$P2_1$ with $Z = 2$. The molecules are stacking along the b axis(Figs.) to construct two types of water channel structures (I and II) in the dihydrate crystal. The hydrogen bond donor/accepter distances suggest that the channel I forms stronger hydrogen bonds than channel II. Therefore, the first dehydration from dihydrate may occur through the channel II to form the monohydrate crystal without major molecular conformation change. Then the water in channel I may be eliminated with rotation of the phenylethyl substituent of Lisinopril molecule.

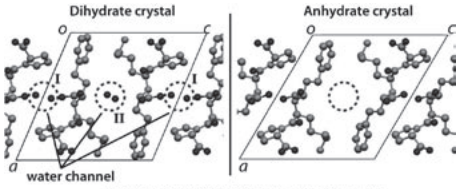

Figure : Crystal structure of Lisinopril

Keywords: powder structure determination, pharmaceutical compounds, crystalline hydrates

MS.80.3

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What do polymorphs teach us about crystal nucleation and growth?

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The ability of a liquid to crystallize as multiple polymorphs is a phenomenon of industrial importance and an opportunity to study crystal nucleation and growth. Using polymorphs to study crystallization follows the tradition of using polymorphs to test principles of thermodynamics and structure-property relations. Part 1 concerns the use of polymorphs to study the nucleation of one crystalline phase on the advancing growth front of another, a phenomenon of interest for controlling crystallization in polymorphic systems. The fastest-nucleating polymorph need not be the product of crystallization, but may nucleate another, faster-growing polymorph. The new polymorph may have higher or lower thermodynamic stability than the initial polymorph. The kinetics of such cross-nucleation were measured and compared with the kinetics of other types of nucleation (primary and growth-front nucleation) in the same liquid. Part 2 concerns the use of polymorphs to study the diffusionless crystal growth that is abruptly activated in certain fragile organic liquids near the glass transition temperature. The phenomenon is important for understanding the stability of amorphous solids. For the ROY system, currently the top system for the number of coexisting polymorphs of solved structures, diffusionless growth exists for some polymorphs but not others, with those showing the growth mode being denser and more isotropically packed.

Keywords: polymorph, crystal growth, nucleation

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Modeling single crystal diffuse scattering on polymorphs of the drug benzocaine

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Understanding and predicting the occurrence of polymorphism is of great importance, particularly for pharmaceuticals. Despite the attention that has been devoted to this problem, progress has been difficult and slow - a fact that may reflect the use of average (Bragg) crystal structures in the development of theoretical approaches. While efforts at crystal structure prediction, including the prediction of polymorphs, have been quite successful for rigid molecules, for conformationally flexible molecules success has been limited [1]. Diffuse X-ray scattering provides information over and above anything that can be learned from conventional crystallography and gives direct information of the local structure of materials and how the atoms and molecules are interacting. The present study is part of a research program in which we are using diffuse scattering methods to probe the local structure and dynamics of molecular systems that exhibit polymorphism, with particular emphasis on pharmaceuticals and molecules with conformational degrees of freedom. We describe a study of the diffuse scattering present in crystals of benzocaine (ethyl 4-aminobenzoate), which is commonly used as a topical local anesthetic. This has two polymorphs: form I is monoclinic $P2_1/c$; form II is orthorhombic $P2_12_12_1$. We have collected three dimensional diffuse X-ray scattering data for the two polymorphs on the 11-ID-B beamline at the Advanced Photon Source (APS). We describe the development of Monte Carlo simulation models used to interpret and analyse these data. Subsequent interrogation of the derived models provides details of the local structure of the two polymorphs and gives insight into the relationship between them.

[1] Day, G. M. et al (2005). Acta Crystallogr. Sect. B, 61(5), 511-8211;527.

Keywords: diffuse scattering, polymorphism, pharmaceuticals

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Computed crystal energy landscapes as an aid to understanding polymorphism

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The fundamental scientific and industrial interest in controlling crystallisation is inspiring the development of methods of predicting which crystal structures are thermodynamically feasible. Frequently, computing this crystal energy landscape will reveal that there are many crystal structures that are approximately equi-energetic compromises between the various intermolecular interactions allowed by the conformational flexibility. Contrasting these crystal energy landscapes with the solid forms found experimentally shows the capacity to rationalise and predict polymorphism, disorder and a propensity for solvate formation. This will be exemplified by molecules such as uracils, carbamazepine, fluoroisatins, chloronitrobenzenes as well as the subjects of “blind tests”.

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