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Solid Solution Hardening of Molecular Crystals: Tautomeric Polymorphs of Omeprazole

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Supporting Information

ABSTRACT: In the context of processing of molecular solids, especially pharmaceuticals, hardness is an important property that often determines the manufacturing steps employed. Through nanoindentation studies on a series of omeprazole polymorphs, in which the proportions of the 5- and 6-methoxy tautomers vary systematically, we demonstrate that solid-solution strengthening can be effectively employed to engineer the hardness of organic solids. High hardness can be attained by increasing lattice resistance to shear sliding of molecular layers during plastic deformation.

As crystal engineering[1] shifts its emphasis from structure design to property design, there is increased interest in modulation of properties across a series of related solid compounds. Mechanical properties of molecular materials constitute an important subset.[2] While such properties have always been technologically relevant, especially in the context of pharmaceutical manufacturing processes,[3] quantitative scientific studies have gathered momentum only recently. This is due, in large part, to the demonstrated utility of nanoindentation with which it is possible to probe the mechanical behavior of small organic crystals.[4] The ultimate aim of all these studies is to be able to systematically design organic solids with a desired combination of mechanical properties. Through a recent study of nine compounds in a single structural family, we have identified common features that are essential for obtaining highly flexible (or elastic) crystals.[5] The focus of the present study is to demonstrate experimentally how one can obtain molecular crystals that are resistant to plastic deformation, which can be quantified with relative ease through hardness, *H*, measurements.

The importance of *H* of molecular solids used in the pharmaceutical industry can be understood through the following observations.[3d] If a material is too soft, it is impossible to mill as it will become pasty. On the other hand, if it is too hard, tabletability gets adversely affected. Accordingly, a material with an optimal hardness is always sought.[6] Is it possible to vary *H* in a systematic fashion? If yes, what structural factors will allow for such control over *H*? In trying to answer such questions, it is instructive to examine the metallurgical principles with which *H* of a crystalline metal can be enhanced. This is, of course, a topic that has attracted attention over millennia, and processes have been obtained that are both routinely and remarkably successful. In all these cases, the underlying principle used is the engineering of the microstructure such that the dislocation mobility in the crystal lattice is reduced.[7] While this can be met in a number of ways for metals, solid-solution strengthening[7a] is perhaps the only way that is available to engineer molecular solids with high *H*. Through a nanoindentation study on a series of omeprazole polymorphs, which may be likened to solid solutions, we demonstrate here a crystal engineering design principle that the hardness of molecular solids can be enhanced by increasing the lattice resistance to shear sliding of the molecular layers during plastic deformation.

Omeprazole, 5(6)-methoxy-2-{(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl}-1*H*-benzimidazole, is a block buster antiulcer drug. In its crystalline forms, both the 5- and 6-methoxy tautomers are observed (see Figure 1) and these have also been seen in solution.[8] To date, many patents have been filed on methods of preparation, crystallization, and characterization of the solid forms of the drug using PXRD, single crystal XRD, and Raman analysis. Three solid forms namely, A, B, and C, have been patented through their PXRD traces, but the observations and results in these patents do not correlate well with one another. It is not clear if the differentiating aspect among these polymorphs is structure or properties.

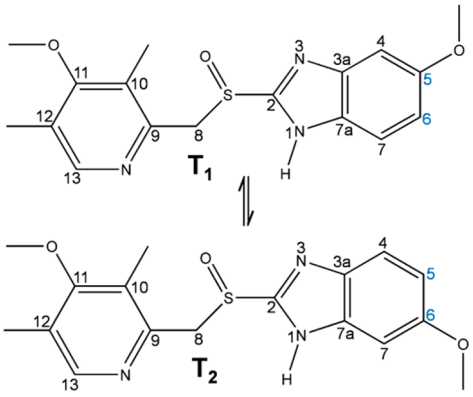

Figure 1. Tautomeric forms of omeprazole.

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In 2007, Bhatt and Desiraju reported that the five different solid forms of omeprazole have varying proportions of the 5-methoxy (T_1) and 6-methoxy (T_2) tautomers (Figure 1).[9] Form I is the pure 6-methoxy tautomer, while the T_1:T_2 ratios in the other forms are as follows: form II, 8:92; form III, 10:90; form IV, 12:88; and form V, 15:85. All these forms take the triclinic space group $P\bar{1}$ with one molecule in the asymmetric unit and are essentially isomorphous. The methoxy group may be situated either at the 5- or 6- position of the benzimidazole ring without changing the mutual disposition of the molecules. In effect, the crystals forms I–V can be viewed as substitutional solid solutions of tautomer T_1 in T_2. The different crystal structures of the omeprazole forms are modulations at the molecular level, as the forms contain two tautomers in different amounts within the same crystal packing. Since the forms contain different amounts of tautomeric structures, they can be classified as tautomeric polymorphs.[10] We repeated the work of Bhatt and Desiraju and found that the T_1:T_2 ratios of the omeprazole tautomers that they obtained are reproducible. However, other ratios between 0% and 15% T_1 were not obtained by us, despite several crystallization attempts under different pH conditions.

The crystal structure of all the forms of omeprazole contains centrosymmetric N–H···O=S dimers (Figure 2). Except for

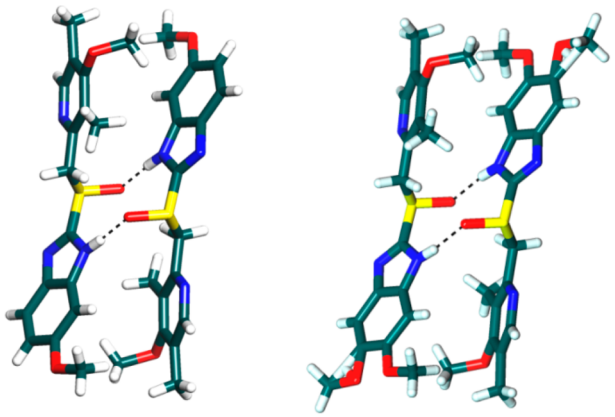

Figure 2. All five forms of omeprazole contain centrosymmetric N–H···O=S dimers. Note the positioning of the 5- and 6-methoxy groups on the benzimidazole ring.

the N–H···O hydrogen bonds, there are no other strong interactions in the structure. There is a weak intermolecular C–H···O dimer between the methylene hydrogen atoms of one molecule and the sulfoxide oxygen of another molecule. In form I (pure T_2) the 6-methoxy group of a reference molecule close packs with the phenyl methoxy group of the centrosymmetrically related molecule. In forms II–V, which contain both T_1 and T_2 tautomers, the 5-methoxy group is on the distant side of the phenyl methoxy group of the centrosymmetric molecule.

Large well-shaped single crystals ($1 \times 1 \times 0.3$ mm^3) of all five forms of omeprazole were obtained using the procedures reported by Bhatt and Desiraju.[9] In all the cases, the major face is {001}, on which nanoindentation experiments were carried out (see SI for experimental details). Representative load, P, vs depth of penetration, h, curves are displayed in Figure 3; these show that the residual depth of penetration upon complete unloading, h_r, is in descending order going from form I to V. This observation implies that the resistance to plastic flow is the

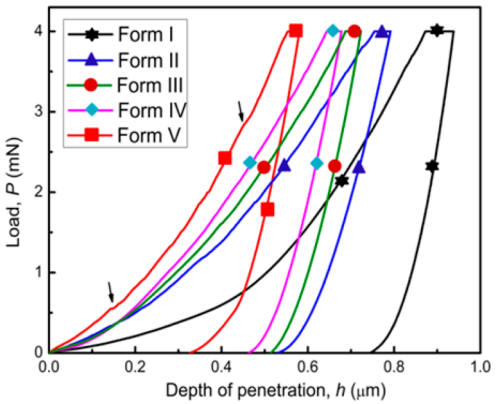

Figure 3. Representative P–h curves of the five forms of omeprazole.

least in form I and the highest in form V of omeprazole. Indeed, the average values of H extracted from the measured P–h responses, listed in Table 1, show that the hardness of form V is

Table 1. Average Values of Elastic Modulus (E) and Hardness (H) of Omeprazole Forms Obtained Using Nanoindentation

form	tautomer proportion, T_1:T_2	elastic modulus, E (GPa)	hardness, H (MPa)
I	0:100	12.02 ± 0.35	432 ± 2
II	8:92	12.14 ± 0.37	596 ± 2
III	10:90	12.20 ± 0.2	680 ± 1
IV	12:88	12.38 ± 0.3	725 ± 3
V	15:85	13.32 ± 0.41	855 ± 3

nearly twice that of form I. In contrast, the average values of elastic modulus, E, increase, but only marginally with E of form V being higher than that of form I by ~10%.

The mechanical properties E and H of a material reflect its respective resistance to elastic and plastic deformation. For organic crystals, E depends on the structural packing efficiency, the type and number of intermolecular interactions present in the crystal, and their orientation with respect to the loading (or indentation) direction.[4d,e] Since these features are similar in all five polymorphs examined in this work, it is not surprising that there is no significant variation in E among them. In contrast to E, H of an organic crystal depends strongly on the relative ease with which molecular layers can irreversibly slide past each other. Such slip typically occurs on specific slip systems, which are combinations of crystallographic planes with directions referred to as slip plane {hkl} and slip direction [$h'k'l'$] respectively.[4d] In general, slip planes are the ones with the least attachment energy, E_{att}, whereas the slip directions are those along which the lattice translation is the shortest.[11] For all omeprazole forms examined here, the slip system is {011}⟨111⟩. Further, the crystal packing in all of them is similar to a layered structure and the {011} planes are oriented with respect to the indentation direction at a similar angle. However, the dimer of the 5-methoxy tautomer (T_1) in forms II–V is present between the molecular layers on the slip plane, as schematically illustrated in Figure 4. As a result of these dimers, the shear stress on the slip planes that is required to overcome the lattice friction increases. As the percentage of the 5-methoxy group increases from forms II through V, one can expect the friction between molecules also to increase, and this in turn should enhance H. Indeed, a linear correlation between

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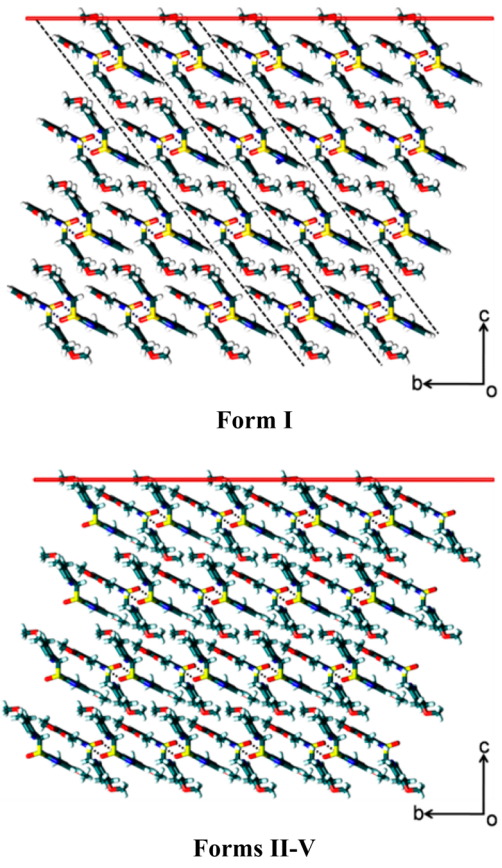

Figure 4. Molecular packing of omeprazole forms. Red lines represent the plane on which indentation is made (the major face, {001}), and black dotted lines (in form I) represent slip planes.

H and the percentage of T_1 in the polymorph, displayed in Figure 5, confirms our hypothesis.[12,13] Further support for this

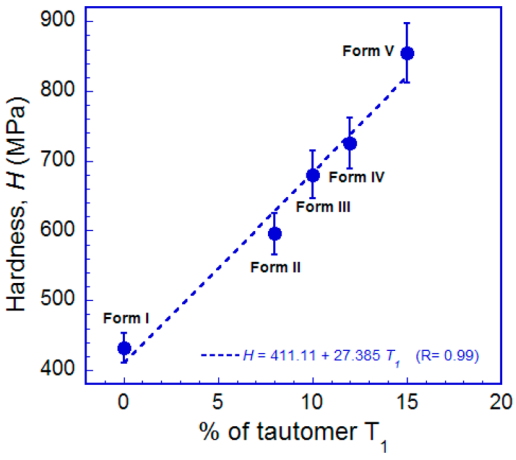

Figure 5. Correlation between hardness, *H*, and proportion of the 5-methoxy tautomer, T_1, in omeprazole polymorphs.

can be obtained through a closer examination of the *P*–*h* responses shown in Figure 3. For forms I through IV, the curves are smooth. This is because sliding of the molecular layers on the slip plane can occur easily, albeit with increasing resistance as one goes from form I to IV. In form V, however, the lattice friction is perhaps so high that smooth and continuous sliding is not possible. Instead, the sliding occurs in a jerky manner, resulting in the observation of discrete displacement bursts (or "pop-ins") on the *P*–*h* curves. Interestingly, the magnitude of the pop-ins ($h_{pop\text{-}in}$) in form V were found to be either ~10 nm or integer multiples thereof (d_{001} is 0.96 nm). This confirms the collective sliding of multiple {001} planes during indentation results in the pop-ins.

A schematic depiction of the mechanism for hardening is given in Figure 6. The dimer of the 6-methoxy tautomer (T_2) in

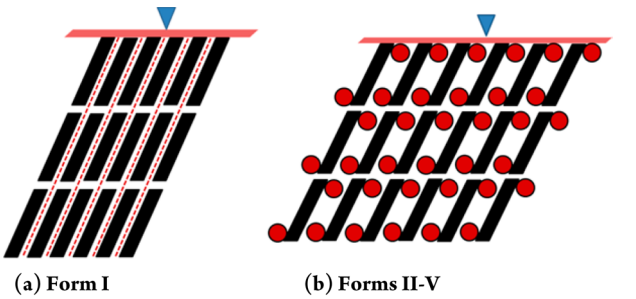

Figure 6. Schematic diagram of the crystal packing of omeprazole form I (a) and forms II–V (b). The dimers are represented as solid parallelograms. The indentation direction is shown as a solid triangle. Red dotted lines represent slip planes in form I. Methoxy groups are shown as red circles in forms II–V.

form I is represented as a parallelogram in Figure 6a. Under the indenter load, the layered structure of form I slides easily resulting in low *H*. On the other hand, the dimer of the 5-methoxy tautomer (T_1) in forms II–V is represented in Figure 6b with the red circles representing the 5-methoxy group of the benzimidazole ring. The crystal packing of forms II–V is similar to that of form I, i.e. a layered structure, but the 5-methoxy group is present between the molecular layers, providing a higher friction for shear sliding, which in turn results in higher *H* values compared to form I. As the percentage of the 5-methoxy group increases from forms II through V, the friction between molecules also increases. Consequently, the *H* value also varies with the percentage of T_1 in the polymorph.

In summary, our results show that the hardness of a molecular crystal can be systematically varied as a function of chemical composition and structural variation. We show here that hardness is a function of increasing resistance to movement of the slip planes in the omeprazole crystal. Engineering the shear resistance of slip planes in a molecular crystal is a strategy to control the hardness of the material and inter alia its solubility as these properties are correlated.[3d] Thus, we may expect that the solubility of the omeprazole polymorphs would decrease systematically on going from form I to form V. We are currently exploring extensions of this crystal engineering strategy through formation of solid solutions of plastic solids between compounds that are substitutionally distinct, for example using the phenyl-thienyl exchange.[14]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, supplementary figures and tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) It is of interest to ask if the elastic response of a material is of importance in tabletability. Generally, elasticity is not so significant in this regard, as long as the material is not compliant. This is indeed the case for most APIs, which have E values in the GPa range. The omeprazole polymorphs also have similar E values, and elastic strains in them during tableting are too low to cause concern.

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(12) It is interesting to note that the hardness scales linearly with the solute (minor tautomer) concentration, whereas in metallic alloys typically it varies as the square root of the concentration.

(13) Nanoindentation on the other facets of these crystals was not meaningful or possible, because (and respectively) these minor faces vary from polymorph to polymorph, and their sizes are too small to perform valid nanoindentation tests. However, the fact that nanoindentation was done only on the major facet is not a limiting factor in this study. The overall molecular packing features in the five polymorphs are very similar. Therefore, it is reasonable to expect that the anisotropies in hardness, if one were able to measure them, would also be similar in the other directions. In other words, the major facet may be considered to be representative of the crystal itself.

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