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Powder X-ray Diffraction as an Emerging Method to Structurally Characterize Organic Solids

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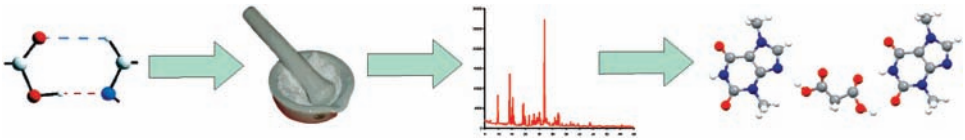
ABSTRACT



The current level of laboratory instrumentation and computational resources allows X-ray powder diffraction to be implemented into the toolbox of organic chemists, providing a means for rapid (i.e., within a day) structural characterization of organic solids, without the need for single crystals. We illustrate such use of powder diffraction using two case studies of molecular cocrystals of trifluoroacetic acid and malonic acid, involving theobromine, a model active pharmaceutical ingredient. We also report on a previously unobserved conformation of malonic acid in the solid state.

Through the past decade, synthetic organic chemists have begun to focus on the synthesis of molecular targets designed for applications in areas such as materials chemistry.[1] In particular, a large number of targets have been molecules conceived as building blocks for the construction of functional organic solid-state materials:[2] semiconductors,[3] molecular inclusion hosts,[4] optical materials,[5] and reactive solids.[6] The interest in such targets has been stimulated by advances in crystal engineering, especially the development of a synthon-based approach to the design of organic solids.[7] The approach is based on the assumption that suitably substituted molecular building blocks will assemble in the solid state in a predictable fashion via such noncovalent forces as hydrogen bonds or $\pi\cdots\pi$ interactions.[8,9] The synthesis of the required building blocks is facilitated by a large toolkit of reactions and methods available to synthetic organic chemists.[10] Modern methods of analysis, most of which are spectroscopic, allow full characterization of the synthesized target at a molecular level in a short time. However, detailed information on the molecular assembly in the solid state, which is the ultimate purpose of the target, is less readily available. Indeed, direct information of the arrangement of molecules in the organic solid state is provided principally by single-crystal X-ray diffraction. Although this method will provide the most complete and

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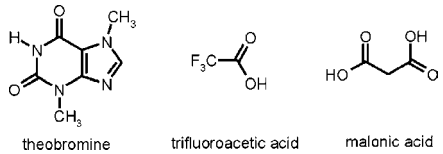
accurate structural information on the molecular and supramolecular structure (i.e., crystal structure), its use is often restricted by the requirement of having single crystals of sufficient size and quality.[11] The result is a paradoxical situation wherein the organic chemist interested in functional materials can readily characterize the product at the level of a single molecule, whereas the objective of exploring the molecular assembly in a solid may not be achieveble. The need for a more efficent method for characterizing solid-state supramolecular architectures becomes even more apparent with the recent growth of interest in multicomponent organic solids, or cocrystals,[12] as modular materials with tunable properties.[13] In less than a decade, cocrystals have found numerous applications as pharmaceutical,[14] electronic,[15] or optical solids[16] as well as media for conducting stereochemically controlled organic synthesis.[17] A number of research groups, including ours,[18] have recently shown that the synthesis of cocrystals from solution can be severely restricted by solubility factors and that mechanochemical routes to cocrystals, specifically neat[19] and liquid-assisted grinding,[20] are much more efficent than solution methods. That mechanochemical synthesis cannot readily provide diffraction-quality single crystals provides an additional impetus to tackle the possibility of obtaining crystal structure information without the need for single crystals.[21] X-ray powder diffraction (XRPD) has long been known as an alternative to single-crystal X-ray diffraction. However, XRPD is usually not considered viable for that purpose, since the amount of data obtained is typically much smaller than in the case of single-crystal diffraction. In addition, XRPD data is usually characterized by a high degree of overlap, making the extraction of structural information difficult and frequently impossible.[22] We demonstrate here that over the last several years developments in laboratory XRPD equipment, as well as computational methods and resources, have reached a level where structure solution from powder diffraction data is possible without specialized equipment (e.g., sample spinning). As a result, we conclude that XRPD can now be rediscovered as a powerful tool of structural characterization for the solid-state organic chemist. Indeed, this opinion is supported by the growing number of structures of organic solids determined annualy using XRPD.[23] To illustrate our argument, we herein discuss supramolecular architectures of two model pharmaceutical cocrystals of a relatively unexplored model active pharmaceutical ingredient (API), theobromine (**tb**), with trifluoroacetic acid (**tfa**) and with malonic acid (**ma**) as the cocrystal formers (Scheme 1). Notably, due to low solubility in common organic solvents, cocrystals of **tb** could not be obtained by any other means except via liquid-assisted grinding. The low solubility is a possible explanation for the low representation of **tb** within the Cambridge Structural Database (CSD), as compared to related xanthines theophylline and caffeine.[24] Cocrystal formers were chosen with the intention of testing the viability of XRPD structure analysis against two solids of different complexity.

Scheme 1. Chemical Diagrams of **tb**, **tfa**, and **ma**



Mechanochemical syntheses were performed using a Retsch MM200 Mixer Mill, equipped with 10 mL stainless steel grinding jars and two 7 mm stainless steel grinding balls per jar. Each grinding experiment was conducted for 20 min with the mill operating at a frequency of 30 Hz. Routine XRPD data was collected on a laboratory Philips X'Pert Pro diffractometer, using Ni-filtered Cu K_α radiation (λ = 1.5418 Å) at 40 kV and 40 mA equipped with an X'Celerator RTMS detector. Each XRPD pattern was collected over a time period of 10 min. Indexing of XRPD patterns and structure solution was performed using the programs DASH[25] and DICVOL04,[26] and the structures were refined using the TOPAS[27] program. Typically, an acceptable solution for each structure was obtained and refined within 1 day.[28]

Cocrystallization of **tb** with **tfa** was conducted by grinding 180 mg of **tb** with 10 drops of **tfa** (approximate volume: 0.30 mL). After the product was dried in air, the formation

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of new material was established by comparing the XRPD patterns of reactant **tb** and the product (Figure 1). The

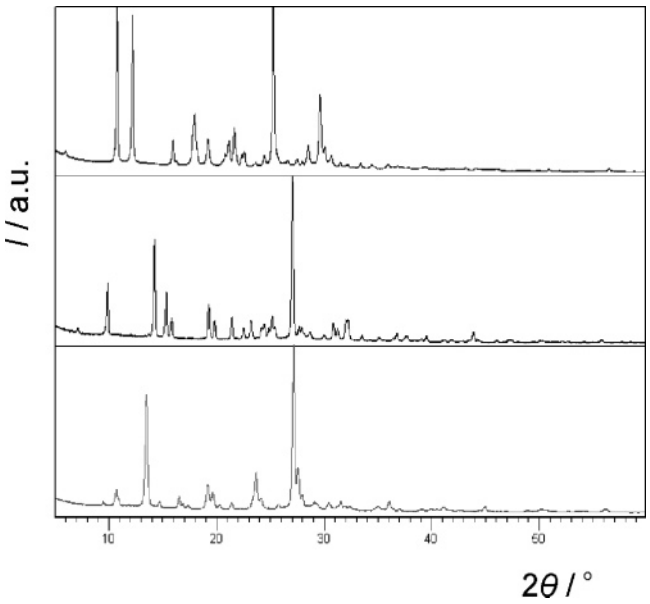

Figure 1. XRPD patterns for cocrystal of **tb** with **tfa** (top); cocrystal of **tb** with **ma** (middle); pure **tb** (bottom).

product was characterized via FT-IR and Raman spectra that were similar to those of **tb**.

Thermogravimetric analysis indicated that the solid contained 38.6% of **tfa**, corresponding to the cocrystal formula (**tb**)·(**tfa**). Crystal structure solution from XRPD data[28] revealed that **tb** and **tfa** assemble into four-membered assemblies of the composition (**tb**)$_2$·(**tfa**)$_2$. The assemblies consist of a central **tb** dimer that is held together by amide−amide synthons and "capped" with **tfa** molecules. The **tfa** molecules are attached to **tb** by way of previously reported imidazole-carboxylic acid synthons that involve an O−H···N hydrogen bond, supported by a C−H···O bond (Figure 2a). The formation of a dimer via an amide−amide synthon is reminescent of the crystal structure of pure **tb**.[29] Interestingly, "capping" of the imidazole nitrogen atoms with **tfa** molecules in (**tb**)$_2$·(**tfa**)$_2$ results in a "slippage" of molecules within the dimer. As a result, the recognition between the **tb** molecules is achieved in a way different from that in pure **tb** (Figure 2b), by forming N−H···O bonds using the **tb** keto oxygen atom adjacent to the methylimidazole ring of each molecule.The packing of the (**tb**)$_2$·(**tfa**)$_2$ units in the solid results in

(27) Bruker AXS, TOPAS v3: General profile and structure analysis software for powder diffraction data. Bruker AXS, Karlsruhe, Germany, 2005.

(28) Crystallographic Data. (a) (**tb**)$_2$·(**tfa**)$_2$: triclinic, space group *P*-1, a = 5.0926(1) Å, b = 8.3354(4) Å, c = 14.8968 (4) Å, α = 90.165(2)° β = 95.587(2)°, γ = 99.728(2)°, χ = 1.585, R_{wp} = 0.0573, R_p = 0.0443, $R_{(Bragg)}$ = 0.0312. (b) (**tb**)·(**ma**): monoclinic, space group $P2_1/c$, a = 12.4425(6) Å, b = 12.9036(6) Å, c = 7.6726(3) Å, β = 91.246(2)°, χ = 1.570, R_{wp} = 0.0749, R_p = 0.0517, $R_{(Bragg)}$ = 0.0287.

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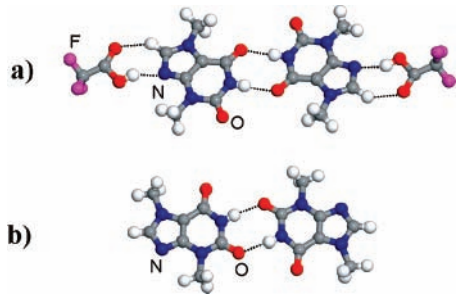

Figure 2. Ball-and-stick representations of (a) the (**tb**)$_2$·(**tfa**)$_2$ dimeric assembly and (b) **tb** dimer in pure solid **tb**.

the segregation of layers containing aromatic **tb** moieties and the CF_3 groups of **tfa** molecules (Figure 3a). This is similar

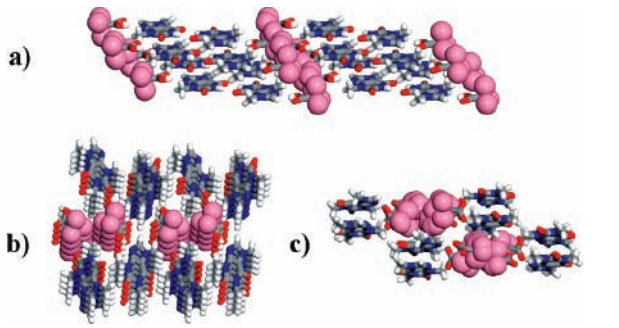

Figure 3. Fragments of crystal structures of (a) (**tb**)$_2$·(**tfa**)$_2$ and (b, c) two polymorphs of the **tfa** and caffeine cocrystal. For clarity, fluorine atoms are shown using the space-filling model.

to the previously reported polymorphs of the cocrystal of caffeine and **tfa**, where CF_3 groups segregate to form columns (Figure 3b,c).

Cocrystals of **tb** and **ma** were prepared by liquid-assisted grinding of the two components in the presence of a small amount of nitromethane. Analysis of the XRPD patterns of products obtained by liquid-assisted grinding of different stoichiometric amounts of reactants indicated the composition of the cocrystal was (**tb**)·(**ma**). The formula was confirmed by crystal structure solution from the powder data.[28] Unlike in (**tb**)$_2$·(**tfa**)$_2$, molecules of **tb** do not form amide−amide dimers. Instead, one of carboxylic acid groups of **ma** participates in a imidazole−carboxylic acid synthon, whereas the second forms an amide−carboxylic acid heterodimer with **tb**. In that way, molecules of **ma** and **tb** link into infinite hydrogen-bonded chains that run through the crystal parallel to the *b* direction (Figure 4). The formation of chains in (**tb**)·(**ma**) contrasts the behavior of related xanthines caffeine and theophylline. Namely, both compounds form cocrystals with **ma** composed of molecular assemblies that contain **ma** and the xanthine derivative in a 1:2 ratio, held together by two imidazole−carboxylic acid synthons. The molecule of **ma** in the cocrystal with **tb** adopts an almost syn conformation,

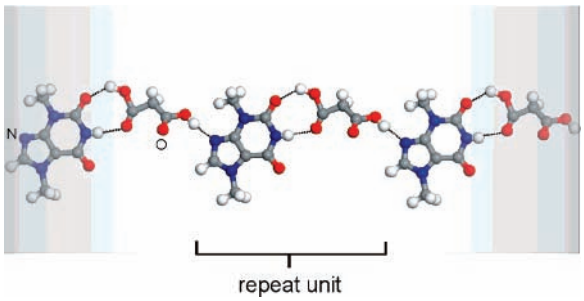

Figure 4. Ball-and-stick representation of a single hydrogen-bonded chain in the structure of (**tb**)·(**ma**).

with the keto oxygen atoms of each carboxylic acid functionality positioned at the same side of the **ma** hydrocarbon backbone (dihedral angle between the two keto groups: 41.1(4)°, Figure 5a,b). This conformation of **ma** is

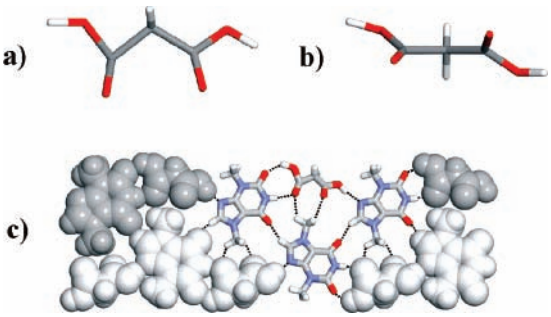

Figure 5. (a, b) Two views of the conformation of **ma** in (**tb**)·(**ma**); (c) two neighboring hydrogen-bonded chains of (**tb**)·(**ma**) with the wireframe model revealing hydrogen bonds within and between the chains.

among the energetically least favored, and its appearance can be rationalized by the C−H···O hydrogen bond.[30] The syn conformation is most likely stabilized by a pair of "chelating" C−H···O bonds to a **tb** methyl group in a neighboring hydrogen-bonded chain. These two chelating bonds between **tb** and **ma**, along with two C−H···O bonds between **tb** molecules, represent a recognition site for **tb** that also connects pairs of hydrogen-bonded chains (Figure 5c).

In summary, we have illustrated how XRPD can be utilized for rapid structural characterization of molecular cocrystals. Notably, both cocrystals have been structurally characterized in less than a day, without the need for single-crystal growth. Structural information obtained using XRPD allowed us to begin exploring molecular recognition properties of a highly insoluble model API, **tb**, as well as to identify the possibility of stabilizing an energetically unfavorable conformation of **ma** through "chelating" C−H···O bonds. We believe that the two case studies presented herein illustrate that XRPD is increasingly closer to becoming a standard structure characterization tool for organic solid-state chemists. Recent structural characterization of a system involving three different chemical species and 24 degrees of freedom suggests that the technique can be used to tackle problems significantly more difficult than the ones presented herein.[31] Indeed, the growing importance of XRPD as a structure determination tool is illustrated by a large number of communications, within the last 5 years, concerned with determining the structures of single-[23,32] and multicomponent[20,21,33] organic solids using XRPD.[33]

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Supporting Information Available: Crystal structure data (CIF); X-ray powder diffraction patterns, TG and DSC analysis curves, FT-IR and Raman spectra of cocrystals and starting materials, and a plot of the number of crystal structures solved from powder data vs time. This material is available free of charge via the Internet at http://pubs.acs.org.

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