Insight to the Thermodynamic Stability of Molecular Crystals through Crystallographic Studies of a Multipolymorph System

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ABSTRACT: Five solvent-free polymorphs of a pharmaceutical compound were discovered during polymorph screening. Out of the five polymorphs, only one has strong intermolecular N–H···N hydrogen bonding, whereas the others exhibit only weak C–H···N and π–π stacking interactions in addition to all the other weak C–H···X and van der Waals interactions. The relative thermodynamic stability relationships among the polymorphs are not intuitive and quite complex due to enantiotropic phase behavior. For instance, the polymorph with the most efficient packing (i.e., highest density) is not always the most thermodynamically stable form, and the polymorph with strong intermolecular interactions is not thermodynamically more stable than the polymorph with weak intermolecular interactions at all temperatures. Nevertheless, systematic examination and comparison of the molecular packing and intermolecular interactions of these polymorphs provide insight into the importance of H-bonding and packing efficiency to the thermodynamic stability of a crystalline form, and how these effects are dependent on temperature. This study seeks to correlate single-crystal structure features with experimentally established thermodynamic stability, and provides an example where a polymorph with only van der Waals forces and weak intermolecular interactions can be more stable than a polymorph that displays strong H-bonding in its structural make-up. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3423–3431, 2014

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INTRODUCTION

Thermodynamic stability is an important property in the development of a crystalline active pharmaceutical ingredient (API). Unexpected polymorphic conversion during API manufacturing, formulation, and storage can jeopardize the robustness of the process and quality of the product, which can ultimately compromise the performance of the drug. These events in late-stage drug development can cause substantial loss in revenue through market disruptions and spending of additional resources to address the issue, including the re-examination of polymorphic phase behavior as well as building additional steps or control strategies to improve process consistency. A prime example of a predicament caused by polymorphic conversion is the case of *ritonavir*, in which a more stable and less soluble form emerged unexpectedly after the launch of the drug, and resulted in a major product recall and a significant formulation and manufacturing overhaul.[1] The risk of missing the thermodynamically most stable form during drug development motivates pharmaceutical companies to place emphasis on the thoroughness of polymorph screening. Although polymorphism does not always have a substantial impact on bioavailability, due to usually insignificant differences in solubility,[2] working with the most stable form at an early stage significantly simplifies the technical transition from pharmaceutical development to manufacturing and eventually to regulatory filing. In addition, thorough characterization of API crystalline forms, phase behavior in thermodynamic space, and the relevance of polymorphism to drug product performance are mandated information in the regulatory filings.[3] In light of these benefits and requirements, the study of API polymorphs and their relative stability is of paramount importance in the pharmaceutical industry.

For organic solids, the common characterization techniques such as IR and Raman spectroscopy, powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and thermogravimetric analysis provide most of the essential information about a bulk solid. However, these analyses do not necessarily provide an in-depth understanding of physical behavior. To learn why a crystalline form exhibits specific physical characteristics (e.g., hygroscopicity, solid-state stability, morphology, density, etc.), we need to look at the basic building block of its crystal structure that gives rise to the intrinsic nature of the crystalline form. By the same token, the relative stability among polymorphs can be unambiguously established in most cases through competitive slurry conversion experiments. However, insight into the characteristics that make one polymorph more stable than another has to come from examination of their respective crystal structures, which offer a wealth of information about intermolecular interactions, bonding preferences, lattice energy, and molecular conformations. In fact, there have been many publications that attempt to qualitatively assess the stability of a crystal form based on crystallographic information, such as the number of molecules per asymmetric unit (Z'),[4] crystal density,[5] packing fraction or efficiency,[6,7] and types of intermolecular interactions.[8,9] Similarly, this

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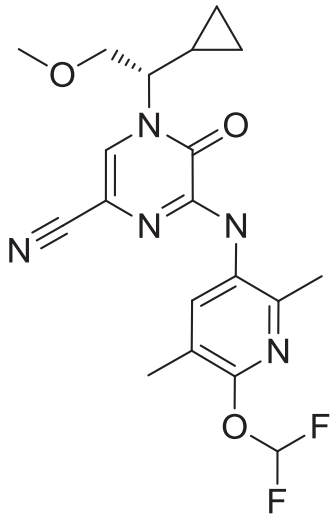

Figure 1. Chemical structure of compound **1** (C19 H21 F2 N5 O3, MW = 405.41).

work applies a qualitative approach to gain an understanding of H-bonding contributions to three-dimensional molecular packing compared with van der Waals forces and/or stacking interactions, and how these differences are translated into thermodynamic stability of a polymorph.

Compound **1** (Fig. 1) was developed as a corticotropin-releasing factor-1 (CRF_1) receptor antagonist for the treatment of depression and anxiety-related disorders.[10] Through polymorph screening, five distinct neat (solvent free) polymorphs of compound **1** (**N1, N2, N3, N4, N5**) were found. This system of five neat polymorphs allows comparative studies of their physical properties with the advantage of no additional components (solvents or counterions) to consider outside of the interactions of the API molecules with each other. The crystal structures of polymorphs **N1** to **N5** reveal how an organic molecule can arrange itself in a variety of packing motifs by varying the intermolecular interactions and/or molecular conformations, which in turn translate to polymorphs of distinct physical characteristics. By examining the differences in molecular packing, H-bonding schemes, π–π stacking interactions, and van der Waals forces, the established thermodynamic relationships among the five polymorphs can be better understood. The observations and ensuing deductions made through this work can contribute to the general understanding of interconversion and relative thermodynamic stability of polymorphic forms.

EXPERIMENTAL

Single-Crystal Growth of the Polymorphic Forms

Compound **1** was obtained from Discovery Chemistry of Bristol-Myers Squibb (Wallingford, CT). Single crystals of **N1** were grown from isopropyl acetate using the vapor diffusion technique with heptane as the anti-solvent. Single crystals of **N2** were prepared by immersing **N1** in 2:1 heptane/isopropyl acetate at 52°C. **N3** and **N4** single crystals were obtained by seeding concentrated solutions of compound **1** in dichloromethane/heptane and ethanol/acetonitrile/water, respectively, with powders of the corresponding solid form. The discovery and crystallization of **N3** and **N4** are detailed in a paper by Hsieh et al.[11] Single crystals of **N5** were grown in absolute ethanol by solvent evaporation at room temperature. The crystal habits of these five polymorphs are listed in Table 1.

Single-Crystal X-ray Diffraction Analysis

Single-crystal X-ray data for **N1**, **N2**, and **N4** were collected at room temperature on Bruker-Nonius Kappa-CCD diffractometer with Mo Kα radiation. Data collection strategy, integration, and scaling for these three data sets were computed and processed using the SuperGUI program suite.[12] Crystal data for **N3** and **N5** were collected at room temperature on Bruker X8-APEX II and APEX II MICROSTAR diffractometers, respectively, with Cu Kα radiation. Data collection strategy, integration, and scaling for **N3** and **N5** were computed and processed using the APEX2 software suite.[13] All five crystal structures were solved by direct methods using SHELXS-97, and refined using SHELXL-97.[14] All nonhydrogen atoms were refined anisotropically, whereas the hydrogen atoms were refined using the riding model with idealized bond lengths and angles. Analysis of the crystal packing, intermolecular interactions, and interatomic distances, as well as graphical representation of these analyses, were carried out and generated using Mercury.[15] The crystallographic data for **N1**, **N2**, **N3**, **N4**, and **N5** are summarized in Table 1.

RESULTS AND DISCUSSION

The thermodynamic stability relationships between the polymorphs were determined through competitive slurrying experiments and further verified by pure component free energy calculations and the eutectic melting depression method.[11] The relative thermodynamic stability ranking at room temperature is found to be **N3** > **N2** > **N5** > **N4** > **N1**, where **N3** is the most stable form and **N1** is the least stable form. Based on crystal densities calculated from the crystal structures (Table 1), the sequence of polymorphs arranged in the order of decreasing crystal density is **N3** > **N5** > **N4** > **N2** ≈ **N1**. Note that **N1** and **N2** have similar crystal densities, which are the lowest among all the polymorphs. Since this system is composed of true, neat polymorphs (i.e., not solvates, salts, or cocrystals), the crystal density relates to intermolecular distances between molecules of compound **1**, which is a function of packing efficiency, and thus also relates to the strength of van der Waals (vdW) interactions, which are inversely proportional to intermolecular distances.[16,17] Hence, for this case, higher crystal density implies greater packing efficiency and stronger vdW interactions. It does appear that the order of crystal density is by and large correlated with the order of relative stability for this system. The only incongruence between these two sequences is **N2**. Removing **N2** from the sequences, the order of decreasing thermodynamic stability now agrees with the order of decreasing crystal density: **N3** > **N5** > **N4** > **N1**. Therefore, with the exception of **N2**, all the other polymorphs are in agreement with Kitaigorodskii's close-packing principle or Burger's density rule, which rationalizes that a thermodynamically more stable polymorph would have a higher density than a less stable polymorph.[18–21]

The exception of **N2** observed in this polymorphic system leads to three questions that we want to answer in this paper: (1) What are the characteristics in the crystal structure of **N2**