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RESEARCH PAPER

Solid-Solid Transformation in Racemic Ibuprofen

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ABSTRACT

Purpose To clarify the polymorphism of racemic Ibuprofen and to determine the kinetic of the phase transformation that follows crystallisation of phase II.

Methods Differential Scanning Calorimetry (DSC), X-ray powder diffraction and Hot Stage Microscopy are complementarily used to perform a kinetic investigation of the particular temperature range where competition between the occurrence of phases I and II is suspected.

Results Experiments performed with the three techniques reveal that at 273 K the crystallisation to phase II is then followed by a solid-solid transition towards phase I. This transformation is exothermic (conversion enthalpy of 8.0 ± 0.5 kJ/mol), which proves that the two phases form a monotropic set. The kinetics of conversion deduced from X-Ray experiments follows a Johnson-Mehl-Avrami equation and the Hot Stage Microscopy allows us to establish that the transformation proceeds by the growth of some nuclei of phase I probably formed at lower temperature.

Conclusions These results allow us to precise the stability pattern of racemic Ibuprofen and to establish the kinetic conditions of appearance and interconversion of the different phases. Therefore such real time resolved investigations would help if applied in the screening of polymorphs when competitive crystallisations occur.

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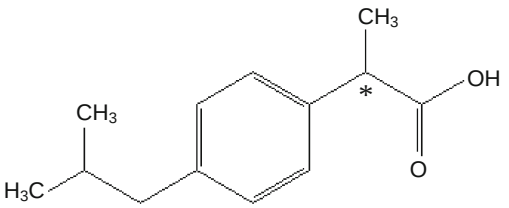
INTRODUCTION

The role of crystalline polymorphism in solid state pharmacy was recognised in the two last decades (1–3). Polymorphism is basically involved in the issues of solubility and physical stability of drugs. Several factors emerge in the course of the investigations referred to above which have a controlling influence on the polymorphs generations and lifetimes: metastable phases and the kinetics of transformations. Their combination in the specific case of racemic Ibuprofen is the subject of this paper.

Ibuprofen, 2(4-isobutylphenyl)propanoic acid is a widely used non-steroidal anti-inflammatory drug having analgesic and antipyretic activities. The molecular structure is as follows:



This molecule contains a chiral carbon so two enantiomeric forms can be found: S(+)-Ibuprofen and R(−)-Ibuprofen, the S(+)-Ibuprofen being the pharmacologically active form. The commercial drug is in fact the racemic compound. It appears at ambient temperature as a white crystalline powder. This crystalline phase I is stable up to the melting point T_{mI} = 349 K (4). Its structure was resolved long time ago (5,6): monoclinic, space group $P21/c$, Z=4. Crystallisation of the phase I from the undercooled melt occurs between T_{mI} and T_g, the glass transition temperature

of the undercooled liquid ($T_g \approx 228$ K (7,8)); it has been shown (9) that it follows a classical nucleation and growth process in which preferential temperature domains are clearly distinct: the nucleation preferential domain is situated just above T_g between 233 K and 263 K, while the growth one is located between 313 K and 343 K. As a result racemic Ibuprofen is a good glass former upon cooling. Crystallisation to phase I thus efficiently occurs upon reheating the undercooled melt after a low temperature excursion above T_g. In a previous paper (9) we have shown the possible existence of another crystalline form II, the structure of which has been analysed (10). This new form melts at T_{mII} =290 K as shown by the occurrence of an endothermic peak in Differential Scanning Calorimetry (DSC) and the disappearance of Bragg peaks in X-Ray diffraction at this temperature (9). Phase II is thus of lower stability than phase I, at least in a temperature domain not far from T_{mII}. It also has a density lower than that of phase I. The appearance of phase II is triggered by a quench of undercooled racemic Ibuprofen under T_g, a deep quench–60° below T_g–being seemingly efficient to promote further appearance of this phase upon heating. Indeed crystallisation to phase II occurs upon reheating the deeply undercooled melt *via* a presumably predominant growth process above 260 K. This behaviour emphasises the possibility of the occurrence of a nucleation process far below T_g as already reported by Legrand *et al.* (11) and Oguni *et al.* (12,13). It has been observed that the temperature range of crystal growth of phase II partly overlaps with the temperature range of nucleation of phase I from the undercooled melt. The resulting possible interplay of the crystallisation kinetics of the two phases makes difficult a precise characterisation of the polymorphism, stability pattern and thermodynamic behaviour of racemic Ibuprofen.

In this paper we try to understand if the preferred apparition of phase II at low temperatures has only a kinetic origin–in a monotropic situation–or if it could benefit from a more favourable thermodynamic driving force–in an enantiotropic situation. In the previous paper (9) several observations were made which are in favour of a monotropic situation according to Burger and Ramberger rules (14,15): melting enthalpy of phase II apparently lower than that of phase I and absence of an endothermic solid-solid transformation. However these observations can be blurred by the competing occurrence of transformations in the temperature range of melting. Furthermore the melting enthalpy of phase II observed in the course of a DSC scan (ΔH_{mII} = 7.0±0.5 kJ/mol) appears to be very small. We may thus wonder if it is an indication that phase II is highly disordered or if it is the result of a partial conversion to phase I at lower temperature. Besides solid-solid transformations can be hidden for kinetic reasons. We present the results of a kinetic investigation of the phase transformations of quenched liquid racemic Ibuprofen. This study allows bypassing the difficulties mentioned above. We combine time resolved Differential Scanning Calorimetry (DSC), X-Ray powder diffraction (XRPD) and hot stage microscopy to explore the particular temperature range where competition between the occurrence of phases I and II is suspected. This study basically aims at obtaining a precise determination of the stability pattern of crystalline racemic Ibuprofen. However the applied strategy is of general relevance in the screening of polymorphs. In a wider applicability, it provides an interesting illustration of the involvement of kinetics into the manifestation of the popular, but debated, Ostwald's rule of stage (16,17).

MATERIAL AND METHODS

Racemic Ibuprofen, of molecular weight M=206.29 g/mol, was purchased from Sigma (CAS 15687-27-1), catalogue number I4883, lot number 026 H1368. The purity is 99.8% (gas chromatography assay). Samples were analysed without further purification.

Differential Scanning Calorimetry experiments were carried out in a DSC Q10 from TA Instruments with a heating rate of 10 K/min. A small amount of sample (less than 5 mg) was enclosed in a hermetic aluminum pan. Measurements were realised under dry helium (at flow rate of 25 ml/min) to improve the thermal conductivity. A liquid nitrogen cooling system was used in order to reach temperatures as low as 143 K. Temperatures and enthalpies were calibrated with Indium using the same heating rate and the same environmental conditions as the experiments.

The powder X-Ray diffraction experiments were performed with an INEL CPS 120 diffractometer ($\lambda_{Cu\ K\alpha 1}$ = 1.54056 Å) equipped with a 120° curved position sensitive detector coupled to a 4096 channel analyzer. A Cryostream Plus controller from Oxford Cryosystems was used to regulate the temperature. Samples were placed into Lindemann glass capillaries ($Ø$=0.7 mm). The latter is also spun around its axis during diffraction measurement to avoid preferred oriented crystallisation.

The observations by microscopy were made with an Olympus BX51 polarizing microscope, equipped with a Cohu 2252 camera and a hot stage (Linkam TMS 94) allowing the control of temperature between 113 K and 393 K.

RESULTS

The protocol described in reference 4 is applied to form the crystalline phase II of racemic Ibuprofen: after the melting of phase I, the liquid is quenched to 143 K. The glass (Tg = 228 K ± 1 K) is then re-heated at 10 K/min to 273 K where

the sample is maintained during an annealing time, ta, to allow sizeable crystallisation of phase II. Indeed preliminary experiments have shown that its crystallisation kinetics is improved at this temperature and that the process occurs in a reasonable experimental time. After annealing at 273 K, the sample is cooled to 173 K. The calorimetric response is then recorded during a subsequent heating run to 373 K. Three experiments are realised with ta = 60 min, ta = 90 min and ta = 300 min. Thermograms recorded during the isotherm at 273 K and on subsequent heating are reported in Fig. 1 respectively on the left and on the right side.

For ta = 60 min, during the isotherm at 273 K, an exotherm can be observed which marks the complete crystallisation of phase II as it is demonstrated by the absence of a Cp-jump around 228 K on subsequent heating. The melting of the sample is then observed at T_{mII} = 290 K (endothermic event A), which is the expected melting temperature of phase II. At higher temperature, the sample recrystallises (exothermic event B around 303 K) to phase I which eventually melts at 348 K (endothermic event C). For ta = 90 min, during the isotherm, the exothermic crystallisation of phase II is again observed but the beginning of a second exothermic event is detected. On the subsequent heating, no glass transition can be observed indicating that the sample is 100% crystalline. However, the melting endotherm of phase II at 290 K is strongly reduced. In the same way the re-crystallisation towards phase I (exotherm B) is less important. Nonetheless, at 348 K, the melting of phase I can still be seen and the melting enthalpy is comparable to the one of the previous experiment ($\Delta H_{mI} = 22 \pm 1$ kJ/mol). For ta = 300 min, during the isothermal annealing, the exotherm of crystallisation of phase II overlaps with another exothermic event which is this time fully observed. On subsequent heating, the lack of a Cp-jump around 228 K again indicates that the sample is 100% crystalline but neither the melting of phase II nor a re-crystallisation towards phase I can be detected. However the melting endotherm of phase I still occurs at 348 K with the same melting enthalpy. Thus, as the second exotherm develops during ta, we may notice the disappearance of the melting endotherm of phase II and of the re-crystallisation exotherm towards phase I around 303 K. However the fact that the sample is 100% crystalline at the end of the isotherm and that the melting enthalpy of phase I observed at 348 K is still the same, seems to indicate that this second exothermic event marks the conversion of the newly formed phase II towards phase I.

In order to clarify the nature of the structural evolution corresponding to the intermingled exotherms, the response of the sample during an isotherm at 273 K was then followed by XRPD. A capillary filled with racemic Ibuprofen is heated to 363 K to melt the sample; liquid Ibuprofen is then cooled to 143 K in order to promote efficient nucleation of phase II and the vitreous Ibuprofen is re-heated at 6 K/min to 273 K where a series of acquisitions of 300 s are recorded for more than 6 h. Some of the obtained diffraction patterns are reported in Fig. 2. In the first recording (pattern a), a diffusion halo can only be seen indicating that the sample is completely amorphous. After 15 min, Bragg peaks characteristic of phase II, in particular the one located at 7°, begin to appear (pattern b) and develop (patterns c and d). As time goes on, Bragg peaks characteristic of phase I, in particular the one located at 6°, appear and develop (patterns e, f, g and h) while, in the meantime, Bragg peaks characteristic of phase II decrease and finally disappear (pattern h) after

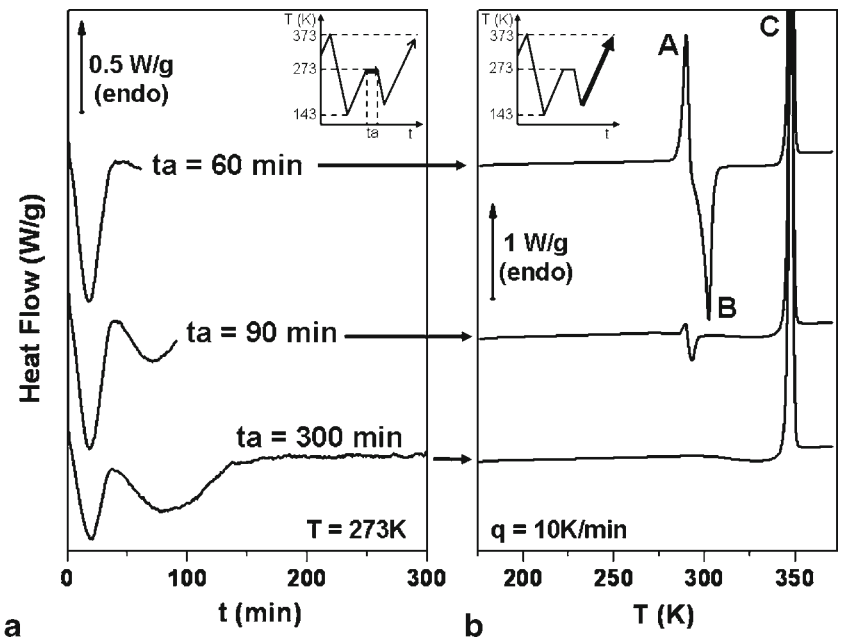


Fig. 1 DSC thermograms recorded (**a**) on the left side: during isotherms at 273 K of 60 min, 90 min and 300 min; (**b**) on the right side: on the corresponding subsequent heating at 10 K/min. The complete thermal history is reported on insert.

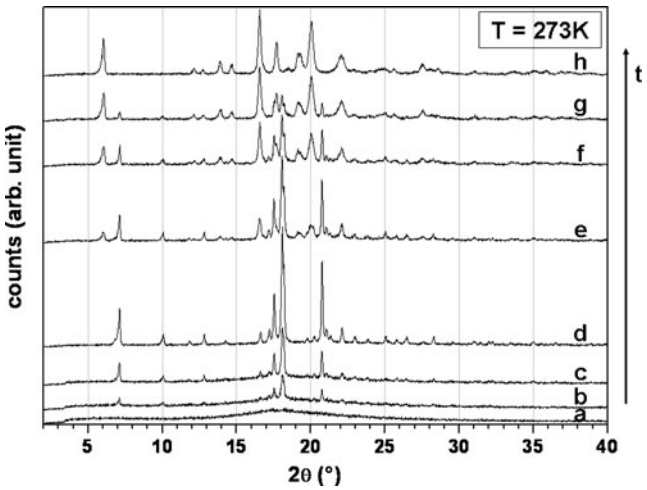


Fig. 2 Successive X-ray diffraction patterns recorded at 273 K for 6 h (each pattern is recorded for 300 s): (**a**) initial pattern, (**b**) after 35 min, (**c**) after 45 min, (**d**) after 75 min, (**e**) after 160 min, (**f**) after 195 min, (**g**) after 230 min and (**h**) after 350 min.

approximately 6 h. Thus, X-ray diffraction experiments show that, during an isotherm at 273 K, the Ibuprofen initially completely amorphous firstly crystallises upon phase II, then the phase I develops to the detriment of phase II leading to Ibuprofen completely crystallised upon phase I, which confirms the proposed interpretation of DSC results experiment.

From the X-Ray experiments, it is possible to quantitatively characterise the kinetic evolutions of the two phases by following the evolution of the intensity of a Bragg peak characteristic of each phase. The Bragg peak located at 7° (phase II) and the one located at 6° (phase I) have been chosen. After baseline correction, the integrated intensities are reported in Fig. 3. Both steps in the evolution can clearly be seen: in a first step, the phase II appears and develops, and in a second step, this phase starts disappearing exactly when phase I starts appearing.

In order to quantitatively study this second step, the origin of time has been chosen when the intensity of the Bragg peak characteristic of the phase II (peak at 7°) reached its maximum after crystallisation from the initial amorphous form. Then, by normalising the intensity by the maximal intensity reached by the peak, it is possible to determine the proportion X(t) of each crystalline phase in the sample:

$$X(t) = \frac{I(t)}{I_{max}},$$

where I(t) is the integrated intensity of the considered peak at time t and I_{max} is the maximal integrated intensity of that peak ($I_{max} = I(\infty)$ for phase I and $I_{max} = I(0)$ for phase II). The time evolution of the proportion of each crystalline phase *versus* the rescaled time is reported in Fig. 4.

The symmetric evolution of the phases proportions X(t) confirms that the appearance of the phase I and the disappearance of the phase II are linked and that they are not two independent concomitant phenomena. The observed evolutions thus reveal a direct solid-solid conversion of phase II towards phase I. Moreover, it can be seen in Fig. 3 that the initial appearance of phase II is more rapid than its later complete conversion towards phase I.

These DSC and XRPD results thus show the possibility of the existence of a solid-solid transition from phase II towards phase I when racemic Ibuprofen is maintained in a temperature zone around 273 K. It should be noted that this conversion is not systematic since some DSC experiments did not show any sign of a second exotherm during the isotherm at 273 K, even after 5 h.

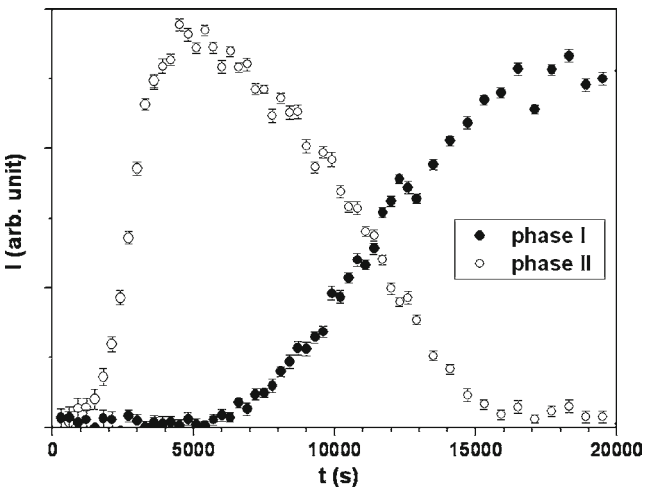


Fig. 3 Evolution *versus* time of the integrated intensity of the Bragg peak at 6° (characteristic of phase I) (*black circle*) and of the Bragg peak at 7° (characteristic of phase II) (*white circle*) determined from X-ray diffraction experiments at 273 K.

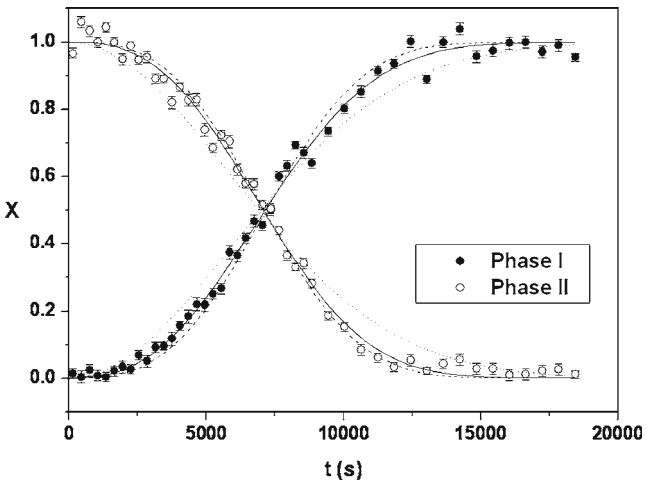


Fig. 4 Evolution *versus* rescaled time of the proportions X of phase I (*black circle*) and phase II (*white circle*) determined from X-ray diffraction experiments at 273 K. Fitting curves are added: with fitting parameters being free to vary (__), with $n_1=n_2=2$ (….) and with $n_1=n_2=3$ (- - -) (see text).

To visually confirm these results, hot stage microscopy has been used. The experiment was prepared considering that the nucleation of phase II is assisted by the formation of cracks, even if their precise role is not yet understood (9). However, in the confined space between two cover slips, the development of cracks is less easy. Thus a small amount of powder spread on a thin microscope slide was melted on a Köfler bench and a piece of another slide was then laid across the melted sample in a such way that only part of the sample was sandwiched between the two cover slips. So the non-confined area could help promoting the formation and spreading of cracks in the glass at low temperature and thus the nucleation of phase II, while, upon reheating, the confined area had the thickness allowing a sharp observation of the growth of nuclei. The whole of the slide preparation was then placed into the Linkam stage of the microscope, melted at 373 K and quenched till 128 K. After a heating ramp at 10 K/min the temperature was maintained at 273 K while pictures under polarised light were taken every minute. Some of them are reported in Fig. 5 (the area located between the two dashed lines is the part of the sample sandwiched between the two microscope slides).

As can be seen in Fig. 5a, the growth of some nuclei begins instantaneously. For the first 40 min (Fig. 5a–e), these nuclei radially grow and occupy all the space. After 110 min (Fig. 5f–h), on one side of the confined part of the sample, a darker area (surrounded by a dotted line in Fig. 5) develops and gradually invades the confined zone. After 160 min at 273 K, an increase of temperature (10 K/min) is applied. The darker area keeps on developing as shown by the picture taken at 288 K (Fig. 5i). Then between 288 K and 293 K (Fig. 5j), the crystallites that had developed in the first times disappear. Since this temperature range corresponds to the melting temperature range of phase II, it confirms that the nuclei which initially appeared and grew where that of phase II. However, the darker area persists and even keeps on growing before melting around 348 K. It thus corresponds to crystallites of phase I. The microscopic examination confirms the development at 273 K of phase II followed by its direct conversion towards phase I and also that this conversion is slower than the initial development of phase II within the amorphous Ibuprofen.

DISCUSSION

Stability Pattern of the Two Polymorphic Forms

As it is always the case when solid compounds can take a metastable and a stable form, two types of situations may exist. The two polymorphic varieties can form either a monotropic set or an enantiotropic set. The thermodynamic properties corresponding to these two possible situations have been long ago clearly enumerated by A. Burger and R. Ramberger (14,15). The main differences include the following:

- For a monotropic situation, the metastable phase II is less stable than the phase I at all temperatures till its melting at $T_{mII} < T_{mI}$. Transformation of phase II towards phase I is exothermic and may occur at any temperature lower than T_{mII}. Its occurrence is only limited by kinetics. Furthermore, the enthalpies of melting are in the order $\Delta H_{mI} > \Delta H_{mII}$.
- For an enantiotropic situation, each phase has its proper temperature range of stability. Gibbs free energy curves cross at an equilibrium solid-solid transition temperature $T_{II\text{-}I}$. Phase II is metastable with regard to phase I only above $T_{II\text{-}I}$. Upon heating, phase II may thus transform to phase I but that time endothermically. Such a transition may however be so slow that it can be avoided upon too fast heating. As a result the overheated metastable phase II would thus melt at $T_{mII} < T_{mI}$. In that case, the enthalpies of melting are in the order $\Delta H_{mII} > \Delta H_{mI}$.

In our previous paper (9) several observations were made which are in favour of a monotropic situation: upon heating there was no evidence of endothermic anomaly at a temperature lower than T_{mII} which could indicate some partial transformation of phase II towards phase I. Furthermore, the melting enthalpy of phase I is seemingly larger than that of phase II as we found a melting enthalpy of $\Delta H_{mI} = 25.8 \pm 0.5$ kJ/mol for phase I and $\Delta H_{mII} = 7.0 \pm 0.5$ kJ/mol for phase II.

Results presented here emphasise the possible existence of a solid-solid conversion from phase II to phase I for temperatures lower than T_{mII}. However the DSC results presented in Fig. 1 clearly indicate that the II to I transformation is an exothermic event. It confirms that the two crystalline phases of racemic Ibuprofen form a monotropic set. These results allow us to clearly assign the various events revealed by the DSC experiments. From these DSC measurements we thus tried to determine the enthalpy values attributed to the events which involve phase II, namely its crystallisation enthalpy ΔH_{crII}, its melting enthalpy ΔH_{mII} and the enthalpy of conversion $\Delta H_{II\text{-}I}$ at 273 K. During the isotherm, the overlapping of the exotherm of crystallisation of phase II with the one of the II to I conversion prevents us directly obtaining a precise value of $\Delta H_{II\text{-}I}$. However the microscopic observation shows that during the isotherm at 273 K no development of the phase I within amorphous Ibuprofen is observed. A good estimation of the conversion enthalpy of phase II towards phase I can thus be achieved by subtracting from the total enthalpy of the two processes the enthalpy of crystallisation of phase II. This latter enthalpy was deduced from a DSC experiment where the II to I transition was not detected. We found a crystallisation enthalpy at 273 K of $\Delta H_{crII} = 7.5 \pm 0.5$ kJ/mol. It should be

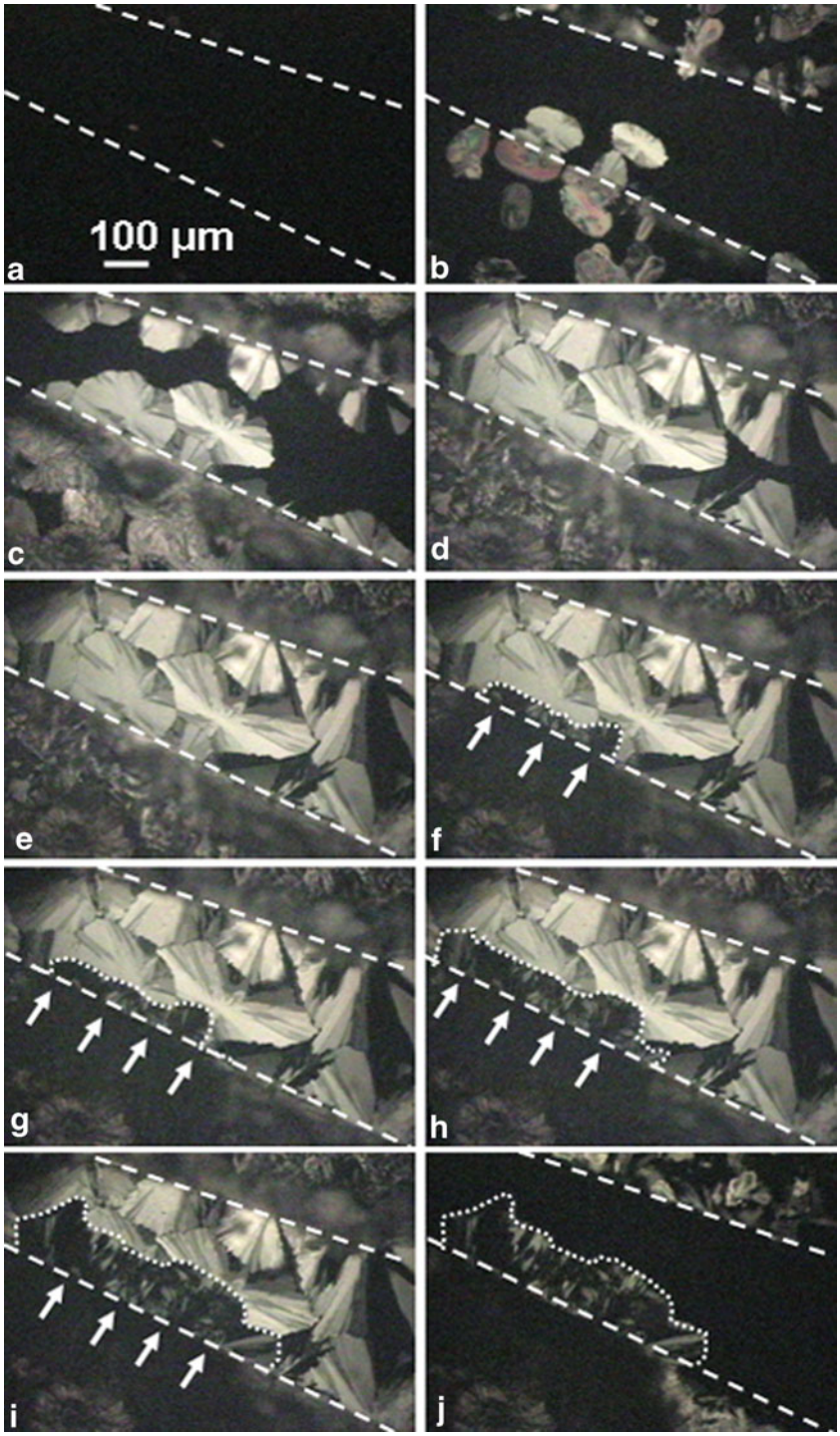


Fig. 5 Micrographies, under cross polarizers, of the growth of phase II and its conversion towards phase I. From a to h: pictures taken at 273 K after (**a**) 1 min, (**b**) 10 min, (**c**) 21 min, (**d**) 31 min, (**e**) 41 min, (**f**) 131 min, (**g**) 141 min and (**h**) 151 min. Picture (**i**) is taken at 288 K and picture (**j**) at 293 K after the melting of phase II. *Dash lines* delimit part of the sample between two microscope slides. *Dotted line* delimits the moving boundary of phase I.

noted that this enthalpy of crystallisation obtained at T_{cr} = 273 K leads to an enthalpy of melting at T_{mII} = 290 K of $\Delta H_{mII} = 8.8 \pm 0.5$ kJ/mol according to the equation:

$$\Delta H_m(T_m) \approx \Delta H_{cr}(T_m) = \Delta H_{cr}(T_{cr}) + (T_m - T_{cr})\Delta Cp, \quad (1)$$

where T_m and T_{cr} are respectively the melting and crystallisation temperatures, ΔH_m and ΔH_{cr}, the melting and crystallisation enthalpies. ΔCp is the amplitude of the Cp-jump corresponding to the glass transition (ΔCp = 76 J/mol/K (9)). The latter provides a good estimation of difference between the Cp of the liquid and the Cp of the crystal.

The estimated melting enthalpy of phase II is thus a bit higher than the one previously measured at the melting upon a heating experiment. The difference could result from the beginning of the II to I conversion which could happen during the heating but its very slow kinetics could then lead to a response too weak to be detectable.

The total enthalpy of the two processes observed during the isotherm being equal to $\Delta H_{tot} = 15.5 \pm 0.5$ kJ/mol, we found an enthalpy of conversion at 273 K close to $\Delta H_{II\text{-}I} = 8.0 \pm 0.5$ kJ/mol.

Mechanism of Conversion

In order to get a better insight into the mechanism of the solid-solid transition we analysed the kinetics of this transformation from XRPD.

The study of the conversion kinetic is a difficult task. Indeed, it should be noted that the curves presented in Fig. 4 are not reproducible: in some other experiments realised in the same conditions, stages could be erratically observed after the beginning of the process with variable lengths and conversion proportions. In some cases, the conversion even stopped after awhile. This is certainly due to the existence in front of the detector of different parts of the sample isolated by air bubbles (resulting from the melting of the initial powder) that do not encounter the same process–conversion happening in some of them but not in others. But even if these erratic results make difficult the analysis of the kinetic of conversion, it gives some insights into its mechanism.

To specifically investigate the kinetic of the II to I conversion, we chose as the origin of time the point at which the primary development of phase II within amorphous Ibuprofen attains completion. Due to the S-shaped curves, the evolution *versus* time of phase I has been fitted by the following law:

$$X_I(t) = 1 - \exp\left[-\left(\frac{t}{\tau_1}\right)^{n_1}\right], \quad (2)$$

and the one of phase II by the mirrored law:

$$X_{II}(t) = \exp\left[-\left(\frac{t}{\tau_2}\right)^{n_2}\right], \quad (3)$$

where τ_1 and τ_2 are characteristic times of each kinetic and n_1 and n_2 are the time exponents.

In a first approach, all parameters were let free to vary: the obtained fitting parameters are reported in Table I and the corresponding fitted curves are added in Fig. 4. The crossing of the two evolutions for $X(t) = 0.5$ and the good agreement between the values of time exponents and characteristic times emphasize the linked behaviours of the two phases evolutions. Values of these parameters derived independently from $X_I(t)$ and $X_{II}(t)$ agree to within 6% for the time exponent and 2% for the characteristic time, which can be taken as a limit of the absolute error of the measurements.

We shall now discuss the possible information which can be extracted from the shape of X(t). As for crystallisation from the melt, the solid-solid conversion which occurs in a monotropic situation is expected to be a process of nucleation and growth (18). Usually this type of process is well described by the Johnson-Mehl-Avrami (JMA) model (19–21) that expresses the fraction crystallised under isothermal condition X(t) as the function of time:

$$X(t) = 1 - \exp\left[-\left(\frac{t}{\tau}\right)^{n}\right], \quad (4)$$

where τ is a characteristic time that takes into account the nucleation and growth rates and n is a dimensionless exponent that depends on the nucleation mechanism and the space dimensionality of growing crystals. This function has the same form as Eqs. 2 and 3 thus our fit parameters can be interpreted according to the JMA model.

There are several types of nucleation mechanism. Nucleation can be homogeneous or heterogeneous. The heterogeneous nucleation mechanisms where nucleation is catalysed by defects, cracks, etc… certainly predominates over the homogeneous nucleation. Furthermore the nucleation process can be either continuous (nuclei keep on appearing during the growth process) or the nucleation process happened before the beginning of the growth process (the number of nuclei does not change during the growth process and does not depend of time). According to the JMA model and assuming an isotropic growth confined to d dimensions, n is a whole number equal, in the first case, to d + 1 and, in the second case, to d (22). Since the obtained exponents are barely whole numbers and since several reaction mechanisms usually seem possible, the interpretation of n is thus ambiguous and in many cases is more of qualitative use. The values we obtained for n_1 and n_2 were not whole numbers but lay between 2 and 3. So in this framework we reported in Fig. 4 the fitting curves obtained for fixed values of n_1 and n_2 equal to 2 and 3 (the corresponding fitting values are reported in Table I). It is clear that the values of $n_1 = n_2 = n = 3$ are more relevant than $n_1 = n_2 = n = 2$.

According to the JMA model, $n = 3$ can be interpreted through two ways: either nucleation and growth in two dimensions develop in the same time at 273 K or the process

Table I Time Exponents (n_1, n_2) and Characteristic Times (τ_1, τ_2) Obtained for Different Fitting Conditions of Eqs. 2 and 3 (see Text). χ^2 is the Reduced Chi-Squared Statistic

	n	τ (s)	χ^2
Phase I	$n_1 = 2.59 \pm 0.08$	$\tau_1 = 822 \times 10^1 \pm 7 \times 10^1$	0.99495
Phase II	$n_2 = 2.74 \pm 0.10$	$\tau_2 = 809 \times 10^1 \pm 8 \times 10^1$	0.99335
Phase I	2 (fixed)	$\tau_1 = 84 \times 10^2 \pm 2 \times 10^2$	0.98488
Phase II	2 (fixed)	$\tau_2 = 83 \times 10^2 \pm 2 \times 10^2$	0.98025
Phase I	3 (fixed)	$\tau_1 = 813 \times 10^1 \pm 8 \times 10^1$	0.99215
Phase II	3 (fixed)	$\tau_2 = 804 \times 10^1 \pm 7 \times 10^1$	0.99234

corresponds to the growth in three dimensions of nuclei created at temperatures lower than 273 K. The fact that there could sometimes be isolated domains of the sample where the conversion happens whereas it does not in others leading for some X-ray experiments, as previously explained, to the conversion stopping after awhile, seems to indicate that some parts of the sample do not contain nuclei of phase I at the beginning of the isotherm and that no nucleus is formed during the isotherm. This is in agreement with the microscopy observations where it appears that the conversion starts from a point located in the non-confined area (in the bottom left hand corner of Fig. 5e). Then the phase I grows from this point, reaches the sample area enclosed between the two microscope slides (Fig. 5f) and invades this space without the appearance of a new start point. Moreover, the more and more blurred aspect of the pictures outside the confined area as the sample crystallises, reveals a growth in three dimensions. Therefore, the growth in three dimensions of a number of nuclei already created at the beginning of the isotherm is more likely to happen. Taking into account the nucleation preferential domain of phase I (between 233 K and 263 K) (9), these nuclei could have been formed during the crossing of this domain. The small number of these nuclei explains the erratic behaviour observed for kinetics of the solid-solid transition.

CONCLUSION

In this paper we combined DSC, XRPD and hot stage microscopy to perform a detailed time resolved investigation of the crystallisation and phase transformation of racemic Ibuprofen. From the present results and those of the preceding investigations (9) a global picture of the crystalline polymorphism, the relative stability of the phases and their kinetic conditions of appearance and conversion emerge.

Racemic Ibuprofen may exist under two polymorphic crystalline varieties which are well structurally identified by the corresponding X-Ray pattern. Our results have definitely asserted that the two phases form a monotropic set. Phase I is the more stable phase at all temperatures lower than its melting at T_{mI} = 348 K. Metastable phase II may exist up to its melting point at T_{mII} = 290 K.

Phase I can be formed by undercooling the melt. Its preferential nucleation and growth domains are well separated: the preferential nucleation domain is located around 233 K–263 K, while the one of growth is around 313 K–348 K. This relative position and the important temperature gap makes racemic Ibuprofen a good glass former with a glass transition at Tg = 228 K.

In order to induce the crystal growth of phase II, a previous excursion at very low temperatures allows generating a significant number of nuclei of this phase. Indeed we have found that an efficient operational way to accelerate the nucleation process is to deeply quench the melt below Tg (Tg–60 K). It induces cracks which are revealed by microscopy and also by DSC since they give rise to clearly visible spikes in the thermograms when they appear. Upon re-heating the glass, these cracks favour heterogeneous nucleation of phase II rather than phase I, which is conform to the expected Ostwald's rule of stage. Near 273 K, it gives rise to crystallisation of phase II by a quite rapid growth mechanism. This fast growth domain is located approximately 60° lower than the one of phase I. It contributes to kinetically favour the appearance of the less stable phase II even if the temperature is roughly located in the limit of the preferential nucleation domain of phase I. Our results have shown that during an isothermal treatment in this temperature domain the successful appearance of the crystallisation of phase II is then followed by a conversion of this phase to phase I *via* a solid-solid transformation ($\Delta H_{II\text{-}I}$ = 8.0 ± 0.5 kJ/mol).

As revealed by XRPD and hot stage microscopy experiments, the kinetics of this latter II to I process is clearly slower than that of the initial crystallisation of phase II at the same temperature. This explains that in a DSC heating scan phase II can be observed and melted before any significant development of phase I could appear.

A careful investigation of the time evolution of X-Ray patterns at 273 K reveals a Johnson-Mehl-Avrami behaviour of the solid-solid interconversion between phase II and I. The time exponent n of the kinetic law is comprised between 2 and 3, which is significantly lower than the n=4 value expected for an ideal homogeneous nucleation and growth of spherical crystal (22). The conversion process has been nicely followed by microscopy: it is compatible with a growth process from pre-existing nuclei of phase I. However their number is extremely small. This induces an important variability from experiment to experiment in the way the conversion kinetic occurs after the crystallisation of phase II. The condition of appearance of these nuclei is still elusive. Some nuclei of phase I could be formed inside the amorphous undercooled melt during the crossing of the temperature fastest nucleation domain of phase I. These nuclei would thus be engulfed in phase II during crystallisation of the latter. The appearance of cracks could also generate the heterogeneous nucleation of some sparse nuclei of phase I in the glass in addition to those of phase II. However another eventuality which may not be discarded is that nuclei of phase I could be generated inside phase II in an heterogeneous way near intergrain zones. Therefore the precise mechanisms involved, at molecular level, in the solid-solid transformation occurring in racemic Ibuprofen, and more generally, in molecular organic compounds are still loosely understood and remain an important question to address.

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