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CRYSTAL PACKING AND CHEMICAL REACTIVITY OF TWO POLYMORPHS OF FLUFENAMIC ACID WITH AMMONIA

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The objective of this study is to compare the reactivity of two polymorphs of flufenamic acid with ammonia and relate it to crystal packing. Forms I and III of flufenamic acid were exposed to dry ammonia vapor. Optical microscopy, microscopic Raman, and XRPD were used to characterize the possible changes. The different reactivity of Forms I and III was clearly observed under dry ammonia vapor from 12% ammonium hydroxide. Single crystals of Form I gradually became opaque within 180 min, whereas single crystals of Form III retained transparent. FT-Raman analysis revealed that significant ammonium salt was formed at the major face of Form I, while the reaction of Form III was undetectable. So Form I is more reactive than Form III at ambient temperature, which agrees with their thermodynamic order. At 60°C, the thermodynamic order switches and Form I is the stable form. However, Form I is still more reactive with ammonia than Form III at 60° C. The reaction rate is likely to be determined more by kinetic factors. The good accessibility of reaction groups could be one of the reasons that Form I is more reactive.

Keywords: solid-gas reactions; acid-base reactions; polymorph; crystal packing; ammonia; flufenamic acid

INTRODUCTION

Solid-gas reactions are known to be the major reason for metal corrosion [1]. This type of reaction also causes the instability of many pharmaceuticals. Oxidation is the most significant reaction [2]. The attack of water vapor, a type of solid-gas interaction, facilitates the physical and chemical

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transformation of solid pharmaceuticals [3]. Because of their complexity, neither reaction is well understood. Solid-gas acid-base reactions are much simpler and thus provide an opportunity to understand the effect of crystal packing on reactivity.

The pioneering work of Paul and Curtin's lab shows that solid-gas acid-base reactions are related to crystal structure [4–7]. It was demonstrated that the reactions of molecular crystals can show clear anisotropy. The formation of salt by the reactions of benzoic acid derivatives with ammonia is visibly anisotropic. Certain crystal faces are attacked preferentially because the carboxylic groups are exposed there. The resulting reaction front travels more rapidly through the crystal in certain directions, which are correlated with the internal crystal packing. In our study on the solid-gas reaction between indomethacin and ammonia, very different chemical reactivity was observed for the α and γ forms. The α form is quickly reacted whereas the γ form is extremely unreactive [8], which correlates with their thermodynamic order. It is still not clear whether such types of solid-state reactions are determined by thermodynamic factors or kinetic factors. Study on enantiotropic system will provide more information for that.

Unless there is no channel or tunnel in the crystal allowing the vapor to diffuse quickly inside, the solid-gas reaction is generally considered to be a surface-based phenomenon. It can be envisioned that the reaction proceeds layer by layer, like a dissolution process. It is hypothesized that the surfaces being reacted are determined by accessibility of reacting groups and the ease of disruption of crystal packing.

Flufenamic acid is an analgesic and anti-inflammatory drug, whose chemical name is 2-[[3-(trifluoromethyl)phenyl]amino]benzoic acid. Six polymorphs have been identified for this compound [9]. Only Form I (white, m.p. 134°C) and Form III (yellow, m.p. 128°C) can be easily prepared by crystallization. Both crystal structures are known, and, in both forms, individual molecules form dimers via hydrogen bonding [10,11]. Thermodynamically, Form I and Form III are enantiotropically related to each other [9], and the transition temperature has been reported to be 42°C. Form III is the stable form below 42°C. Form I is the stable from above 42°C. It is of interest to determine whether the chemical reactivities of the two polymorphs are correlated to their relative thermodynamic stability.

EXPERIMENTAL

Materials

Flufenamic acid (2-[[3-(trifluoromethyl)phenyl]amino]benzoic acid) was purchased from Aldrich (Milwaukee, WI). Form I and Form III of flufenamic acid were crystallized from toluene with seeding. Single crystals of them

were obtained by slow evaporation from toluene. Reagent grade toluene, ethyl acetate, and ammonium hydroxide were purchased from Mallinckrodt (St. Louis, MO).

Drying of the Ammonia Vapor

A slow stream of nitrogen gas was bubbled through an ammonium hydroxide solution in a gas-washing bottle with a fritted disk. The resulting vapor was passed through a glass-drying tower containing 200 g of potassium hydroxide as desiccant. The resulting dilute ammonia gas in nitrogen gas was used directly.

Gas-Solid Reactions with Ammonia

Single crystals or powder of flufenamic acid were put into a container that had a gas inlet and outlet. The samples were dried by purging nitrogen gas for 1 h. After that, dry ammonia/nitrogen was passed over the solid. For reactions with single crystals, changes were observed online using a microscope and recorded by a digital camera.

X-Ray Powder Diffraction

All diffraction patterns were measured on a Siemens D500 equipped with a vertical goniometer in θ-2θ geometry with slits I, II, and III at 1°, and slit IV at 0.15°. The copper *Ka* radiation was generated at a power of 40 kV and 20 mA. The diffraction was electronically filtered by the Kevex Psi peltier cooled silicon [Si(Li)] detector. About 0.20 g powder sample was put into an aluminium sample holder and gently pressed with a glass slide to make the sample surface and holder surface coplanar. A continuous scan was recorded for all samples from 4–36° 2θ with step size of 0.04° 2θ and a scanning rate of 6° 2θ per minute.

Microscopy

Microscopic analysis was performed with a Zeiss (Jena, Germany) polarized-light microscope connected to a digital camera. The image was recorded with the video program in a powerPC (Macintosh).

Raman Microscopy

A near-infrared Raman imaging microscope (NIRIM) based on fiber-bundle image compression was used for all Raman analysis. The NIRIM was built by Gift et al. in the Department of Chemistry, Purdue University (West Lafayette, Indiana) with support from the National Science Foundation

[12]. The sample was focused with the help of white light. All Raman spectra were collected using a 10× (0.25 NA) microscope objective lens and 10 s exposure time.

Molecular Simulation

Cerius^2 (molecular Simulation, California) was used to visualize the crystal structure, perform geometric measurements, and carry out all crystal lattice-based calculations.

RESULTS AND DISCUSSIONS

The Reactions Between Flufenamic Acid and Ammonia

Form I and Form III of flufenamic acid reacted with NH_3 at ambient temperature. Under dry NH_3 from 17% ammonium hydroxide, both forms were totally reacted after 24 h, as revealed by XRPD in Figure 1. The characteristic XRPD peaks of each form disappeared. The new phases produced from both forms are in good agreement for all diffraction peaks and with the ammonium salt standard diffraction pattern. Microscopic observation revealed that the particles retained their original shape after reaction (data

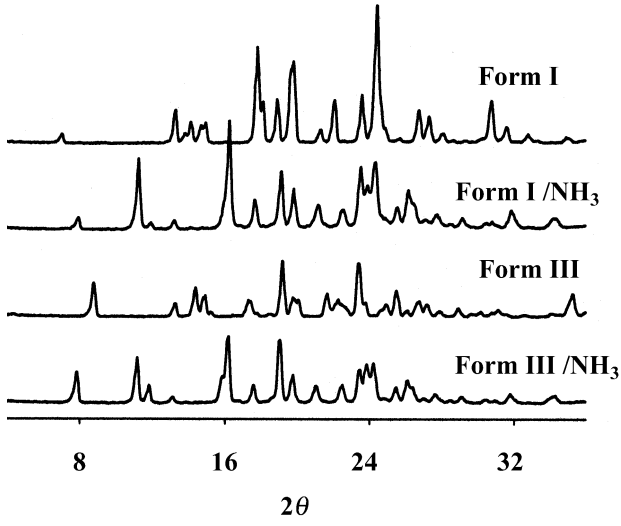

FIGURE 1 Flufenamic acid: X-ray powder diffraction patterns of Form I and Form III before (Form I, Form III) and after (Form I/NH_3, Form III/NH_3) reaction with dry ammonia for 24 h.

TABLE 1 Comparison of the Calculated and Measured Composition of the Reaction Products from the Reaction Between Flufenamic Acid and Ammonia

	C	H	N	F
Calculated (%, 1:1 salt)	56.40	4.36	9.39	19.12
Measured Form I Product (%)	56.53	4.38	9.30	19.11
Measured Form III Product (%)	56.31	4.36	9.32	19.01

not shown). The distinct shapes of original Forms I and III contribute different preferred orientations for the ammonium salt products. That explains why the peak intensity profiles in XRPD patterns of the two products are different.

The stoichiometry between NH_3 and flufenamic acid was confirmed by elemental analysis. The measured composition of reaction products matches that calculated assuming 1:1 ammonium flufenamate, as listed in Table 1.

Microscopic Study

Single crystals of Forms I and III were placed on a glass slide. The changes in these two forms in dry ammonia vapor from 12% ammonium hydroxide were closely examined under the microscope. As shown in Figure 2, the two single crystals of Form I gradually became opaque, starting as soon as they were exposed to ammonia. The change in Form I was not anisotropic: the opaqueness started at one spot on the major face and diffused throughout. The reaction produced microcrystalline ammonium salt, which made the crystals opaque. The change in the Form I crystals from clear to opaque is due to the acid-base reaction with ammonia.

While Form I was totally opaque after 180 min, the single crystal of Form III remained clear. It is more stable to ammonia than Form I. It was found that cleavage did not affect the reactivity of Form III. Thus, these two polymorphs of flufenamic acid exhibit different reactivity with ammonia.

Evidence from Raman Microscopy

The major faces (100 of Form I and Form III) of the above single crystals before and after reaction were studied by Raman microscopy (Figure 3). After exposure to dry ammonia gas, the characteristic peaks of Form I decreased. Several new peaks appeared that matched the spectra of the ammonium salt. This verifies that single crystals of Form I reacted with ammonia to form significant amounts of the ammonium salt. However, the spectra of Form III before and after reaction were nearly identical,

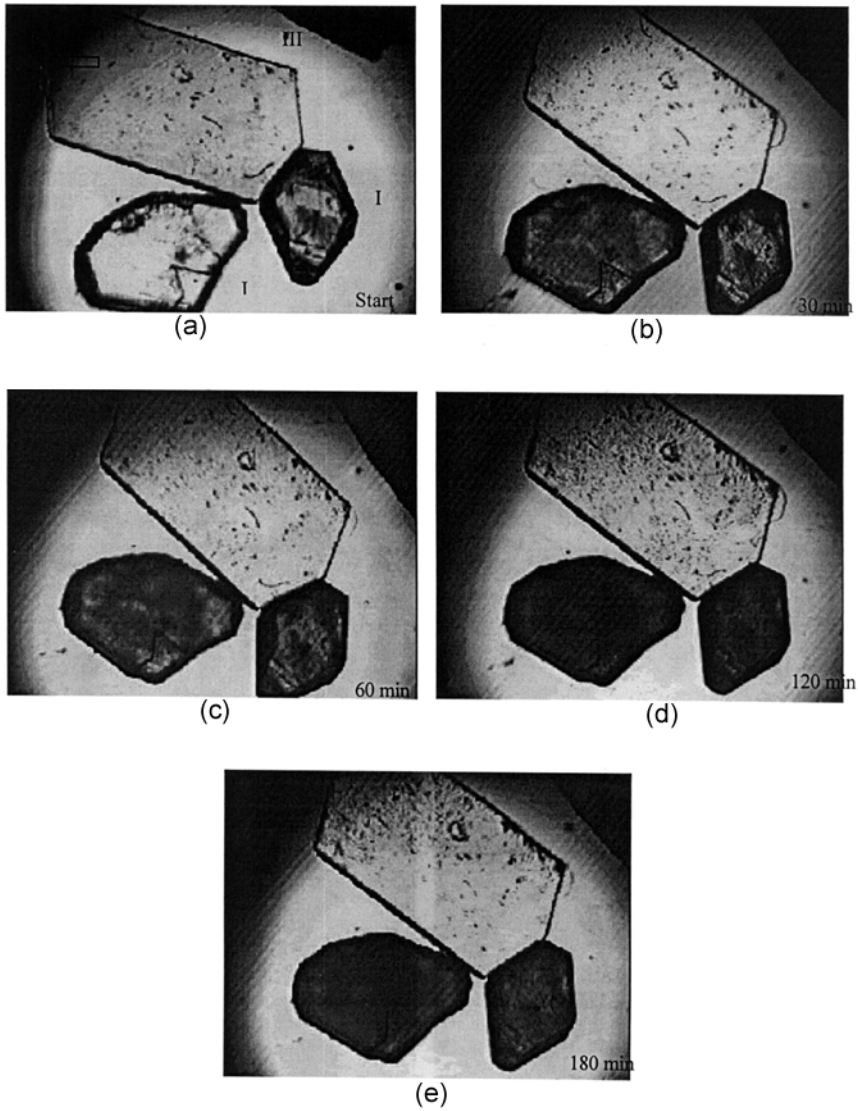

FIGURE 2 Microscopic observation of flufenamic acid Form I and Form III under exposure to dry ammonia vapor (79 × magnification): I; Form I; III, Form III. (a) Start, (b) 30 min, (c) 60 min, (d) 120 min, (e) 180 min.

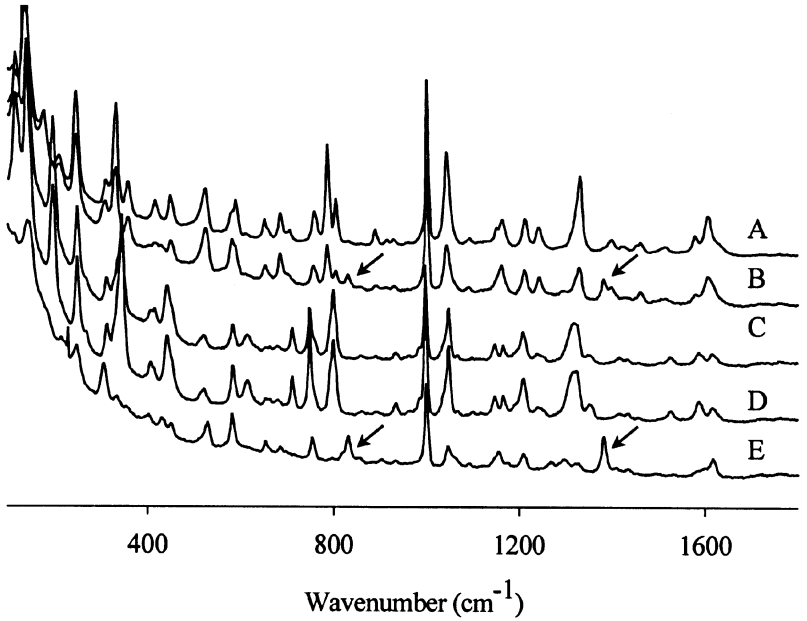

FIGURE 3 Raman spectra of single crystals of flufenamic acid Forms I and III before and after reaction with dry ammonia. A, Form I before reaction; B, Form I after reaction; C, Form III before reaction; D, Form III after reaction; E, ammonium salt of flufenamic acid. Arrows point to characteristic peaks of ammonium salt of flufenamic acid.

indicating that very little reaction occurred. It is clear that Form I is more reactive than Form III with ammonium gas under the same experimental conditions.

Reactions at 60°C

Forms I and III are an enantiotropic pair with a transition temperature at 42°C. At ambient temperature, Form III is the stable form and less reactive with ammonia. At 60°C, Form III is the metastable form of flufenamic acid. If the reactivity is correlated with thermodynamic order, Form III should be more reactive than Form I at 60°C. However, experimental results showed that Form III was still less reactive than Form I with dry ammonia vapor. As illustrated in Figure 4, single crystals of Form I became totally opaque while single crystals of Form III remained clear. This suggests that the reaction is related to the structure and not the energetics of the two forms.

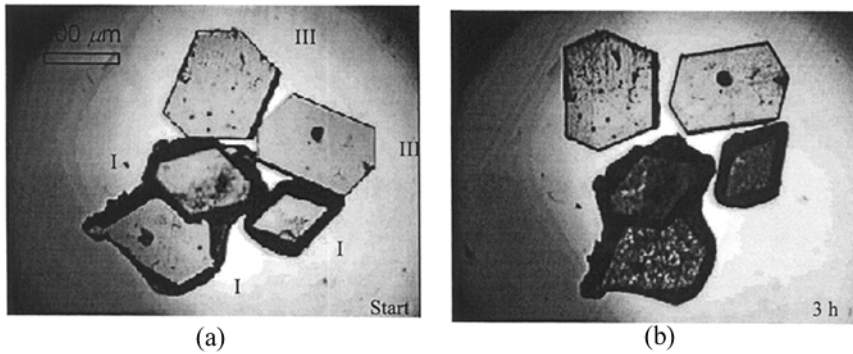

FIGURE 4 Microscopic observation of flufenamic acid Form I and Form III under exposure to dry ammonia vapor at 60°C (79 × magnification). I, Form I; III, Form III. (d) Start, (b) 3 h.

Relationship Between Reactivity and Crystal Packing

The reactivity of Form I and Form III with ammonia is related to their crystal packing. Like most carboxylic compounds, the carboxyl groups in both forms exist in hydrogen bonded dimers (Figures 5, 6). The dimers are arranged in layers, which are parallel to the 100 face of Form I and Form III. The carboxyl groups should have significant exposure on the faces that cut across the dimer layers, and thus those faces tend to be attacked first by ammonia.

However, the 100 face of Form I was attacked by ammonia and became opaque very quickly. This made it hard to observe the expected penetration of ammonia from the peripheral faces. It appears that the layer of hydrophobic phenyl and CF_3 groups on the 100 faces do not provide sufficient shielding from the ammonia vapor. Examination of the molecular arrangement of the top layer indicated that those groups do not pack tightly (Figure 5). It is possible that the carboxylic acid groups are accessible to ammonia through the top face, as they are not efficiently blocked as judged by the molecular packing along a axis relative to the size of the ammonia molecule. The tendency of the top layer to react makes the anisotropy less distinguishable than that demonstrated in the reaction of benzoic acid derivatives with ammonia [4–6].

In contrast, the hydrophobic phenyl and CF_3 groups were packed very tightly on the 100 face in Form III (Figure 6). They provide very good protection for carboxylic acid dimers from ammonia in this specific face. It is obvious that the attack from this direction will be very difficult. Poor accessibility to ammonia may be one of the reasons that Form III is less reactive than Form I.

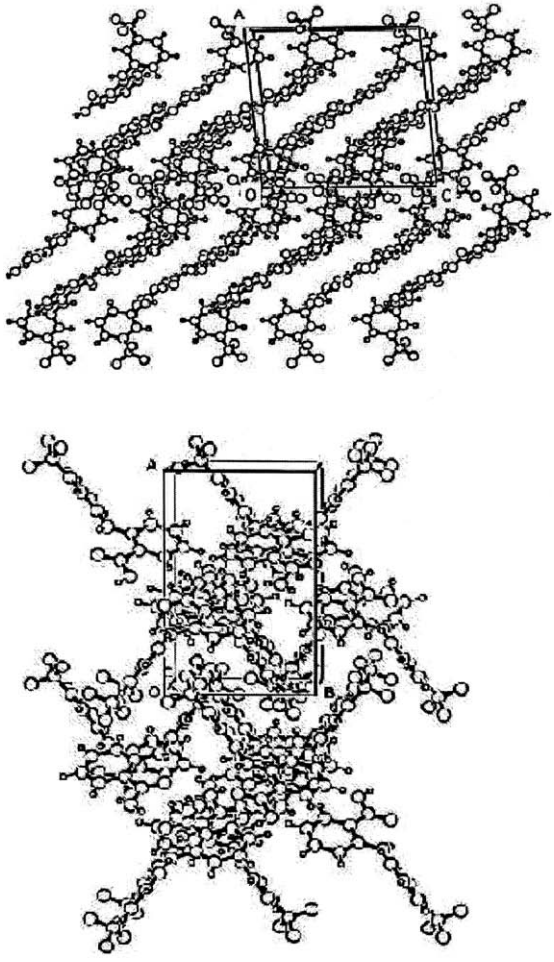

FIGURE 5 The crystal packing of Form I of flufenamic acid viewed down b and a axis.

It becomes more evident as the cell parameters of Form I and III are examined. Both crystal structures belong to monoclinic. Form I has a cell parameters of a = 12.5 Å, b = 7.9 Å, and c = 12.9 Å. Form III has a cell parameters of a = 39.8 Å, b = 5.1 Å, and c = 12.2 Å. On 100 faces, Form III takes less surface area to packing two functional groups than Form I (62.2 $Å^2$ vs 101.1 $Å^2$). So Form III is more efficiently packed in 100 face than Form I.

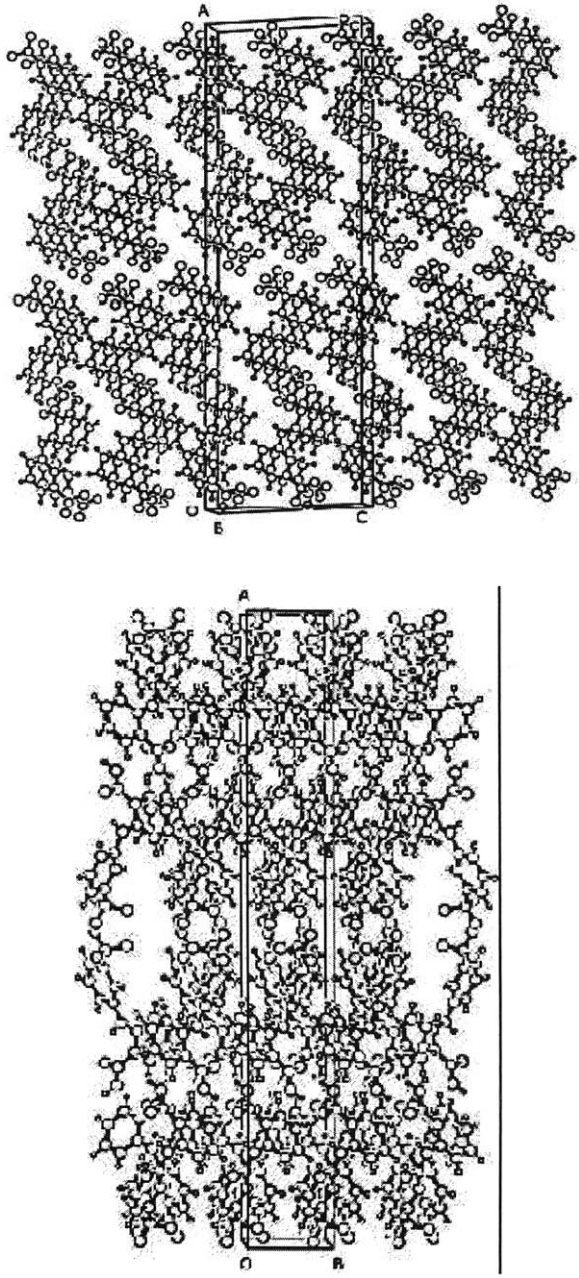

FIGURE 6 The crystal packing of Form III of flufenamic acid viewed down b and c axis.

For Form III, it is expected that the carboxyl groups also have significant exposure in the peripheral faces, which cut across the dimer layers. However, it seems that those faces are stable to ammonia vapor.

CONCLUSIONS

Form I and Form III of flufenamic acid can react with dry ammonia vapor from 17% ammonium hydroxide. XRPD indicated that the same crystalline product was formed from both forms. Under the dry ammonium vapor from 12% ammonium hydroxide, different reactivity of Form I and Form III was observed. The good accessibility of reaction groups might be one of the reasons that Form I is more reactive.

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