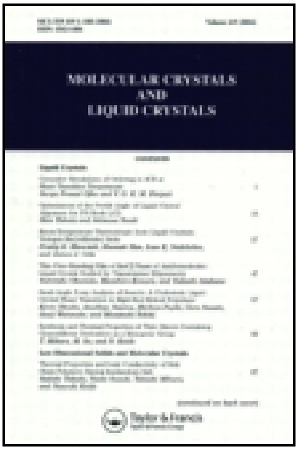

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Solid-State Stability of Indomethacin Solvates

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Desolvation kinetics of two indomethacin (IMC) solvates namely methanolate and *tert*-butyl alcohol (TBA) solvate were studied at 60–100 °C by isothermal thermogravimetric analysis. The solvates can transform to one of two true polymorphic forms, α or γ. Solid-state desolvation of IMC predominantly proceeds by a nucleation-limited mechanism as described by Avrami-Erofeev kinetics. The activation energies of desolvation as determined from these kinetic data were 34.1 kcal/mol and 17.6 kcal/mol for the methanol and TBA solvates respectively. The rank order of activation energy correlates well with the hydrogen-bonding strength and the crystal packing of the solvates. The methanolate desolvates to the metastable α form, whereas the TBA solvate desolvates to the equilibrium γ form at all the temperatures studied.

Keywords: indomethacin; solid state; desolvation; kinetics; polymorphic transitions

INTRODUCTION

Increased molecular mobility in the crystal lattice can explain certain physical and chemical properties of a compound such as reactivity, hygroscopicity, stability, and bioavailability. The long range goal of this research is to determine if solid-state nuclear magnetic resonance (NMR) in correlation with single crystal X-ray crystallography can be used to investigate molecular "looseness" of a solid substance. An important area that preoccupies preformulation groups is structure-property-reactivity relationships. If a positive correlation between molecular "looseness/ mobility" and solid-state reactivity is achieved in the early stages of development, it can serve as one of the most crucial factors in determining the "most desirable crystal form for manufacture."

Indomethacin (IMC) is a potent non-steroidal anti-inflammatory agent. IMC was chosen as a model compound for our research because of its ability to crystallize in different polymorphic forms, and to form stoichiometric solvates from a range of organic solvents. It exists in two true polymorphic forms (α and γ) and an amorphous form. This paper addresses the following issues: (i) desolvation kinetics of two IMC solvates namely methanolate and *tert*-butyl alcohol solvate (TBA); (ii) correlation of the desolvation behavior with the molecular "looseness" of the solvates as obtained from single-crystal X-ray structures of the solvates; and (iii) polymorphic transitions of the two solvates.

RESULTS AND DISCUSSION

Crystals of the two IMC solvates were grown by slow evaporation of the

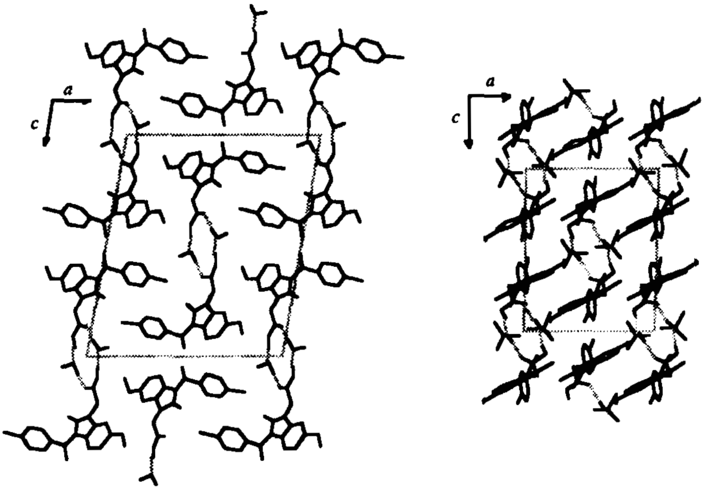

FIGURE 1 Crystal packing diagrams for IMC methanolate (left) and IMC TBA solvate (right). Both unit cells are viewed down their *b* axis.

methanol and TBA solution, respectively, under ambient conditions. Both solvates crystallized in the space group $P2_1/n$ with 4 molecules per unit cell.[1] Fig. 1 shows the crystal packing of the two solvates.

Desolvation studies of the IMC solvates were carried out at a range of temperatures (60–100 °C) using isothermal thermogravimetric analysis (TGA). Since IMC solvates can transform to one of two true polymorphic forms, α or γ, the characterization of polymorphic transitions of these solvates is also extremely important. The solvates and the unsolvated crystal forms of IMC have unique FTIR absorption spectra and X-ray powder patterns, and hence were characterized by a combination of these two techniques. Molecular looseness in the solid-state can be expressed in terms of the static disorder as determined from the packing density and hydrogen-bonding strength in the crystal lattice.

Desolvation Kinetics

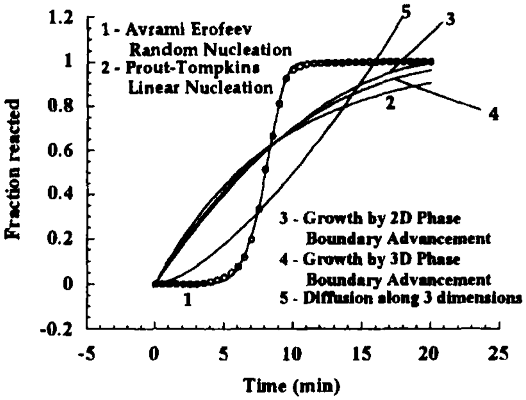

FIGURE 2 Curve fits of IMC desolvation data to standard kinetic equations in the solid-state.[2]

Desolvation is monitored by isothermal TGA at various temperatures. The fraction reacted, *f*, is plotted against time and and modeled to several classic solid-state nucleation-growth equations.[2] The best-fit equation is chosen to calculate the overall desolvation rate constant k. Fig. 2 illustrates Avrami-Erofeev kinetics (Eq. 1) which most closely fits the desolvation data.

$$f = 1 - \exp[(-kt)^n] \qquad (1)$$

The shape of the curve is sigmoidal as is common for most non-topochemical reactions in the solid-state. The curves are characterized by (1) an induction period at low f values, (2) a growth period with an inflection at intermediate values of f, and (3) a decay period at high f values. Avrami-Erofeev kinetics assume that the reaction is controlled by the growth and propogation of high-energy sites or nuclei. Once the product is formed it becomes a source of strain in the crystal lattice and then acts as a new nucleus, disrupting the molecular interactions of the neighboring molecules and causing them to react. This chain is propogated from one molecule to the next until it is terminated when a product molecule is encountered.

The Arrhenius dependence of the rate determining parameter, k, is tested by plotting $\ln(k)$ as a function of reciprocal temperature. The slope of this line is the activation energy (E_a) of desolvation and it describes the energy barrier that the solvate has to overcome to undergo desolvation. Fig. 3 shows the Arrhenius plots for the two solvates. It is clear that the methanolate has an activation energy (34.1 kcal/mol) almost twice that of the TBA solvate

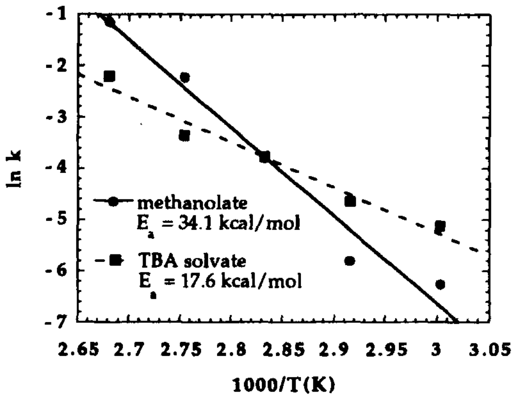

FIGURE 3 Arrhenius plots of rate constants of IMC desolvation.

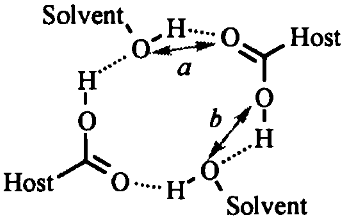

FIGURE 4 Hydrogen bonding network in IMC solvates

(17.6 kcal/mol). This behavior can be explained by Kitaigorodskii's close-packing theory.[3] He suggests that the basic factor that affects free energy of a crystal is its packing density. The methanolate and the TBA solvate have a packing density of 1.393 g/cm^3 and 1.296 g/cm^3 respectively. According to Kitaigorodskii, the denser or more closely packed crystal has the smaller free energy. The lower packing density results in increased intermolecular space from loose packing, which could facilitate the faster release of product gas molecules.

Looking closely at Fig. 1, it can be seen that in both the solvates, the host and the solvent form a twelve membered ring which must be disrupted to effect desolvation. Fig. 4 represents a diagram of the hydrogen bonding network in the two crystal solvates. The distance *b* between the host carboxyl oxygen and the solvent hydroxyl oxygen is 2.589 Å in both the solvates. However, the distance *a* between the host carbonyl oxygen and the solvent-OH oxygen is 2.728 Å and 2.841 Å in the methanol and TBA solvates respectively. This significantly longer bond length in the TBA solvate implies a weaker hydrogen bonding network, which is consistent with a lower barrier to desolvation. Thus, the rank order of activation energy of the two solvates correlates well with the hydrogen-bonding strength and crystal packing.

Polymorphic Transitions

Fig. 5 shows the FTIR absorption spectra of the solvate and non-solvate forms. The different crystal forms show unique absorption in the carbonyl stretching region. The C=O band at 1700 cm^{-1}, 1691 cm^{-1}, 1734 cm^{-1} and 1716 cm^{-1} were used as indicators for the methanolate, TBA solvate, α and γ-

forms, respectively. The methanolate desolvates to first form a desolvated solvate, which has a melting point of 134 °C as determined by DSC. This form, upon further exposure to elevated temperatures, converts to the α-form, indicating that the desolvated material has similar energetics to the α-form rather than the γ-form. The TBA solvate does not form an isolable intermediate, but transforms directly to the γ-form.

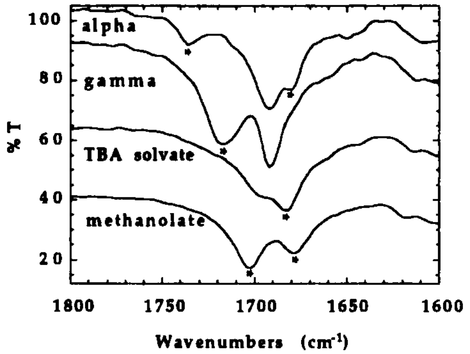

FIGURE 5 Solid-state FTIR spectra showing the characteristic carbonyl stretching frequencies (labeled with an asterisk,*) of the different crystal forms of IMC in KBr pellet.

These trends in the polymorphic transitions illustrate how the final crystal form can be manipulated the by varying the solvent used in the final purification step.

Acknowledgements

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