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**Abstract** □ The objective of this work was to investigate a common but poorly understood category of crystalline organic substances: isomorphic desolvates. When solvent is lost from a crystal lattice but the lattice retains its three-dimensional order, a lattice is created which is in a high-energy state relative to the original solvate structure. The desolvated lattice can reduce its internal energy by either resorbing solvent or by relaxation processes which increase the packing efficiency of the solid by reducing the unit cell volume. In the following paper, solid-state properties of isomorphic desolvates of cephalexin, cefaclor, erythromycin A, and spirapril hydrochloride hydrates are investigated. The hygroscopicity of the compounds are evaluated using a vacuum moisture balance, and structural relaxation is measured using a combination of X-ray powder diffraction and isothermal microcalorimetry. The study results are explained in terms of Kitaigorodski's close packing principle.

## Introduction

Hydrates which desolvate yet retain their original crystal lattice are common. The dehydrated structure is extremely hygroscopic when reexposed to elevated humidities. The Latin proverb "natura vacuum abhorret" provides insight into this solid-state behavior. A paper by Pfeiffer et al. characterizes such systems as a "frequently undetected or poorly described property of powder technology".<sup>1</sup> A crystalline form is described therein which is stoichiometrically solvated while in equilibrium with a saturated solution, loses most of its solvent upon drying, but does not convert to a different crystalline form. The term isomorphic desolvate accurately defines a desolvate which retains the structure of its parent solvate form, since it indicates that the desolvated structure retains the three-dimensional order of the original crystal, as defined by space group symmetry and the lattice parameters. Pfeiffer further emphasizes the importance of referring to the parent solvated structure when naming the desolvated structure. The "desolvated acetonitrilate of cephalexin" would be used to designate a form which maintains the structure of the acetonitrile solvate yet no longer possesses the solvent of crystallization.

The relationship of an isomorphic desolvate to its solvated form is readily apparent through similarities in X-ray diffraction patterns. Despite crystallographic similarities, the physical properties of the solvate and desolvate may differ substantially. One difference is the indiscriminate voracity for small molecules to fill void space in the desolvated crystal lattice. In the case of the acetonitrile disolvate of cephalexin, the acetonitrile molecules can be

removed and replaced with a different solvent without altering its crystal lattice substantially from that of its original solvate form.<sup>1</sup> The reduced packing efficiency of the desolvated lattice results in a net decrease in lattice energy; i.e., it becomes less stable, relative to the solvated structure. The thermodynamic driving force, or molecular vacuum, created by desolvation can be relieved through density-increasing processes, either by incorporation of small molecules into the lattice (resolvation) or by structural relaxation (annealing). The formation of isomorphic desolvates can result in an extremely hygroscopic solid or reduced chemical stability.<sup>2-4</sup> The following paper will use the concepts developed by Kitaigorodski et al.<sup>5</sup> to understand the physical properties of isomorphic desolvate crystalline forms of cephalexin monohydrate, cefaclor monohydrate, erythromycin A dihydrate, and spirapril hydrochloride monohydrate. Erythromycin A dihydrate and spirapril hydrochloride monohydrate provide an interesting perspective on isomorphic desolvate systems since their crystallographic structures have been determined.

**Packing Efficiency**—Kitaigorodski developed a theory of crystal packing for organic molecules that states that the lowest energy structure is that which minimizes the void space in the lattice and maximizes the number of close contacts with neighboring molecules.<sup>5</sup> Calculations of packing coefficients, as in eq 1, make the assumption that molecular volume does not change from one crystal form to another. Gavezzotti has demonstrated that this is a reasonable assumption through his analysis of organic molecular structures.<sup>6,7</sup> By statistical analysis of 204 polymorphic pairs, he showed a linear correlation of unit slope between the difference in densities of polymorphic pairs and difference in packing coefficients for polymorphic pairs. The density rule is used as an indicator of the relative stability of crystalline polymorphic forms.<sup>5,8</sup> The rule states that the modification which has the lowest density will be the least stable one at absolute zero. The theory is often applied to polymorphic forms at room temperature; the polymorphic form having the closest packing, highest density at a given temperature is considered to have the lowest overall free energy at that temperature. Exceptions to the rule can occur due to neglect of consideration of the entropic contribution to the free energy of polymorphs<sup>8</sup> or when strong hydrogen bonds are present in the less densely packed structure.<sup>9</sup> The density rule still remains one of the common criteria for assessing relative stabilities of polymorphic systems.

When chemical composition changes, as in the case of comparing a solvate to its isomorphic desolvate form, density comparisons are inappropriate. Packing coefficients provide a convenient means for comparing structures of different composition. In an effort to understand the thermodynamic instability imparted on the crystal lattice due to reduced packing efficiency of isomorphic desolvates, one may turn to Kitaigorodski's packing coefficient, as in eq 1.

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