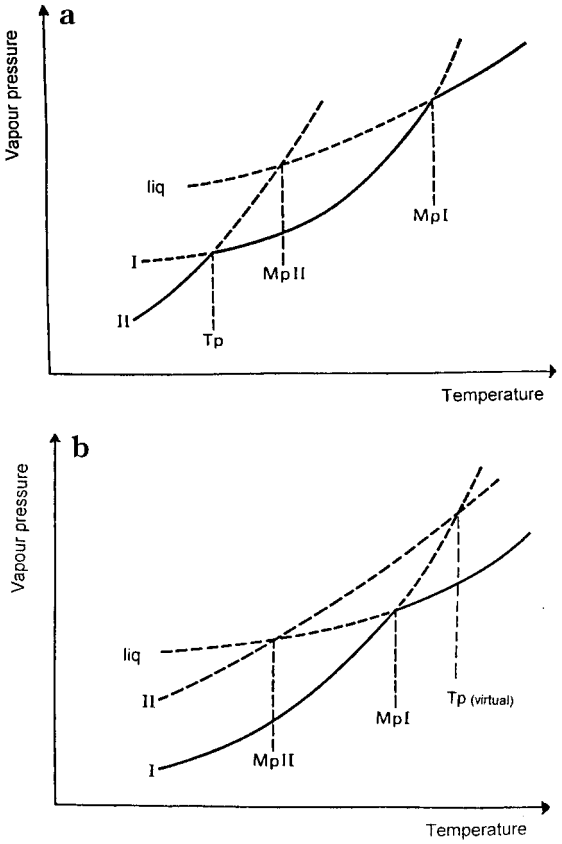


**Figure 1**—(a) Vapor pressure/temperature diagram: enantiotropy (*Mp*, melting point; *Tp*, thermodynamic transition point). (b) Vapor pressure/temperature diagram: monotropy (*Mp*, melting point; *Tp (virtual)*, thermodynamic transition point).

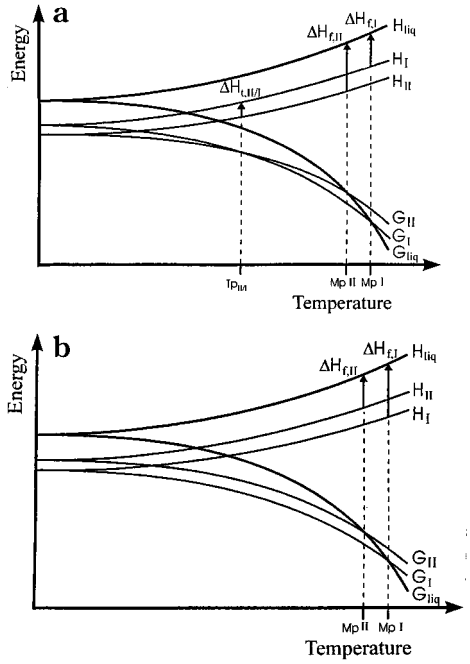


**Figure 2**—(a) Energy/temperature diagram: enantiotropy (*G*, free energy; *H*, enthalpy; $\Delta H_f$, enthalpy of fusion; *liq*, melt; *Mp*, melting point; *Tp*, thermodynamic transition point; $\Delta H_t$, enthalpy of transition). (b) Energy/temperature diagram: monotropy (*G*, free energy; *H*, enthalpy; $\Delta H_f$, enthalpy of fusion; *liq*, melt; *Mp*, melting point).

able kinetic stability and show a very low transition tendency, if kept dry. Such modifications are called metastable and they may be enantiotropic or monotropic. One example is piracetam, where mod. II and mod. III appeared to show equivalent thermodynamic stability. Only after stirring a suspension of both forms in dioxane did the enantiotropic transition of the metastable and thermodynamically unstable mod. II into mod. III take place.[7]

Because of the increasing spread of generics, more drugs are appearing that exhibit different crystal forms. Often, their stability relationships need to be explained. One example should be mentioned here: 17 different samples of piroxicam supplied by eight pharmaceutical companies were investigated for polymorphism at the Instituto National de Medicamentos (Buenos Aires, Argentina). It was shown that some of the samples contained the pure $\beta$ form (mod. I), some the 2 °C lower melting pure $\alpha$ form (mod. II), and some contained mainly the $\alpha$ or $\beta$ form contaminated with the other polymorph.[8] The two forms are monotropically related.

The difference between enantiotropy and monotropy was defined by Ostwald[9] more than 100 years ago using a vapor pressure/temperature diagram, which was brought close to students for decades in standard textbooks of physical chemistry. The difference between enantiotropy and monotropy is defined by the position of the vapor pressure curves. In the case of enantiotropy, the vapor pressure curves intersect below the melting points, whereas in the case of monotropy, the intersection is above the melting points. The intersection point of two vapor pressure curves is the thermodynamic transition point (tp). Therefore the difference between enantiotropically and monotropically related modifications is based on the relative position of the melting points and tp. In an enantiotropic system, the two modifications of interest are in equilibrium at tp and the transition can take place in either direction depending on the temperature (Figure 1a). On the other hand, the tp is virtually in a monotropic system; therefore, the transition can only occur in one direction from the unstable to the stable form. (Figure 1b). The crystal form that shows the lowest vapor pressure at any temperature is the most thermodynamically stable one. The condition for validity of this rule is constant pressure (atmospheric pressure).

The semischematic energy/temperature diagram[10,11] (*E*/*T* diagram), which is based on the Gibbs function, offers more information than the vapor pressure/temperature diagram. For a detailed discussion on the construction and interpretation of *E*/*T* diagrams in general, refer to the literature.[10,11] To draw the *E*/*T* diagram, the isobars of the Gibbs free energy *G* and of the enthalpy *H* of (at least) two modifications, I and II, as well as of the melt *liq* are related to each other. At a given temperature, the thermodynamically stable modification has the lowest Gibbs free energy. Figure 2a represents a given enantiotropically related system of two modifications. Modification II shows the lowest Gibbs free energy until the tp is reached and is therefore thermodynamically stable from absolute zero up to tp. Beyond tp, the Gibbs free energy of mod. II is larger than for mod. I; therefore, this mod. II is thermodynamically unstable from tp up to its mp. At tp, mod. I and mod. II have equal Gibbs free energy and equal thermodynamic stability. The two modifications are enantiotropically related. $\Delta H_t$ represents the enthalpy of transition for the transformation II/I and $\Delta H_f$ the enthalpy of fusion for mod. II and mod. I, respectively.

Figure 2b describes the relations in a monotropic system. Modification II shows a larger Gibbs free energy than mod. I and is therefore thermodynamically unstable compared with mod. I from absolute zero up to its mp. There is no tp in this temperature region, but a transition in the solid state of mod. II into mod. I is possible; however, never the reverse transition.

**Table 1—Flurbiprofen: Important Physicochemical Parameters of the Modifications**

| parameter | mod. I | mod. II | mod. III |
|---|---|---|---|
| preparation | crystallization from given solvent at 20 °C | crystallization from *n*-heptane, rapid cooling to –18 °C | crystal film |
| Mp [°C] DSC–onset | 114.5 | 91[a] | —[e] |
| thermomicroscopy | 113–114 | 92 | 87 |
| enthalpy of fusion [kJ mol$^{-1}$] | 27.9 ± 0.2[c] | —[e] | 25[b] |
| enthalpy of transition [kJ mol$^{-1}$] to mod. I | | —[e] | –2.9 ± 0.4 |
| entropy of fusion [J mol$^{-1}$ K$^{-1}$] | 72.0[d] | —[e] | 69.4[d] |
| measured density [g cm$^{-3}$] | 1.279 ± 0.001[c] | 1.231 ± 0.002[c] | —[e] |

[a] Incongruent melting. [b] Calculated by heat-of-fusion rule:[10] $\Delta H_{f,III} = \Delta H_{f,I} + \Delta H_{t,III\rightarrow I}$. [c] ±95% CI. [d] Calculated by entropy-of-fusion rule:[11] $\Delta S_f = \Delta H_f/T_m$. [e] Not determined.

The heat physicists and mineralogists of the turn of this century were well aware of the fact that enantiotropic transition of the modification that is thermodynamically stable below tp into the higher temperature stable one is an endothermic process. On the other hand, the crystal form that is thermodynamically stable above tp shows an exothermic transition if cooled well below tp. Also it was very well-known that a monotropic transition is an exothermic process.[12] This knowledge, in connection with results using the DSC method, was laid down in modern literature as the **heat-of-transition rule**.[10]

## Experimental Section

**Materials and Solvents**—The studies of flurbiprofen (FBP) INN [2-(2-fluorobiphenyl-4-yl) propionic acid; $C_{15}H_{13}FO_2$, $M_r$, 244.3] were carried out using the commercial product (mod. I) provided by Profarmaco Nobel (Italy). Modification II was obtained by rapid cooling of a warm saturated solution of FBP in *n*-heptane (analytical grade) to −18 °C. Modification III was obtained by quenching a melt film of flurbiprofen to 20 °C on a metal block. Afterward, heating the liquid amorphous material to 30 °C leads to crystallization of mod. III.

**Thermoanalytical Methods**—*Polarized thermomicroscopy*[13,14] was performed using a Kofler hot stage microscope (Thermovar, Reichert, Vienna, Austria). To prepare a crystal film, ca. 2 mg of FBP were heated between a microscope slide and a cover glass using a Kofler hot bench (Reichert, Vienna, Austria). The molten film was quenched to 20 °C using a metal block. To determine the melting points of mod. II and mod. III the hot stage was preheated to 85 °C. A crystal film preparation containing the two modifications was watched immediately after being placed onto the hot stage. The heating rate was 2 or 5 K min$^{-1}$. The *solubility test for stability relationships*[15] is made by carefully loosing the cover slip over a crystal film containing the three modifications and touching a drop of solvent to its edge so that the solvent flows in under the cover slip. The solvent must not be so good that the entire film is dissolved away. In the case of FBP, ethanol (70%) was used.

*Differential scanning calorimetry* (DSC) was carried out with a DSC-7 and Pyris software for Windows NT (Perkin-Elmer, Norwalk, CT) using perforated aluminum sample-pans (25 μL). Sample masses for quantitative analysis were 1−3 (±0.0005) mg (Ultramicroscales UM3, Mettler, CH-Greifensee, Switzerland). Nitrogen 99.990% (20 mL min$^{-1}$) was used as the purge gas. Calibration of the temperature axis was carried out with benzophenone (mp, 48.0 °C) and caffeine (mp, 236.2 °C). Enthalpy calibration of the DSC signal was performed with indium 99.999% (Perkin-Elmer, Norwalk, CT). The normal heating rate was 2 or 5 K min$^{-1}$.

**Spectroscopic Methods**—*Fourier transform infrared (FTIR) spectra* were recorded with a Bruker IFS 25 FTIR spectrometer (Bruker Analytische Meβtechnik GmbH, Karlsruhe, Germany) connected to a Bruker FTIR microscope (15 × Cassegrain-objective and visible polarization). Samples were scanned as potassium bromide pellets at an instrument resolution of 2 cm$^{-1}$ (50 interferograms, internal mode). For recording microscope spectra,[16] small samples were rolled on a round zinc selenide window (13 mm diameter x 1 mm thickness) or a crystal film was made between two zinc selenide windows. The spectral resolution is 4 cm$^{-1}$ (focus diameter 50 μm, 100 interferograms).

*FT-Raman spectra* were recorded with a Bruker RFS 100 FT-Raman spectrometer (Bruker Analytische Meβtechnik GmbH, Karlsruhe, Germany) equipped with a diode pumped 100 Nd:YAG Laser (1064 nm) as excitation source and a liquid nitrogen-cooled high-sensitivity detector (64 scans at 4 cm$^{-1}$ instrument resolution).

*X-ray powder diffraction* patterns were obtained on a Siemens D-5000 X-ray diffractometer equipped with Θ/Θ-Goniometer (Siemens AG, Karlsruhe, Germany) using monochromatic Cu Kα radiation (tube voltage 40 kV, tube current 40 mA) from 2 to 40° 2Θ at a rate of 0.005° 2Θ s$^{-1}$. The diffractometer was fitted with a Göbel mirror and a scintillation counter. The single-crystal data for mod. I (data from Flippen and Gilardi[17]) were used to calculate the idealized X-ray powder pattern for a Cu Kα radiation with the program *PowderCell for Windows* (Kraus, W.; Nolze, G. PowderCell for Windows (V 1.0), *Program for manipulation of crystal structures and calculation of X-ray powder patterns*; Federal Institute for Materials Research and Testing: Berlin, Germany, 1997).

**Density Measurements**—The determination of the powder volumes were carried out with an air comparison pycnometer (Ultrapycnometer 1000, Quantachrome Corp., Syosset, NY) provided with a small sample cell at 25 °C. The samples (2−3 ± 0.0005 g) were purged with helium for 15 min. Calibration was carried out with a steel sphere.

## Results

**Thermomicroscopy**—A melt film of FBP quenched on a metal cooling block (20 °C) and afterward heated (heating rate: 5 K min$^{-1}$) on the polarizing hot stage microscope leads to gray quadrangles and hexagons of mod. III (ca. 30 °C) and varicolored columnar aggregates and spherulites of mod. II (ca. 45 °C) and mod. I (ca. 45 °C). According to its morphology, mod. III differs considerably compared with the other crystal forms, whereas mod. I and mod. II are very similar. Continued heating leads to the transition of mod. III into mod. II and to the transition of mod. III into mod. I at about 50 to 60 °C at first, followed by the transition of mod. II into mod. I at about 75 °C. Transfer of a crystal film preparation that contains the three modifications to a preheated hot stage microscope allows the detection of the melting points (Table 1). After cooling the crystal film, the spherulites of mod. I show concentric shrinkage cracks, which are absent in mod. II. Modification II from *n*-heptane, consisting of fine needles, melts incongruently with separation of coarse prisms of mod. I.

The result of the *solubility test for stability relationships*[15] showed that the thermodynamically most unstable form (mod. III) dissolves immediately followed by mod. II after a few seconds. Because of the differences in solubility, crystals of the modification thermodynamically stable at room temperature (mod. I) grow in this solution.

**Differential Scanning Calorimetry**—Melting the commercial product in an aluminum pan using a hot bench and afterward quenching on a cooling block leads to a liquid amorphous phase, analogous to the melt film used for thermomicroscopy. Heating such a cooled melt in the DSC at a start temperature of 25 °C (heating rate: 2 K min$^{-1}$)

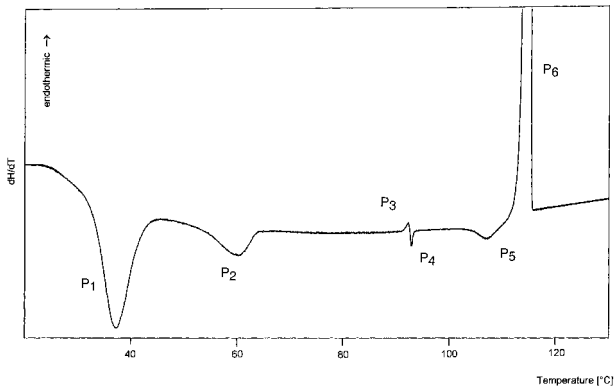


**Figure 3**—DSC curve of the quenched melt of flurbiprofen starting at 25 °C (heating rate: 2 K $min^{-1}$).

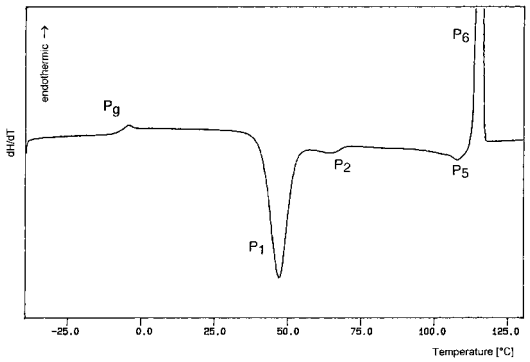


**Figure 4**—DSC curve of the quenched melt of flurbiprofen starting at −40 °C (heating rate: 5 K $min^{-1}$).

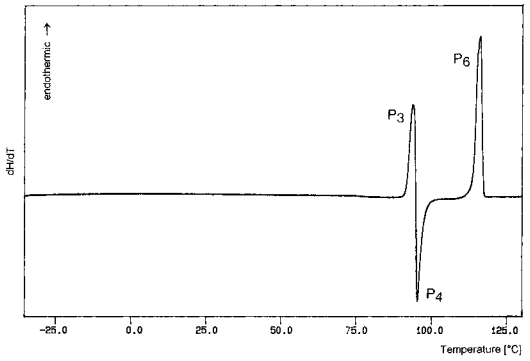


**Figure 5**—DSC curve of flurbiprofen starting with crystals of mod. II from *n*-heptane (heating rate: 5 K $min^{-1}$).

leads to crystallization of mod. III between 35 and 40 °C ($P_1$). The second exothermic peak ($P_2$) with a maximum at 60 °C represents the transition of mod. III to mod. I. In very few cases, small amounts of mod. II may also sometimes appear; these melt incongruently as indicated by $P_3$ and $P_4$. $P_5$ represents crystallization of remaining melt and $P_6$ marks the melting of mod. I (Figure 3). Cooling the melt to −40 °C leads to a solid amorphous phase. The DSC trace (Figure 4) of such a glass shows an endothermic peak ($P_g$), representing the glass transition at −8.5 °C, followed by an exothermic crystallization peak ($P_1$) and the transition peak ($P_2$). The DSC trace of pure mod. II (Figure 5) shows the incongruent melting ($P_3$), followed by the solidification of the melt to form mod. I ($P_4$) and the melting of mod. I ($P_6$).

DSC experiments where heating rates of up to 80 K $min^{-1}$ were applied also show the incongruent melting of mod. II. Therefore it was not possible to measure the enthalpy of fusion for this crystal form. Also, attempts to determine the enthalpy of transition for the exothermic

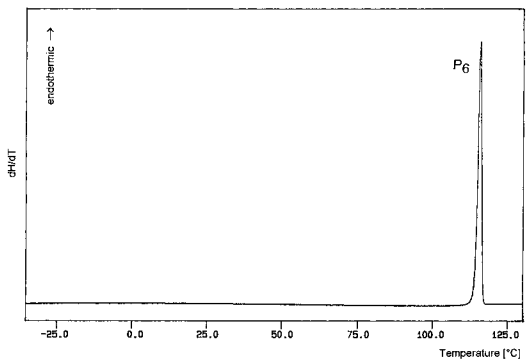


**Figure 6**—DSC curve of flurbiprofen starting with crystals of mod. I (commercial product, heating rate: 5 K $min^{-1}$).

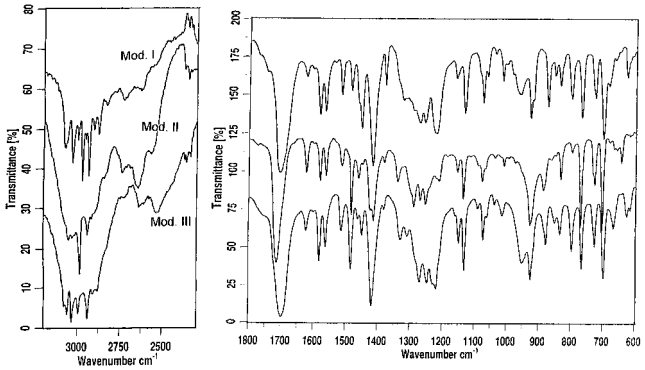


**Figure 7**—IR spectra of mod. I, mod. II, and mod. III of flurbiprofen recorded by FTIR microscopy.

transition of mod. II into I using a heating rate of 1 K $min^{-1}$ were not successful. Thus, these two values are not given in Table 1. But the negative enthalpy of transition for mod. III into mod. I could be measured using preparations that contained this crystal form purely. The thermogram of mod. I shows one endothermic peak representing the melting of this crystal form (Figure 6).

**FTIR Spectroscopy**—The FTIR spectra of mod. I and mod. II were recorded using both the crystal powder (by means of KBr pellets) and using a crystal film on a zinc selenide window containing two kinds of spherulites representing the two crystal forms by FTIR microspectroscopy. Due to the two different methods of sampling, the spectra are identical except for small differences in the intensity of several absorption bands.[16] The spectrum of mod. III was only obtained by FTIR microscopy using a crystal film on zinc selenide. Because all three modifications show numerous shifts of significant absorption bands, they can easily be distinguished by their FTIR spectra (Figure 7). Good diagnostic value can be particularly attributed to the band representing the C═O (acid) functional group. The C═O stretching vibration appears to be located for mod. III at 1699 $cm^{-1}$, for mod. II at 1715 $cm^{-1}$, and for mod. I at 1705 $cm^{-1}$.

**Raman Spectroscopy**—FT-Raman spectra of mod. I and mod. II were also recorded. They show substantial differences in the region around 3000 $cm^{-1}$ and between 300 and 50 $cm^{-1}$ (Figure 8). Modification III could only be obtained as a crystal film, therefore a Raman spectrum of this crystal form could not be recorded.

**X-ray Diffractometry**—All three modifications were analyzed by X-ray powder diffractometry (Figure 9). A special method was used to prepare mod. III. The crystallization conditions were modified in such a way that in a melt film only this crystal form was created. The cover slip was removed from this preparation and the crystal film

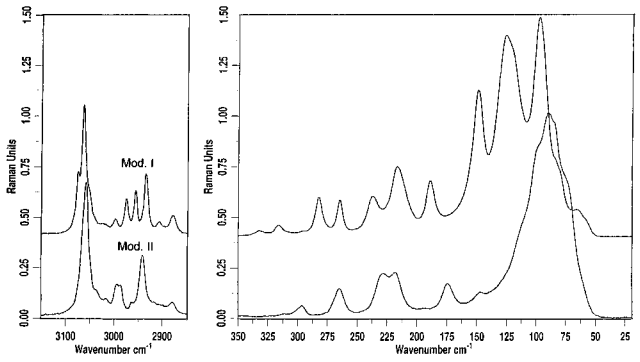


**Figure 8**—Raman spectra of mod. I and mod. II of flurbiprofen.

surface was used instead of the crystalline powder. The powder pattern calculated from the single-crystal structure data[17] is in very good agreement with the experimental pattern obtained for mod. I (Figure 9).

**Density**—The density is a very important parameter for determining which one of two modifications is the thermodynamically stable one at absolute zero. Therefore, the true densities of FBP mod. I (commercial product) and mod. II were determined. The result is that mod. I has the higher density than mod. II (Table 1). Because mod. III cannot be produced in macroscopic amounts, this value is missing in Table 1. According to the **density rule**[10] the modification with the lower density is thermodynamically unstable at absolute zero compared with the crystal form with the higher density. Therefore, mod. II is thermodynamically unstable from zero Kelvin up to its melting point compared with mod. I. More detailed remarks will be given in the Discussion.

## Discussion

The measured and calculated physicochemical parameters for the three modifications of FBP are summarized in Table 1. The enthalpy of fusion could only be measured directly for mod. I. The enthalpy of fusion for mod. III was calculated by applying the heat-of-transition rule[10] using the enthalpy of transition for mod. III into mod. I measured by DSC. The enthalpy of fusion of mod. I is higher than that of mod. III. Therefore, it follows by means of the heat-of-fusion rule,[10] that these two crystal forms are monotropically related. The same is true for the entropy of fusion.[11] As already described, it was not possible to measure the enthalpy of fusion for mod. II because of its incongruent melting. The proof for the monotropic relation between mod. I and mod. II arises from the comparison of the density of these two crystal forms. Modification I shows higher density than mod. II and thus, according to the density rule,[10] monotropism is realized in this case. The *E*/*T* diagram[10,11] of FBP illustrates the thermodynamic relationships of the three modifications (Figure 10). Because the relevant physical parameters (Table 1) indicate monotropy between mod. III and mod. I (heat-of-transition rule[10]), as well as between mod. II and mod. I (density rule[10]), the diagram is in principle similar to the one given in Figure 2b. Modification I is the most stable crystal form of FBP. The result of the *solubility test for stability relationships* proves that mod. III is the most thermodynamically unstable crystal form at 20 °C and that mod. II is more stable than mod. III at ambient conditions because of its lower solubility. The thermoanalytical behavior of mod. III allows the assumption that monotropy is realized in relation to mod. II with high probability. In the case of FBP, this question is not of practical relevance. The FTIR spectra of the three modifications show significant differences. Compared with the IR spectra published by Lacoulonche et al.,[2] it is clear that our mod. I corresponds to their form I and our mod. II to their form II "recrystallized in heptane".[2] Comparison of the X-ray powder patterns of the different crystal forms clearly indicates that their form II[2] obtained by crystallization from the melt corresponds to our mod. III. This fact is also confirmed by the morphological description[2] of the crystals.

The results of our study on the polymorphism of FBP clearly show that three crystal forms can be obtained by crystallization from solution and the melt. Lacoulonche et al.[2] did not realize that they had obtained three modifications instead of two. Therefore, the physical properties of the modifications could not be assigned in a correct way and, hence, this led to the wrong conclusion on the thermodynamic relationships of this polymorphic system.

Modification III of FBP is only of analytical interest because this modification is not only thermodynamically unstable at 20 °C but also kinetically unstable. This crystal form can only be obtained in microscopic amounts. It transforms into mod. I at ambient conditions within a few minutes. Modification II is also thermodynamically un-

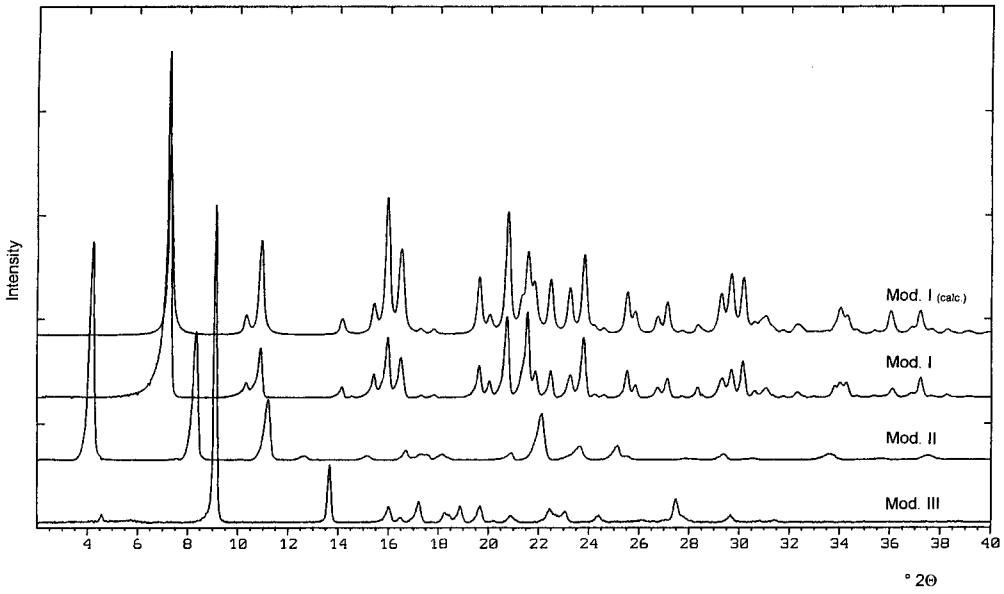


**Figure 9**—X-ray powder diffraction patterns of mod. I (also calculated from single-crystal data), mod. II, and mod. III of flurbiprofen.

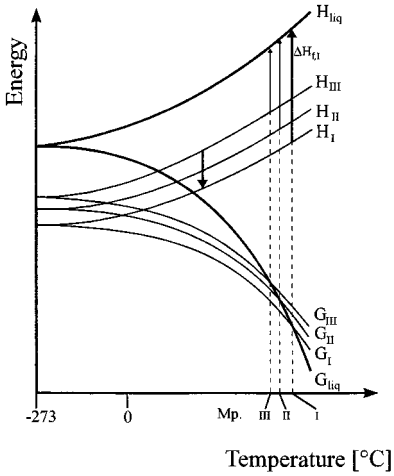


**Figure 10**—Energy/temperature diagram of the crystalline modifications of flurbiprofen and its melt: *G*, free energy; *H*, enthalpy; $\Delta H_t$, enthalpy of fusion; *liq*, melt; *Mp*, melting point; measured enthalpy effects are drawn bold.

stable at 20 °C, but is durable for more than 6 months if kept under dry conditions. Also, grinding of mod. II with a mortar and pestle has not caused a transition into mod. I. Therefore this crystal form may have some practical implications. As has been shown on other polymorphic drug substances (e.g., paracetamol[18]), this marked kinetic stability could be suitable to perform direct compression experiments using this crystal form.

As a chiral substance, the modifications of FBP are in principle able to crystallize as conglomerates, racemic compounds, or solid solutions. Unfortunately, we did not have one pure enantiomer to investigate the phase diagram of this binary system and to answer this question on the nature of the three modifications.

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JS9801945