J|A|C|S
ARTICLES
Published on Web 11/22/2002

Reactivity Differences of Indomethacin Solid Forms with Ammonia Gas

Xiaoming Chen,[†,‡] Kenneth R. Morris,[‡] Ulrich J. Griesser,[§] Stephen R. Byrn,[‡] and Joseph G. Stowell*[,‡]

Contribution from the Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, Indiana 47907-2051, and Institute of Pharmacy, University of Innsbruck, Innrain 52, A-6020 Innsbruck, Austria

Received December 1, 2001

Abstract: The present study deals with the acid−base reaction of three solid-state forms of the nonsteroidal antiinflammatory drug indomethacin with ammonia gas. X-ray powder diffraction, optical microscopy, gravimetry, and spectroscopic methods were employed to establish the extent of the reaction as well as the lattice changes of the crystal forms. The glassy amorphous form readily reacts with ammonia gas to yield a corresponding amorphous ammonium salt. In addition, the metastable crystal form of indomethacin (the α-form) also reacts with ammonia gas, but produces the corresponding microcrystalline ammonium salt. This reaction is anisotropic and propagates along the *a*-axis of the crystals. The stable crystal form (the γ-form), however, is inert to ammonia gas. Amorphous indomethacin can react with ammonia gas because it has more molecular mobility and free volume. The reactivity differences between the α- and γ-forms are dictated by the arrangement of the molecules within the respective crystal lattices. The recently determined crystal structure of the metastable α-form of indomethacin (monoclinic $P2_1$ with $Z = 6$, $V = 2501.8$ Å^3, $D_c = 1.42$ g·cm^{-3}) has three molecules of indomethacin in the asymmetric unit. Two molecules form a mutually hydrogen-bonded carboxylic acid dimer, while the carboxylic acid of the third molecule is hydrogen bonded to one of the amide carbonyls of the dimer. The carboxylic acid groups of the α-form are exposed on the {100} faces and are accessible to attack by ammonia gas. After one layer of molecules reacts, the reactive groups in the subsequent layer are accessible to the ammonia gas. This process proceeds along the *a*-axis until the ammonia gas has penetrated the entire crystal. In contrast to the α-form, the γ-form has a centrosymmetric crystal structure in which the hydrogen-bonded carboxylic acid dimers are not accessible to ammonia gas because they are caged inside a hydrophobic shield comprising the remainder of the indomethacin molecule. In view of the significantly lower density of the stable γ-form as compared to the metastable α-form (1.37 and 1.42 g cm^{-3}, respectively), it became apparent that the reactivity of the crystal forms depends exclusively on the molecular arrangement and not on the packing density of the indomethacin crystals.

Introduction

Solid-state reactions of solids with gases have been known for many years. Hochstrasser and Porter,[1,2] as well as Scheffer and Ouchi,[3] have investigated the oxidation of polycyclic aromatic hydrocarbons in the presence of oxygen gas. Desvergne and Thomas[4] determined that the reaction of *trans*-stilbene and *trans*-diethylstilbestrol with ozone was dependent on crystal defects. Lamartine and Perrin[5] have explored the chlorination of a series of substituted phenols via an addition−elimination mechanism. For example, when 2-methylphenol crystals are exposed to anhydrous chlorine gas, the reaction affords a mixture of 4-chloro-2-methylphenol and 6-chloro-2-methylphenol; the ratio of the product isomers is dependent on which crystal face is exposed to the reacting chlorine gas.

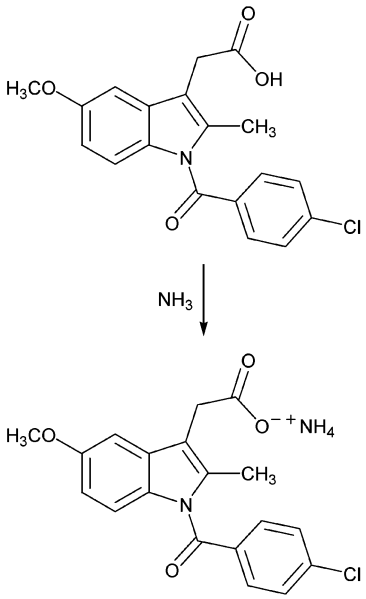
Studies by the Curtin and Paul group[6−11] revealed that crystals of many carboxylic acids react with anhydrous ammonia gas to afford the corresponding ammonium salts. Some of these processes are visibly anisotropic. In other words, certain crystal faces are attacked preferentially, and the reaction rates along particular crystallographic directions are very different. These studies also investigated the reaction rate of the carboxylic acid crystals with ammonia gas at constant pressure. Interestingly, the reaction rate does not correlate with the acidity of the carboxylic acid, the crystal density, nor the melting point of

* To whom correspondence should be addressed. Phone: (765)-494-7090. Fax: (765)-494-6545. E-mail: jstowell@purdue.edu.
† Current address: K-11-2 J-4, Schering-Plough Research Institute, 2000 Galloping Hill Road, Kenilworth, NJ 07033-1328.
‡ Purdue University.
§ University of Innsbruck.

(1) Hochstrasser, R. M. *Can. J. Chem.* **1959**, *37*, 1123.
(2) Hochstrasser, R. M.; Porter, G. B. *Q. Rev.* (*London*) **1960**, *14*, 146.
(3) Scheffer, J. R.; Ouchi, M. D. *Tetrahedron Lett.* **1970**, *11*, 223.
(4) Desvergne, J. P.; Thomas, J. M. *J. Chem. Soc., Perkin Trans. 2* **1975**, 584.
(5) Lamartine, R.; Perrin, R. *J. Org. Chem.* **1974**, *39*, 1744.
(6) Lin, C.-T.; Paul, I. C.; Curtin, D. Y. *J. Am. Chem. Soc.* **1974**, *96*, 3699.
(7) Lin, C.-T.; Curtin, D. Y.; Paul, I. C. *J. Am. Chem. Soc.* **1974**, *96*, 6199.
(8) Curtin, D. Y.; Miller, R. S.; Paul, I. C. *J. Am. Chem. Soc.* **1971**, *93*, 2784.
(9) Miller, R. S.; Curtin, D. Y.; Paul, I. C. *J. Am. Chem. Soc.* **1974**, *96*, 6329.
(10) Miller, R. S.; Paul, I. C.; Curtin, D. Y. *J. Am. Chem. Soc.* **1974**, *96*, 6334.
(11) Miller, R. S.; Curtin, D. Y.; Paul, I. C. *J. Am. Chem. Soc.* **1974**, *96*, 6340.

10.1021/ja017662o CCC: $22.00

Scheme 1. Reaction between Indomethacin and Ammonia



the crystal. It is not evident how just a small change in crystal packing can produce a large change in reaction rate. Solid-state studies of polymorphs provide good models to probe the effect of crystal packing on chemical reactivity. We report herein our investigation on the chemical reactivity of indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid] solid forms (two polymorphs and the glassy amorphous form) with ammonia gas (Scheme 1). This study provides some new insight into the relationship between chemical reactivity and crystal packing.

The α- and γ-forms (mp 152−154 °C and 160−161 °C, respectively) can be obtained from an array of solvents under various conditions.[12−14] The various forms of indomethacin have been extensively investigated.[12−22] The crystal structure of the stable γ-form has been determined by two independent groups.[23,24] However, the crystal structure of the metastable α-form has not been previously published. We report herein the crystal structure of the α-form, and we hypothesize that the distinct crystal packing of the two polymorphs has a profound impact on the chemical stability of the forms, which is demonstrated in the pronounced reactivity differences with ammonia gas.

Methods

Reagents. Indomethacin, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid, was purchased from Sigma (St. Louis, MO). Potassium iodide was obtained from Aldrich (Milwaukee, WI). Mercury(II) iodide, ethylenediaminetetraacetic acid, potassium hydroxide, ammonium hydroxide, and ammonium chloride were from Mallinckrodt (St. Louis, MO). Anhydrous ethanol was purchased from Pharmco-products, Inc. (Brookfield, CT). Glacial acetic acid and concentrated ammonium hydroxide solution (28%) were obtained from Fisher Scientific (Pittsburgh, PA). Water was deionized and then distilled.

α-Indomethacin. Needlelike α-indomethacin crystals were prepared by dissolution of the commercial material in hot ethanol followed by precipitation with water at room temperature as previously described.[25] Chunky α-indomethacin crystals were obtained by crystallization of indomethacin from a mixture of water:acetic acid (60:40 v/v). Large single crystals of the α-form suitable for single-crystal X-ray diffraction studies were obtained by diffusion of water vapor into a solution of indomethacin in glacial acetic acid. All samples were dried in vacuo overnight before being used.

γ-Indomethacin. The γ-form was prepared by recrystallization in 60% aqueous ethanol. Single crystals of the γ-form were obtained by slow evaporation of an ethanolic solution. All samples were dried in vacuo overnight before being used.

Amorphous Indomethacin. A small amount of amorphous indomethacin for microscopic study was prepared by melting indomethacin on a glass slide in a Mettler FP52 hot stage apparatus (Mettler, Inc.; Greifensee, Switzerland) at 165 °C and then slowly cooling the fused sample to ambient temperature. Bulk amorphous indomethacin was produced by melting γ-indomethacin at 165 °C for 5 min and then quench-cooling the fused material by rapid addition of a thin stream of the melt to liquid nitrogen. All samples were dried in vacuo overnight before being used.

Preparation of Ammonia Gas Diluted with Nitrogen Gas. A slow stream of nitrogen was bubbled through a concentrated ammonium hydroxide solution (28%) in a gas-washing bottle with a fritted disk (Fisher Scientific; Pittsburgh, PA). The resulting vapor was passed through a glass-drying tower (Fisher Scientific; Pittsburgh, PA) containing about 200 g of potassium hydroxide pellets as desiccant. The resulting dilute ammonia gas in nitrogen gas was used directly.

Ammonium Assay. Nessler's reagent was prepared according to the USP/NF procedure (Mercuric-Potassium Iodide Test Solution, Alkaline).[26] The resulting solution was stored in a Pyrex bottle out of direct sunlight. Spectrophotometric analyses were performed on a Beckman DU650 spectrophotometer (Beckman Coulter, Inc.; Fullerton, CA) using a quartz 1-cm cuvette.

Specific Surface Areas. The specific surface areas were measured with an ASAP 2010 (Micromeritics; Norcross, GA) using krypton as the measuring gas at 77.35 K.

X-ray Powder Diffraction. Analyses were carried out on a Shimadzu XRD-6000 X-ray powder diffractometer (Kratos Analytical, Inc.; Chestnut Ridge, NY) equipped with a fine-focus X-ray tube using Cu Kα radiation (1.5406 Å). The tube voltage and amperage were set at 30 kV and 30 mA, respectively. The divergence and scattering slits were set at 1°, and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a sodium iodide scintillation detector. Theta-two-theta continuous scans at 2°/min (with a step size of 0.02°) from 4 to 40° 2θ were used. The instrument was calibrated using silicon standard.

Single-Crystal X-ray Diffraction. A colorless chunk of $C_{19}H_{16}ClNO_4$ having approximate dimensions of 0.50 × 0.30 × 0.25 mm was mounted on a glass fiber in a random orientation. Preliminary examination and data collection were performed with Mo Kα radiation ($\lambda = 0.71073$ Å) on an Enraf-Nonius CAD4 computer controlled κ-axis diffractometer equipped with a graphite crystal, incident beam monochromator.

Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the range $19 < \theta < 22°$, measured by the computer-controlled diagonal slit method of centering. The monoclinic cell

(12) Yamamoto, H. *Chem. Pharm. Bull*. **1968**, *16*, 17.
(13) Borka, L. *Acta Pharm. Suec*. **1974**, *11*, 295.
(14) Pakula, R.; Pichnej, L.; Spychala, S.; Butkiewicz, K. *Pol. J. Pharmacol. Pharm*. **1977**, *29*, 151.
(15) Kaneniwa, N.; Otsuka, M.; Yamaguchi, T.; Hayashi, T.; Hayashi, K.; Matsumoto, T.; Watari, N.; Unezawa, O. *Funsai* **1989**, 30.
(16) Hancock, B. C.; Zografi, G. *Pharm. Res*. **1994**, *11*, 471.
(17) Hancock, B. C.; Shamblin, S. L.; Zografi, G. *Pharm. Res*. **1995**, *12*, 799.
(18) Andronis, V.; Zografi, G. *Pharm. Res*. **1997**, *14*, 410.
(19) Andronis, V.; Yoshioka, M.; Zografi, G. *J. Pharm. Sci*. **1997**, *86*, 346.
(20) Andronis, V.; Zografi, G. *Pharm. Res*. **1998**, *15*, 835.
(21) Taylor, L. S.; Zografi, G. *Pharm. Res*. **1998**, *15*, 755.
(22) Andronis, V.; Zografi, G. *J. Non-Cryst. Solids* **2000**, *271*, 236.
(23) Kistenmacher, T. J.; Marsh, R. E. *J. Am. Chem. Soc*. **1972**, *94*, 1340.
(24) Galdecki, Z.; Glowka, M. L. *Rocz. Chem*. **1976**, *50*, 1139.
(25) Kaneniwa, N.; Otsuka, M.; Hayashi, T. *Chem. Pharm. Bull*. **1985**, *33*, 3447.
(26) *United States Pharmacopeia/National Formulary*, 23rd ed./18th ed.; United States Pharmacopeial Convention: Rockville, MD, 1995; p 2054.

parameters and calculated volume are $a = 5.462(2)$, $b = 25.310(9)$, $c = 18.152(7)$ Å, $\beta = 94.38(3)°$, and $V = 2501.8$ Å^3. For $Z = 6$ and $M = 357.80$, the calculated density is 1.42 g cm^{-3}. As a check of crystal quality, ω scans of several intense reflections were measured; the width at half-height was 0.52° with a takeoff angle of 3.0° indicating good crystal quality. The space group was determined by the program *ABSEN*.[27] From the systematic presences of $0k0$ with $k = 2n$ and from subsequent least-squares refinement, the space group was determined to be $P2_1$ (No. 4).

The data were collected at a temperature of 203 ± 1 K using the $\omega-2\theta$ scan technique. The scan rate varied from 4 to 16° min^{-1} (in ω). The variable scan rate allows rapid data collection for intense reflections where a fast scan rate is used and ensures good counting statistics for weak reflections where a slow scan rate is used. Data were collected within 2θ a range of 5.12−55.64°. The scan range (in deg) was determined as a function of θ to correct for the separation of the Kα doublet;[28] the scan width was calculated using an ω scan width = $0.52 + 0.810 \tan\theta$. Moving-crystal moving-counter background counts were made by scanning an additional 25% above and below this range. Thus, the ratio of peak-counting time to background-counting time was 2:1. The counter aperture was also adjusted as a function of θ. The horizontal aperture width ranged from 1.3 to 2.0 mm; the vertical aperture was set at 4.0 mm. The diameter of the incident beam collimator was 0.7 mm, and the crystal-to-detector distance was 21 cm. For intense reflections, an attenuator was automatically inserted in front of the detector; the attenuator factor was 13.2.

A total of 6660 reflections were collected, of which 6036 were unique. As a check of crystal and electronic stability, three representative reflections were measured every 83 min. The intensities of these standards remained constant within experimental error throughout data collection. No decay correction was applied.

Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 2.5 cm^{-1} for Mo Kα radiation. No absorption correction was used. Intensities of equivalent reflections were averaged. The agreement factor for the averaging was 2.9% on the basis of intensity.

The structure was solved by direct methods using *SIR92*.[29] The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were included in the refinement but restrained to ride on the atom to which they are bonded. The structure was refined in full-matrix least-squares where the function minimized was $\sum w(|F_o|^2 - |F_c|^2)^2$, and the weight w is defined as $w = 1/[\sigma^2(F_o^2) + (0.0411P)^2 + 0.7961P]$, where $P = {}^1/_3(F_o^2 + 2F_c^2)$.

Scattering factors were taken from the *International Tables for Crystallography*.[30] In the refinements, 6036 reflections were used; however, only reflections with $F_o^2 > 2\sigma(F_o^2)$ were used in calculating R. The final cycle of refinement included 694 variable parameters and converged (largest parameter shift was <0.01 times its esd) with unweighted and weighted agreement factors of $R1 = \sum|F_o - F_c|/\sum F_o = 0.054$, $R2 = [(\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2)]^{1/2} = 0.198$. The standard deviation of an observation of unit weight was 1.11. The highest peak in the final difference Fourier had a height of 0.33 e A^{-3}. The minimum negative peak had a height of −0.40 e A^{-3}. The factor for the determination of the absolute structure refined to 0.06.[31] Refinement was performed on a AlphaServer 2100 using *SHELX97*.[32]

(27) McArdle, P. *ABSEN* − a PC computer program for listing systematic absences and space-group determination. *J. Appl. Crystallogr.* **1996**, *29*, 306.
(28) *28.CAD4 Operations Manual*; Enfraf-Nonius: Delft, 1977.
(29) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1994**, *27*, 1045.
(30) *Table 4.2.6.8 and Table 6.1.1.4 in International Tables for Crystallography: Mathematical, Physical, and Chemical Tables*; Wilson, A. J., Prince, E., Eds.; Kluwer Academic: Dordrecht, The Netherlands, 1992; Vol. C.
(31) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *A39*, 876.
(32) Sheldrick, George M. *SHELXS-97*: a program for crystal structure refinement; University of Gottingen: Germany, 1997.

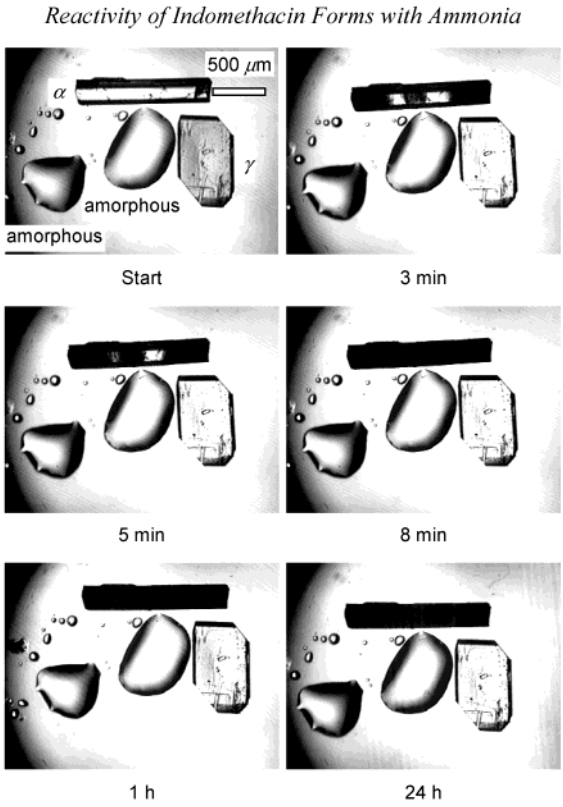


Figure 1. Time-course photomicrographs (79× magnification) of amorphous, α-, and γ-indomethacin interacting with ammonia gas.

Optical Microscopy. Optical microscopic observations were performed on a Zeiss binocular polarizing microscope with rotating stage (Carl Zeiss, Inc.; Thornwood, NY).

Results and Discussion

Optical Microscopy. Optical microscopy was initially used to observe the reactivity of indomethacin with ammonia gas. Three physical forms of indomethacin (a single crystal of the α-form, a single crystal of the γ-form, and a small quantity of the glassy amorphous form) were placed close together on a glass slide (Figure 1). The slide was then placed in a previously dried container (dry nitrogen purge for 1 h) fitted with a gas inlet and outlet. A flow of nitrogen containing a low concentration of ammonia gas was then passed through the container at ambient temperature. Changes in the different forms were closely observed throughout the process. As shown in Figure 1, the glassy amorphous indomethacin shows no visible change after 24 h in the presence of ammonia gas as observed by optical microscopy. From this observation, it was concluded either that the amorphous material does not react, which seems unlikely because amorphous forms are typically more reactive than the crystalline counterparts, or that the reaction product is also amorphous. The α-form single crystal quickly became opaque, indicating that there is a rapid interaction between α-indomethacin and ammonia gas. Furthermore, the change in the α-indomethacin crystal is anisotropic. The opacity starts to develop on the (100) and ($\bar{1}$00) faces (the cleaved ends of the needle) and then spreads along the *a*-axis in both directions. The major faces are thus transparent at the beginning of the process but become opaque as the reaction continues. As seen in Figure 1, the middle of the α-crystal slowly becomes opaque, which most likely is due to the presence of significant lattice defects in that

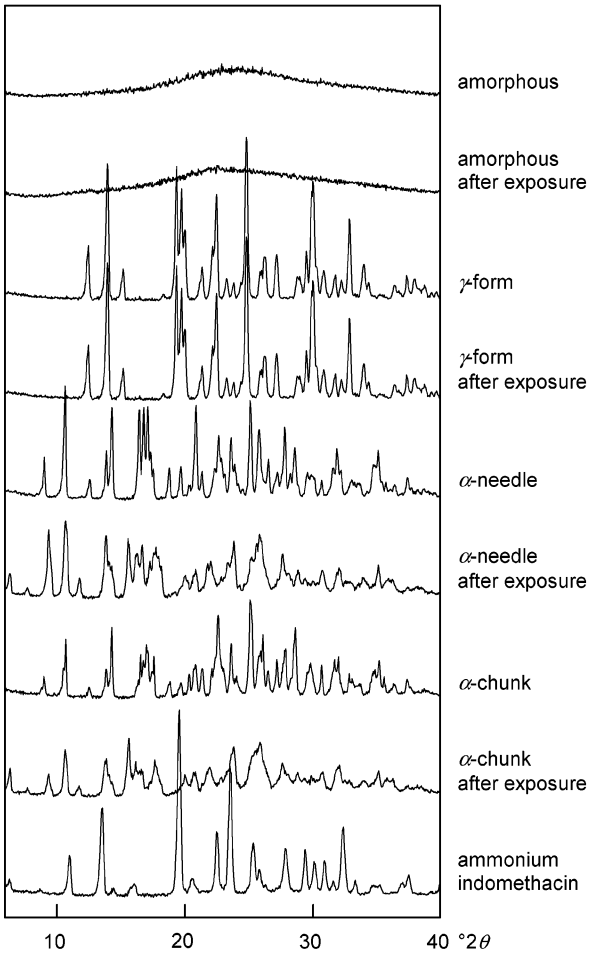


Figure 2. XRPD patterns of different indomethacin modifications before and after exposure to ammonia vapor.

region. The behavior of the α-crystal reported here is very similar to the reactions previously observed between benzoic acid derivatives and ammonia gas in which the reactions produced the corresponding microcrystalline ammonium salt resulting in opaque crystals.[6−11] It is proposed that the development of opacity in α-indomethacin is due to the acid−base reaction with ammonia gas.

While the entire α-form crystal became opaque within 8 min, the γ-form crystal showed no change, even after 24 h (see Figure 1). The γ-form is inert to ammonia gas, even after cleaving (data not shown). Thus, these two polymorphs of indomethacin exhibit extremely different reactivities with ammonia gas. These observations were clarified by further studies, such as gravimetry and an ammonia-specific assay.

Ammonium Assay. A significant weight gain is achieved when indomethacin does react with ammonia gas to form the corresponding ammonium salt. Because the theoretical weight gain is 4.78% if a 1:1 salt is formed, gravimetric evidence was used to assess the reaction. About 100 mg of indomethacin was exposed to ammonia gas for 1 h, and the weight gain was determined. Even though the amorphous indomethacin appeared unchanged by observation with optical microscopy, gravimetric studies determined that samples of glassy amorphous indomethacin increase in weight by 4.60% after reacting with ammonia gas, which is 96.6% of the theoretical weight gain (4.76%). The deviation from 100% of the theoretical weight

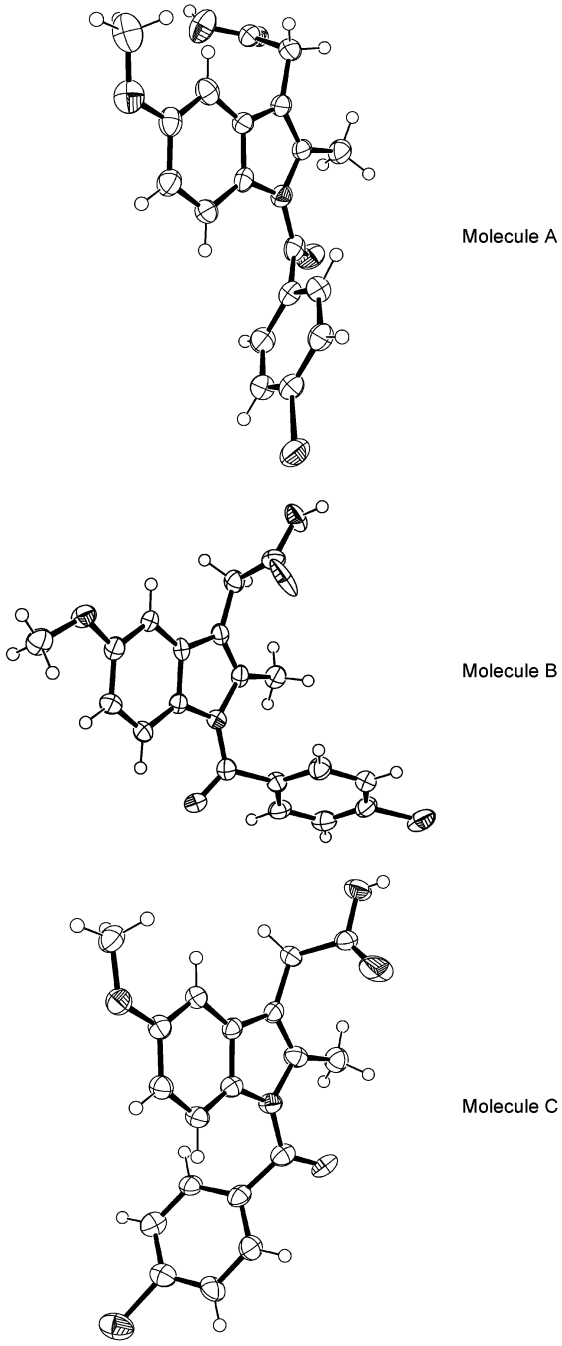


Figure 3. ORTEP[35] representations (50% probability) of the three conformations of indomethacin present in the α-form.

gain was attributed to the rapid metathesis of the ammonium salt to yield ammonia gas and indomethacin. This indicates that the amorphous form reacts stoichiometrically with ammonia gas to form an amorphous product. The claim that the weight gain is from the reaction with ammonia was confirmed by an ammonia-specific assay.

Two separate batches of the α-form were used in subsequent studies. One batch was needlelike with a specific surface area of 1.24 $m^2\ g^{-1}$; the other batch was chunk shaped with a specific surface area of 0.145 $m^2\ g^{-1}$. Despite the fact that the two batches of the α-form have different surface areas and morphologies, they react to about the same extent. The two batches of α-indomethacin picked up significant amounts of ammonia

gas (3.81% for the needles and 3.71% for the chunks) but less than theory (4.76%). One possible explanation of the discrepancy is that the reaction is not complete within the 1 h experiment. The weight gained by the samples after exposure to ammonia gas supports the hypothesis that α-indomethacin reacts with ammonia gas to form the corresponding ammonium salt.

In contrast, the weight gain for the γ-form is close to zero, confirming that the γ-form is inert to ammonia gas. The specific surface area of the γ-form studied is 0.72 $m^2\ g^{-1}$, much larger than the specific surface area of the batch of chunky α-form crystals. Thus, the difference in reactivity between the α- and γ-forms is due to the differences in the crystal structure rather than the surface area of the material studied.

Nessler's reagent[26] was used to quantify the amount of ammonia incorporated in the different forms of indomethacin. Nessler's reagent is an alkaline solution of dipotassium tetraiodomerucrate(II). The reagent reacts with ammonia in aqueous solution to form a reddish-brown colloidal compound with the empirical formula of $NH_2Hg_2I_3$, which can be determined spectrophotometrically with great sensitivity in the visible region of the spectrum (400−425 nm). About 5 mg of test sample is suspended in 10 mL of water in a sealed 10-mL volumetric flask and kept at room temperature overnight before the assay (indomethacin is practically insoluble in water[33]). Any ammonia incorporated in the sample is expected to be released to the aqueous solution to form an ammonium ion. An aliquot of the resulting supernant (25−500 μL) was withdrawn with a micropipet for reaction with Nessler's reagent. Ammonium was not detected by the assay for any of the control samples (indomethacin samples not exposed to ammonia gas). The assay showed that a significant amount of ammonia gas was incorporated in the amorphous form (4.09 ± 0.09%) and the α-form of indomethacin (3.22 ± 0.04% for needle batch; 3.74 ± 0.13% for chunk batch) after exposure to ammonia gas for 1 h at room temperature. The spectrophotometric analysis confirms that the weight gain of the two forms is due to the reaction with ammonia gas. The assayed amount is in reasonable agreement with the value calculated by the gravimetric analysis. The values assayed by the ammonia-specific assay are slightly smaller than the values assayed gravimetrically for the amorphous and α-indomethacin needle batches. This may be due to some degree of degradation of the ammonium salt during sample transfer at atmospheric conditions because the ammonium salt of indomethacin will metathesize back to ammonia and indomethacin upon exposure to ambient conditions or a dry nitrogen purge. Such degradation seems to be dependent on particle size, because the α-chunk batch loses ammonia more slowly than does the α-needle batch. The uptake of ammonia gas by γ-indomethacin is close to zero as determined by the Nessler's reagent (0.060 ± 0.003%). The spectrophotometric assay confirms that γ-indomethacin is inert to ammonia gas, while amorphous and α-indomethacin react with ammonia gas.

X-ray Diffraction. Samples were also analyzed by X-ray powder diffraction (XRPD) after reaction with ammonia gas (see Figure 2). Consistent with the optical microscopy study, the material obtained from the reaction of amorphous indomethacin with ammonia gas is itself amorphous. No difference in the diffractogram was observed for the sample of the γ-form before and after exposure to ammonia gas, confirming that the γ-form is inert to ammonia gas. However, the interaction of α-indomethacin with ammonia gas results in the disappearance of the α-indomethacin diffraction pattern and the appearance of a new diffraction pattern, indicating the formation of a new crystalline phase as established by XRPD analysis (Figure 2). XRPD analysis also confirms that the two different batches of α-indomethacin form the same crystalline product.

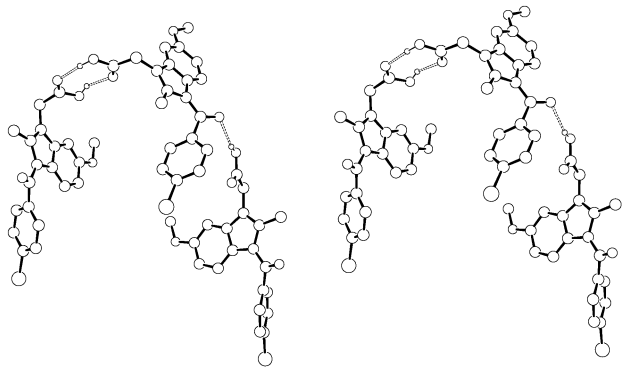


Figure 4. Stereoview of the hydrogen-bonding trimers of indomethacin molecules in the α-form.

Crystal Structure and Chemical Reactivity. The reaction between indomethacin and ammonia gas requires the reactive carboxylic acid group to be accessible to the ammonia gas. It is not surprising that the amorphous indomethacin can react with ammonia gas for it has more molecular mobility and free volume.

Many attempts were undertaken to obtain the crystal structure of the metastable α-form. Repeated crystallization studies from a variety of solvents and conditions always produced the α-form as fine needles or solvated forms. Powder samples of the α-form were submitted for analysis by synchrotron radiation and possible crystal-structure elucidation.[34] The results showed that there are three independent molecules of indomethacin in the asymmetric unit, but it was not possible to determine the crystal structure because of the complexity of the crystal lattice.[23,24] Crystals of size and quality suitable for single-crystal X-ray diffraction studies were eventually obtained from aqueous acetic acid solutions.

Crystals of α-indomethacin are in the noncentrosymmetric monoclinic space group $P2_1$ (No. 4) with $Z = 6$, indicating three molecules in the asymmetric unit, each having a different conformation (Figure 3). The three molecules exist as trimers in which two of the molecules form mutually hydrogen-bonded carboxylic acid dimers and the third molecule forms a hydrogen bond between the carboxylic acid and an amide carbonyl in the dimer (Figure 4).

The elucidation of the crystal structure of the α-form gave confirmatory evidence that this metastable form has a greater density (experimental[36] 1.40 g cm^{-3}; calculated 1.42 g cm^{-3}) as compared to that of the γ-form (experimental[36] 1.38 g cm^{-3}; calculated[23] 1.37 g cm^{-3}; calculated[24] 1.36 g cm^{-3}). Typically, in comparing two polymorphs, the form having a lower density than the other is assumed to be less stable at 0 K. This is known

(33) Hammad, M. A.; Müller, B. W. *Pharmazie* **1998**, *53*, 790.

(34) Stephens, P. W. Private communication; State University of New York, Stony Brook, 1999.

(35) Johnson, C. K. *ORTEP-II*: a FORTRAN thermal-ellipsoid plot program for crystal structure illustrations, report ORNL-5138; Oak Ridge National Laboratory: TN, 1976.

(36) Yoshioka, M.; Hancock, B. C.; Zografi, G. *J. Pharm. Sci.* **1994**, *83*, 1700.

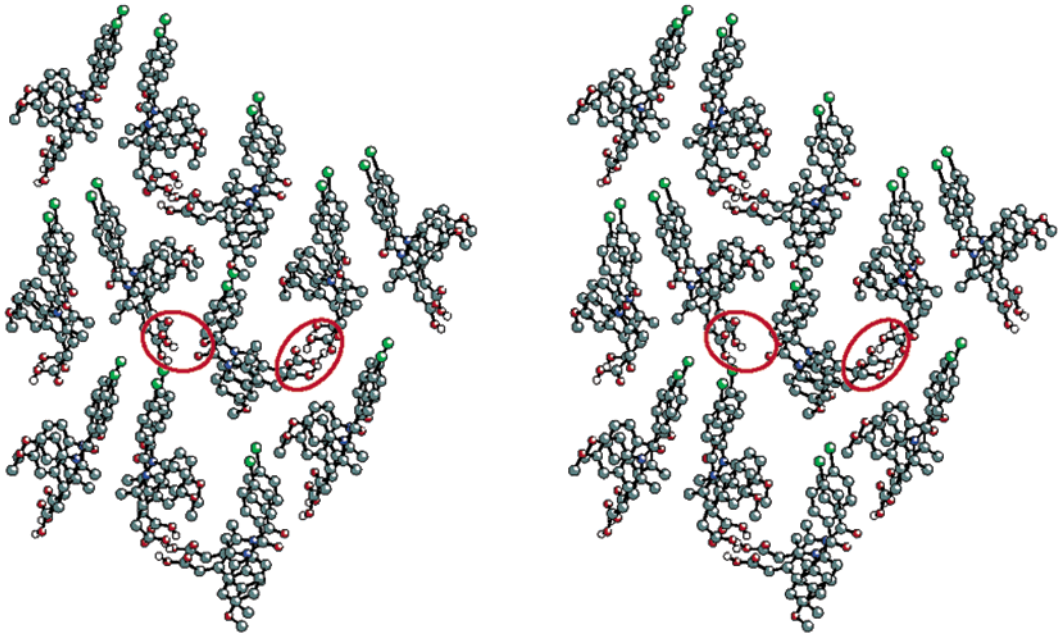


Figure 5. Stereoview of the α-indomethacin crystal packing viewed down the *a*-axis [of the (100) face] showing two layers of the corrugated lattice (non-hydrogen-bonding hydrogens are not shown). The circled areas indicate the freely accessible hydrogen-bonding carboxylic acids.

Table 1. Carboxylic Acid Bond Lengths and Intermolecular Hydrogen-Bonding Distances for the α-Form and γ-Form of Indomethacin

Carboxylic Acid Bond Lengths

molecule	bond	distance (Å)	bond	distance (Å)
α-form, molecule A	C═O	1.204(9)	C−OH	1.308(9)
α-form, molecule B	C═O	1.229(8)	C−OH	1.307(8)
α-form, molecule C	C═O	1.191(8)	C−OH	1.310(8)
γ-form	C═O	1.212(5)	C−OH	1.299(6)

Intermolecular Hydrogen Bonding

molecules	bond	distance (Å)	bond	distance (Å)
α-form, molecules A···B	−O···O═	2.593(9)	−OH···O═	1.946(9)
α-form, molecules B···A	−O···O═	2.704(8)	−OH···O═	1.637(8)
α-form, molecules C···B	−O···O═	2.736(8)	−OH···O═	2.076(8)
γ-form, dimers	−O···O═	2.669(6)	−OH···O═	1.604(6)

Bond Angles

molecules	O–C═O angle (deg)	–OH···O═ angle (deg)
α-form, molecules A···B	123.5(7)	144.2(7)
α-form, molecules B···A	120.5(6)	161.0(6)
α-form, molecules C···B	123.2(6)	153.9(6)
γ-form, dimers	123.1(5)	174.9(5)

as the density rule.[37] In indomethacin, however, the metastable α-form has a greater density than the more stable γ-form. Although exceptions to the density rule are rare,[38] those cases involve strong hydrogen bonding or conformational changes along with hydrogen bonding. Thus, the greater density of the α-form may be related to the additional hydrogen bonding present (between a carboxylic acid hydroxyl group and the carbonyl oxygen of an amide group) and the three conformations that indomethacin adopts in the α-form as compared to the single conformation in the γ-form. The additional conformations of the α-form afford a closer packed crystal and hence a greater density than that possible in the γ-form.

(37) Burger, A.; Ramberger, R. *Mikrochim. Acta* **1979**, *2*, 259.
(38) Burger, A.; Ramberger, R. *Mikrochim. Acta* **1979**, *2*, 273.

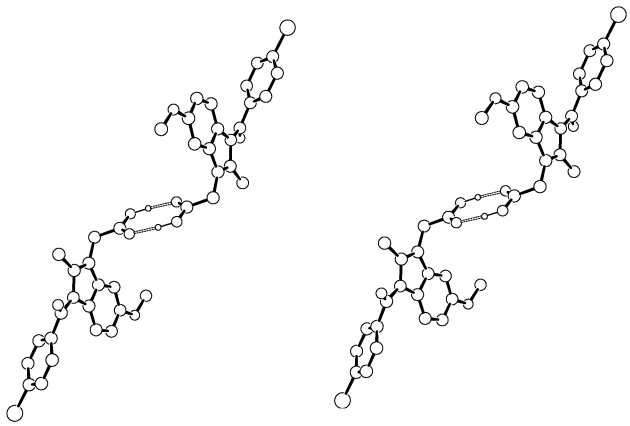


Figure 6. Stereoview of the hydrogen-bonding dimers of indomethacin molecules in the γ-form.

The single crystals of α-indomethacin have a rodlike morphology, consistent with rapid growth along the shortest crystallographic axis, the *a*-axis. The four major faces of the rod were indexed to be the [110] family of faces. The terminal faces of single crystals used in this study were cleaved at the ends of the rods, ostensibly on the (100) and ($\bar{1}$00) faces. The reaction between α-indomethacin and ammonia gas occurs at either end of the cleaved crystal and is anisotropic owing to the crystal packing. The hydrophobic phenyl and indol rings are prevalent on the four peripheral faces, and, thus, the polar carboxylic acid groups are not accessible on the [110] faces of the crystal. To access these reactive groups from the [110] faces requires the diffusion of ammonia gas through the hydrophobic barriers. This inaccessibility is assumed, although some disorder might provide some opportunity as is evident in the reaction of the α-form in the center of the crystal (see Figure 1). Overall, the {110} faces are less affected by the ammonia gas than the (100) and ($\bar{1}$00) faces because the reactive groups are exposed at the two latter faces (see Figure 5). It is proposed that the carboxylic acid group hydrogen bonded to the amide carbonyl

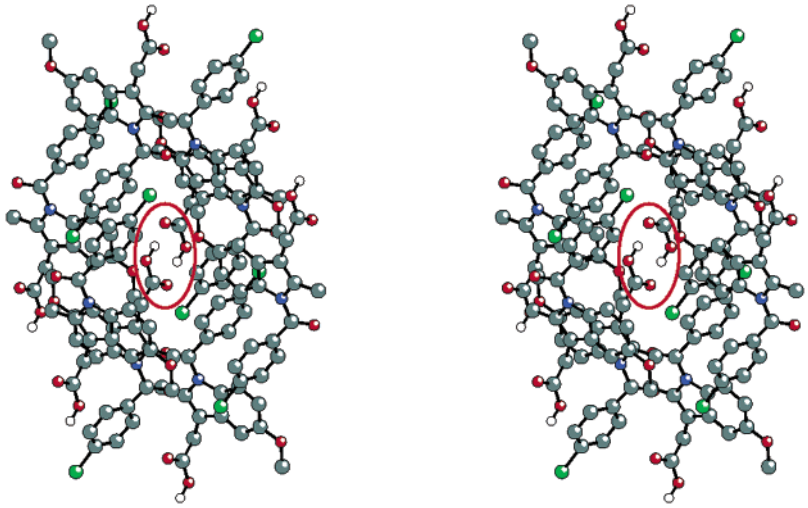


Figure 7. Stereoview of the γ-indomethacin crystal packing around a hydrogen-bonding carboxylic acid dimer (non-hydrogen-bonding hydrogens are not shown). The circled area indicates the inaccessible hydrogen-bonding carboxylic acids.

of an adjacent indomethacin molecule may react more readily because the carboxylic acid groups of the other two molecules in the asymmetric unit form a dimeric pair, with stronger hydrogen bonds. As shown in Table 1, the geometries and covalent bond lengths of the carboxylic acid groups in the γ-form and the three conformations of the α-form are typical of carboxylic acids, and the hydrogen-bonding distances indicate that they are of moderate strength.[39] However, the hydrogen-bond distance ($-$OH$\cdots$O) of the γ-form is shorter than the corresponding distance in the three α-form conformations. Also, the hydrogen-bond angle of the γ-form is much closer to 180° than those in the α-form. Furthermore, the hydrogen bond between the carboxylic acid of molecule C and the amide carbonyl of molecule B in the α-form is the longest in the two modifications, and the hydrogen bond of the A $\rightarrow$ B carboxylic acid dimer is considerably longer than the B $\rightarrow$ A hydrogen bond of the A$-$B dimer and the hydrogen bond of the γ-form dimer. This, coupled with the layering motif, leads to the increased reactivity of the α-form.

The carboxylic dimer subsequently reacts with the ammonia gas once the trimer has been disrupted. The reaction at the first layer in the crystal disorders the crystal lattice allowing ammonia gas to attack the next layer, which is only a few angstroms away. Furthermore, there is no barrier to attenuate the diffusion of ammonia gas between these layers. Thus, the reaction propagates very easily along the *a*-axis, which contains the channels of carboxylic groups. Concomitantly, the corresponding microcrystalline ammonium salt is formed.

As pointed out by the Curtin and Paul group,[6−11] the reaction of ammonia gas with crystalline solids is unlikely to be a simple diffusion process. There is probably not enough free volume for the diffusion of a gas molecule into a crystal lattice except in certain desolvated-solvate lattices. The accessible volume of both forms was calculated in *Cerius*^{2} to be small and confirms the hypothesis that ammonia gas cannot diffuse into the crystal lattice.[40] This also suggests that the reaction initiates at disordered regions or surfaces that expose the reactive groups. Both of these mechanisms provide accessible carboxylic groups to react with the ammonia gas. The progress of the reaction requires easily accessible reacting groups after the initially exposed groups have reacted. This is the case for α-indomethacin. After one layer of α-indomethacin molecules reacts, the reactive groups in the subsequent layer are easily accessible along the *a*-axis. Moreover, poorly accessible reacting groups may account for the extreme stability of γ-indomethacin to ammonia gas.

Crystals of γ-indomethacin are in the centrosymmetric triclinic space group $P\bar{1}$ (No. 2) with $Z = 2$ and consist of mutally hydrogen-bonded carboxylic acid dimers centered at an inversion center (see Figure 6).[23,24] These dimers are caged inside a hydrophobic shield as illustrated in Figure 7. In one direction, the bulky indol and phenyl rings of the molecule protect the dimers. Two indol rings from neighboring unit cells block the second direction. In the third direction, two phenyl rings provide protection. It would be difficult for ammonia gas to penetrate this shield to reach the inner reacting groups. The possibility that some carboxylic groups are situated on the face of the crystal and are thus accessible to ammonia gas cannot be excluded. In addition, disordered regions can be reactive, yet they are limited to a local event. The propagation of the reactions is restricted because every reaction site is sequestered inside the cage described above. As illustrated in Figure 7, either an indol ring or a phenyl ring blocks an ammonia molecule diffusing from one reaction site to the next in all directions. There needs to be substantial molecular loosening to allow the diffusion of ammonia to the next reaction site. Thus, it is proposed that the shielding of the carboxylic groups is a major contributor for the stability of γ-indomethacin. The unique crystal packing of the γ-form provides a consistent explanation of why γ-indomethacin is virtually inert to ammonia gas.

Acknowledgment. This work was supported by the Purdue-Wisconsin Joint Program on Pharmaceutical Solids. We are grateful to Dr. Peter W. Stephens of the State University of New York, Stony Brook, for his work on the crystal structure of the α-form from powder X-ray diffraction synchrotron data; Dr. Phillip E. Fanwick for the solution of the crystal structure

(39) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University: Oxford, U.K., 1997; p 12.
(40) *Cerius*^{2} *Crystal Builder*, Version 4.5; Molecular Simulations, Inc.: Cambridge, U.K., 2001.

of α-indomethacin; and Ann McKenzie for her help in preparing this manuscript.

Supporting Information Available: Crystallographic data for the α-form (submitted to the Cambridge Crystallographic Database). This material is available free of charge via the Internet at http://pubs.acs.org.

JA017662O