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Nanoindentation in Crystal Engineering: Quantifying Mechanical Properties of Molecular Crystals

Sunil Varughese, M. S. R. N. Kiran, Upadrasta Ramamurty, and Gautam R. Desiraju**

crystal engineering · crystallography · elastic modulus · materials science · polymorphism

***N**anoindentation is a technique for measuring the elastic modulus and hardness of small amounts of materials. This method, which has been used extensively for characterizing metallic and inorganic solids, is now being applied to organic and metal–organic crystals, and has also become relevant to the subject of crystal engineering, which is concerned with the design of molecular solids with desired properties and functions. Through nanoindentation it is possible to correlate molecular-level properties such as crystal packing, interaction characteristics, and the inherent anisotropy with micro/macroscopic events such as desolvation, domain coexistence, layer migration, polymorphism, and solid-state reactivity. Recent developments and exciting opportunities in this area are highlighted in this Minireview.*

1. Introduction

The mechanical behavior of molecular solids differs from extended solids because they are stabilized by weak interactions—hydrogen bonds and van der Waals interactions—and also because of their characteristic structural anisotropy. Despite the influence that mechanical properties have on industrial-scale production and handling, their evaluation in organic materials is not common.[1] Nanoindentation[2] has recently emerged as an effective tool with which the mechanical properties of molecular crystals can be examined and assessed. The purpose of this Minireview is to highlight the utility of this technique to crystal engineering—the designed synthesis of functional molecular solids.[3,4]

The mechanical behavior of a crystalline solid depends not only on the type of bonds present and the internal structure, but also on any lattice defects that may be present. In particular, the types and distribution of defects exert a significant influence on the plastic deformation and fracture characteristics of crystals and crystal aggregates. Williams and Thomas, in 1967, examined the effects of lattice imperfections on the mechanical behavior of crystalline anthracene and sucrose.[5,6] Later, Hawthorne and Sherwood examined the role played by defects in the self-diffusion and plastic deformation of pivalic acid, hexamethylethane, and cyclohexane.[7] Kitaigorodskii pioneered the correlation of elastic tensors with crystal structure,[8] while Brown and Hollingsworth examined stress-induced domain reorientation in urea inclusion compounds.[9] As a consequence of the low symmetry of molecular crystals, their mechanical responses can be quite anisotropic, and this makes nanoindentation measurements difficult and their interpretation more complex compared to similar studies on inorganic crystals. The elastic constants of different faces of crystals are generally estimated through in silico modeling studies. The elastic modulus and thermal expansion, being tensorial properties, provide a basis against which one can evaluate and optimize models in terms of derivatives of the calculated energy, rather than single-point calculations.

The hardness H is the resistance offered by the indented material to plastic deformation. Qualitative approaches such as bending and shearing have been utilized to assess the plastic deformation and fracture behavior of single crystals. Crystal anisotropy leads to distinct variations of the plastic deformation within the same structural class. Therefore, deformation processes in molecular materials cannot be described in simple terms: each material has to be assessed independently, and predictions based on broad generalizations are unlikely to be successful.

[*] Dr. S. Varughese, Prof. G. R. Desiraju
Solid State and Structural Chemistry Unit
Indian Institute of Science
Bangalore 560 012 (India)
E-mail: desiraju@sscu.iisc.ernet.in
Dr. M. S. R. N. Kiran, Prof. U. Ramamurty
Department of Materials Engineering
Indian Institute of Science
Bangalore 560 012 (India)
E-mail: ramu@materials.iisc.ernet.in

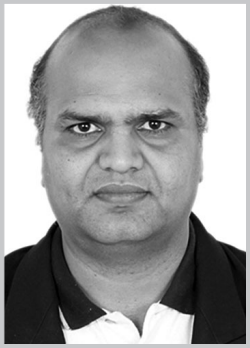
As a result of these lacunae and the lack of a proper instrumentation technique, the field was largely ignored for many years. The advent of nanoindentation made it possible to obtain quantitative and precise experimental information on the mechanical behavior of small-volume materials.[10,11] In the context of crystal engineering, mechanical characterization provides a way to monitor the relative strengths of intermolecular interactions. Since interactions with distinct energy profiles will lead to different elasticity moduli, studies on mechanical properties provide direct inferences on the nature of the interactions themselves. This, in turn, enables one to alter structural parameters, such as types and strengths of interactions and packing events, by modifying the molecular units or by adopting cocrystallization strategies.

1.1. Why Are the Mechanical Properties of Molecular Crystals Important?

Before discussing the mechanical behavior of organic crystals, the motivation for such studies needs to be highlighted. Although organic materials are generally not intended for any load-bearing applications, many processing events in industry involve mechanical operations. Therefore, understanding the mechanical performance of molecular crystals in the context of crystal packing, slip, and defects is not only of scientific significance but also of practical importance. This is especially true for pharmaceuticals,[12–15] because they are often brittle. Fragmentation facilitates consolidation, but compacts containing brittle materials may cap or laminate easily, thereby leading to serious problems in subsequent processing steps. The tableting property of any given crystalline powder is to a large extent a function of the ability of the crystal to undergo plastic deformation. Plasticity results in an increase in the interparticulate contact area and this in turn promotes binding. In contrast, brittle crystals that do not flow but fracture readily may produce cracks within the tablet upon decompression. Below are some examples of the important role played by the mechanical properties in organic materials:

- Soft crystals such as voriconazole become pastelike upon grinding, which make them difficult to mill.[16] Hard crystals such as sildenafil citrate are easier to handle (Table 1).[17]
- 4-Hydroxybenzoic acid anhydrate and monohydrate exhibit distinct compaction properties. The water that is present in the monohydrate facilitates plastic deformation; it makes tablets with better strength and with a larger volume reduction than the anhydrate. The zigzag molecular layers in both forms allow for mechanical interlocking and this reduces the plasticity. However, water molecules present in the monohydrate assume a space-filling role and increase the layer separation, thus facilitating slip between layers.[18]
- The identification of polymorphs with better tableting properties (for example, crystal forms with easy to activate slip systems such as polymorph I of the antibacterial agent sulfamerazine) can make subsequent processing events economically viable.[19]
- The two forms of chlorpromazine hydrochloride have different affinities towards water. Tablets of polymorph II take up water easily and convert into the dihydrate during storage, and consequently develop cracks. Tablets of polymorph I, being inert to water/moisture, do not crack under similar conditions.[20]
- Stress-induced phase transformations are highly undesirable for pharmaceutical ingredients during milling or tableting because such transformations can have serious

Sunil Varughese obtained his PhD in 2007 from the National Chemical Laboratory Pune. After postdoctoral studies (2007–2009) at Trinity College Dublin, he joined the Indian Institute of Science as a DST Young Scientist. His research focuses on the crystal engineering of functional solids and structure–property correlations in molecular crystals.



Upadrasta Ramamurty is interested in the mechanical behavior of materials. His current areas of focus are the mechanics and mechanisms of flow and fracture in amorphous, shape-memory, and a variety of advanced engineering alloys and their composites. He uses the indentation technique as a tool for these studies.

M. S. R. N. Kiran received his PhD in 2009 from the University of Hyderabad, after which he joined the Indian Institute of Science as a postdoctoral fellow. His research interests includes thin films and the mechanical behavior of small-volume materials.

Gautam R. Desiraju joined the Indian Institute of Science in 2009. Prior to this he was at the University of Hyderabad for 30 years. He is currently the President of the International Union of Crystallography. He has been closely associated with the subject of crystal engineering and the structural aspects of weak hydrogen bonds for many years, and has played a major role in the development and growth of these subjects.

implications on the drug's stability and efficacy. Sucrose and γ-indomethacin undergo solid-state amorphism during milling.[21] Mechanical milling of sulfathiazole induces a partial transformation from form III to form I.[22,23]

- With crystals of energetic (explosive) compounds, such as RDX and HMX, determination of the deformation and cracking responses of crystals under various types of mechanical loading is essential for identifying conditions that can potentially lead to chemical decomposition and explosion.[24]
- The poor ability of caffeine and methyl gallate to individually form tablets, is in contrast to the excellent ability of the 1:1 cocrystal with a layered structure.[25]

2. Basic Principles and Definitions

2.1. Elastic and Plastic Deformation

When a solid is stressed it undergoes elastic deformation followed by plasticity unless fracture intervenes. The elastic modulus of a material (E) is a measure of the resistance to elastic deformation so that the solid returns to its original shape once the applied stress is removed. E is a function of the energy of interactions between molecules and their distances of separation. Figure 1a shows a typical Lennard–Jones potential energy curve. If an applied stress displaces molecules in a crystal from their equilibrium positions, intermolecular forces tend to restore them on removal of the applied stress (Figure 2). The restoring force is proportional to the gradient of this energy–separation curve. At equilibrium spacing, E is approximately proportional to the slope of the force versus intermolecular separation curve (Figure 1b). Thus, materials can be classified either as stiff or flexible depending on the slope of the curve at the equilibrium separation distance ($r = r_o$): steep for stiff materials and shallow for flexible materials. As the strength of the bond decreases, the energy minima will become flatter. E is determined from the second derivative of the force–distance curve at the energy minimum. This quantity is high for inorganic materials, moderate for metal–organic hybrids, and low for molecular crystals: this follows directly from the different types of interactions involved.

In contrast to elastic deformation, plasticity in crystals is generally achieved through irreversible glide (or slip), twinning, and kinking motions of molecular layers (Figure 2). Slip occurs along specific crystallographic planes, which are often referred to as slip planes. A slip system consists of a given slip plane (hkl) together with the associated slip direction $< h'k'l' >$. The attachment energy data, cleavage planes, and hydrogen-bond patterns provide inferences on possible slip planes. The attachment energy is the energy released per mole when a new layer is added to each face. The face with the least attachment energy represents the slowest growing face (the major habit face of the crystal) and generally coincides with the primary slip plane of the crystal.[26] Hydrogen-bonding patterns can have a major influence in directing molecular slip. The slip in layered compounds (such as adipic acid) takes place between networks of hydrogen bonds, while in compounds with an intricate network of interactions (such as sucrose) slip involves a breaking of the weakest hydrogen bonds (Figure 3).[27] In molecular crystals, short-range non-directional interactions (such as van der Waals interactions) are likely to influence the inelastic response (plasticity) as they will have a large bearing on how bonds break, whereas directional interactions (such as hydrogen bonds), being

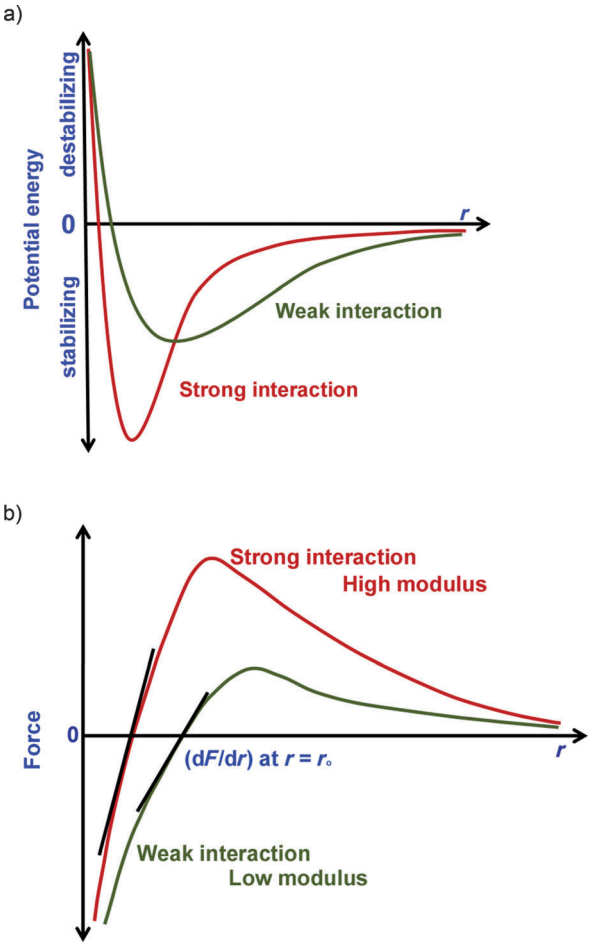


Figure 1. a) Potential energy curves for a strong and a weak interaction. b) Force–distance curve depicting the relation between interactions and E.

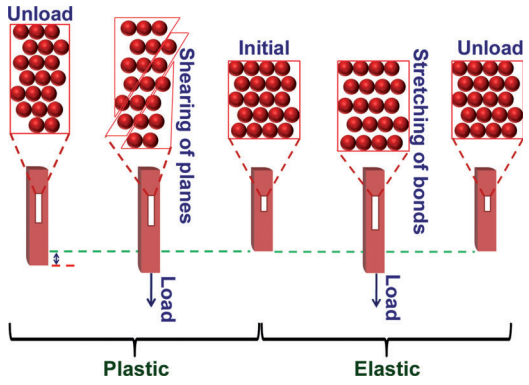


Figure 2. Plastic and elastic deformation in crystalline materials.

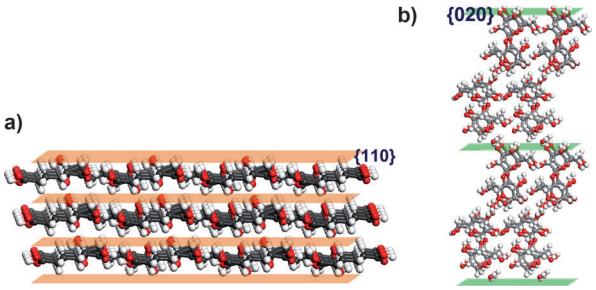


Figure 3. Primary slip planes in a) adipic acid and b) sucrose.

effective at long separations, influence elasticity because of their restorative character.

2.1. Fracture

Fracture is the stress-induced separation of an object into two or more pieces. Fracture in materials can be broadly classified as ductile or brittle. In ductile fracture, extensive plastic deformation occurs prior to fracture. Conversely, brittle fracture is preceded by little or no plastic deformation (Figure 4). Thus, most brittle crystals break when the

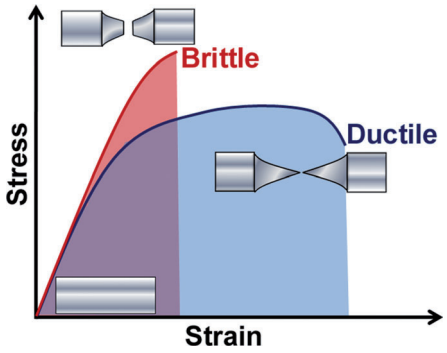


Figure 4. Schematic stress–strain curves for brittle and ductile materials.

deformation is well within the elastic region and prior to plastic deformation. Fracture toughness K_{IC} is a quantitative measure of the resistance of a material to cracking. A material is considered brittle if it has a low fracture toughness. For example, window glass and ceramics fall into this category. Understanding the fracture behavior of crystals is important when developing optimal strategies for process development and formulation.

In molecular crystals, fracture takes place either through cleavage at certain crystallographic planes (brittle crystals) or when the shear stress reaches a level where dislocation pile-up attains a critical density (ductile or plastic crystals). The standard test for estimating the fracture resistance of a material is to conduct a tensile test on precracked specimens, but this is generally inapplicable for organic crystals as it requires relatively large specimens, which is not always possible. The indentation technique, because of the simplicity and expediency of the experiments, is an attractive alternative for assessing fracture toughness. Moreover, it is possible to characterize both the local and bulk fracture properties of materials with this technique. When molecular crystals are indented by using a sharp-tipped indenter, fracture is usually observed when the indenter axis is normal to the slip plane. The fracture toughness of the indentation is estimated on the basis of the length of the cracks.

The brittleness index of a material (H/K_{IC}; Table 1) gives a relative measure of the resistance to fracture. An excellent correlation between H/K_{IC} and milling data suggests that this index can be used to distinguish between materials that are easy, moderate, and difficult to mill.[28] This in turn, allows for the selection of appropriate milling conditions with a minimum amount of material.

Table 1: Fracture toughness and brittleness parameters of various crystalline materials.

Material	Fracture toughness (K_{IC}) [MPa m$^{1/2}$]	Brittleness index (BI) [10^3 m$^{-1/2}$]	Nature of material
adipic acid	0.02	6.3	brittle[35]
aspirin	0.004	49.0	brittle[80]
paracetamol	0.05	8.3	brittle[35]
saccharin	0.02	3.0	brittle[56]
sildenafil citrate	0.05	27.8	brittle[28]
sucrose	0.08	8.3	brittle[35]
voriconazole	not measurable	<1	soft[28]
ice	0.12	2.8	brittle[35]
NaCl	0.50	0.4	brittle[35]
iron	50	0.1	ductile[35]

3. Mechanical Properties of Molecular Crystals

3.1. Qualitative Studies

Molecular crystals with unusual and deformed morphologies have been known to crystallographers over the years, and several qualitative studies on the mechanism of deformation in molecular crystals have been attempted. Desiraju and co-workers established a causative correlation between bending and the crystal structure in 60 or so specimens with 4 and 8 Å axes. Both of these structure types are layered (parallel and antiparallel stacking of planar molecules) and have pronounced interaction anisotropy. A model for bending was proposed using the information obtained from X-ray diffraction (XRD), face indexing, and mechanical property measurements conducted with a needle and forceps (Figure 5).[29,30] Accordingly, molecular crystals were classified as being of bending, shearing, and brittle types. The first two types are observed when the packing is anisotropic so that strong and weak interaction patterns occur in nearly perpendicular directions.[31] The interactions in such molecular crystals, is neither uniform nor similar in various directions, and thus mechanical deformation in an arbitrary manner is not possible. In contrast, there are crystals such as naphtha-

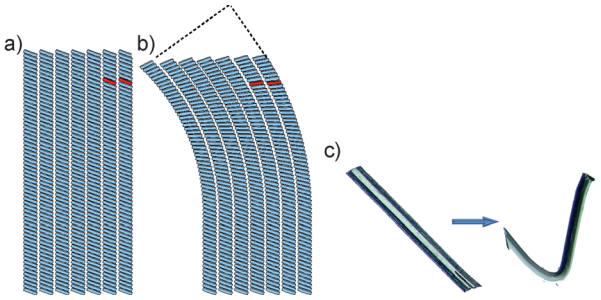


Figure 5. A model for bending in molecular crystals. a) Undeformed crystal. b) Bent crystal.[30] Note the relative movement of the disk highlighted in red and the marked deformation in the interfacial angles. c) Plastic bending in pyrazine-2-carboxamide (α form).[30] Note the variation in the interfacial angles of the crystal. Reproduced with permission from Royal Society of Chemistry.

lene, benzoic acid, and D-glucose where the nature of the intermolecular interactions is nearly the same in many directions, or the materials are highly cross-linked through interactions such as hydrogen bonds. Such crystals break rather than bend when subjected to mechanical stress.[30] However, metals, which are isotropic (in terms of their bonding characteristics) and are not cross-linked, typically display excellent ductility.[32] Molecular crystals show practically no change in volume and the lengths of the inner and the outer arcs as well as the sample thickness are unchanged when bent permanently. Constancy in volume and the arc lengths of the crystal are maintained by an adjustment of the interfacial angles at the crystal ends (Figure 5c).

3.2. Quantitative Studies

Quantitative characterization of the mechanical properties of molecular crystals (or compacted powders) has been performed by using three- or four-point bending (single edged notched beam test), double torsion, and radial-edge cracked configurations. More recently, instrumental indentation methods have gained popularity. In this approach, the load applied P and the corresponding depth of penetration of the indenter h are continuously monitored. The resulting P–h curves are analyzed to obtain H and E of the indented material.[33] When P and h are in the mN and μm ranges, the technique is termed microindentation, and when they are in the μN and nm ranges, it is referred to as nanoindentation.

Microindentation has been employed to assess the mechanical behavior of molecular crystals.[34] Duncan-Hewitt and Weatherly studied the H, H/E ratio, and indentation fracture toughness of crystals of pharmaceutically relevant compounds, and classified them into materials which fragment extensively and those that behave in an essentially ductile manner during compaction.[35,36] The brittleness of acetaminophen crystals, inferred from microindentation, was attributed to the limited slip systems in them.[37] Grant and coworkers utilized indentation to study the effect of counterions on the mechanical properties of L-lysine salts and also to correlate the chain lengths and mechanical properties in a homologous series of benzoate esters.[38–40]

Despite the aforementioned insights gained through microindentation, this method is not commonly used for molecular crystals because it often leads to fracture. Furthermore, the microindentation fracture mechanics approach for the assessment of K_{Ic} is semiempirical.[41] Another limitation of microindentation is that specially grown large crystals are often required to accommodate indentation even at minimum loads. In addition, the preparation time is problematic and the defect densities in such crystals may not reflect those in bulk manufactured crystals; thus they may have different mechanical properties.[42,43] Extremely small loads are, therefore, mandatory for measuring the elastic properties of molecular crystals because they either fracture readily or are very soft. Nanoindentation is, therefore, better suited to study such crystals.[44]

During a typical nanoindentation by a spherical tip on a molecular crystal, an elastic-to-plastic transition[45,46] is usually observed as a displacement burst or pop-in on the P–h curve. Note that even nominally sharp tips such as Vickers, Berkovich, or cube-corner types tend to have a finite radius (of the order of a few tens of nm for a fresh tip to 100–200 nm for a tip that has been used extensively).[47] In a load-controlled test, the pop-in event is a result of the sudden penetration of the indenter tip at a constant load. Pop-ins are rarely observed in crystalline metals because of the availability of a large number of slip systems and because of the general presence of dislocations. When they do appear (for example, in well-annealed single crystals) they are attributed to homogeneous or heterogeneous nucleation of dislocation loops under the indenter tip.[48] Plasticity tends to be heterogeneous in low-symmetry molecular crystals, because of the fewer number of slip systems, thus making occurrences of pop-ins more common. In this case, indentation can also cause the nucleation of dislocations, thereby resulting in serrated P–h curves (Figure 6).[49,50]

Ramos and Bahr examined the elastic and plastic properties of sucrose and RDX as representative examples of brittle crystals and found that the H value of sucrose crystals is relatively independent of the contact orientation.[51,52] However, their focus was on obtaining H and E values, and correlating them to the underlying structure of the crystals was not attempted. The nanoindentation technique was used by us in several studies, where we have taken the initial steps towards correlating the mechanical properties of molecular crystals with crystal packing. Aspects such as interaction anisotropy, desolvation, long-range molecular/layer migration, and polymorphism were examined. Some general examples selected from our research are detailed in the next section.

3.2.1. Anisotropic Properties

An organic crystal is a periodic array of molecules held together by interactions that are much weaker than intramolecular covalent bonds, and with a trade-off between attractions and repulsions.[53–55] Molecules are arranged optimally such that there is the most efficient utilization of space to attain close packing.[8] In three-dimensionally close-packed structures the intermolecular interactions in the three princi-

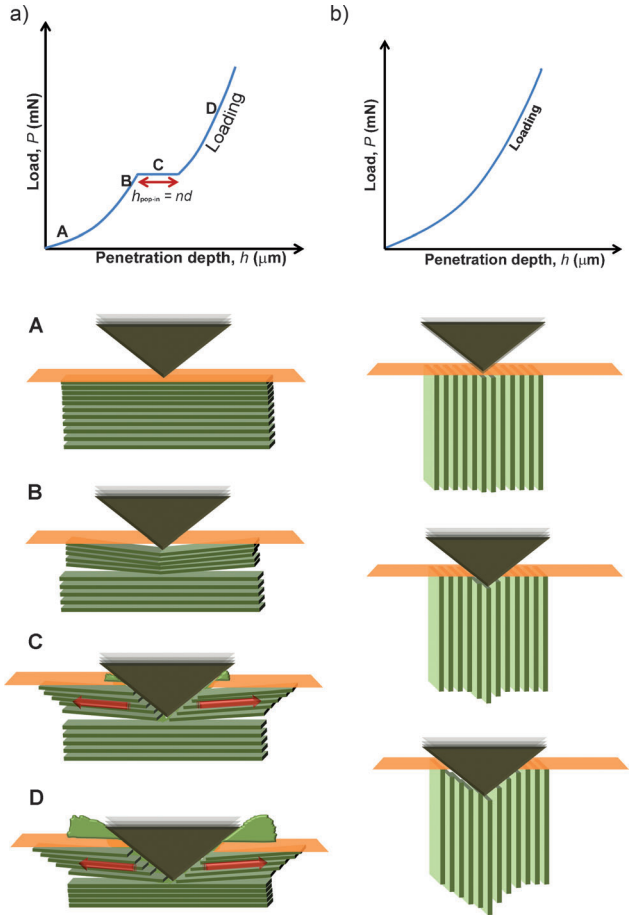


Figure 6. Schematic representation of a) the possible mechanism of pop-in and pile-up in molecular crystals. b) Indenting along the slip direction yields a smooth *P*–*h* curve.

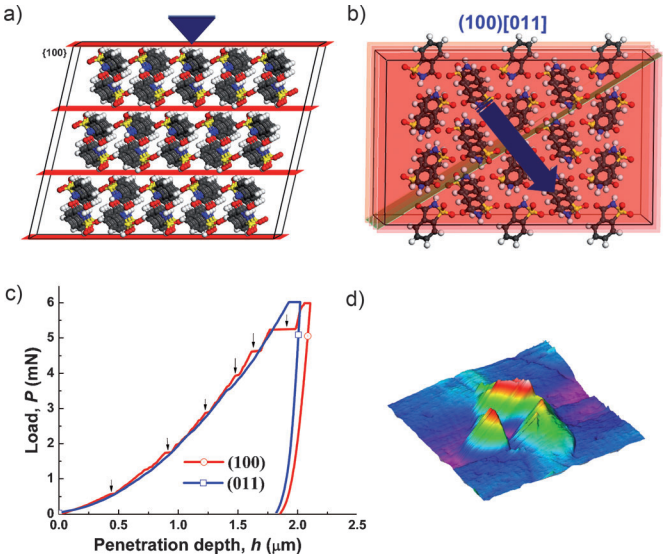


Figure 7. Saccharin. a) Active slip planes. The blue triangle represents the indentation direction. b) Representation of the slip system. c) Representative *P*–*h* curves. d) Anisotropic pile-up on (100).

pal directions are often equivalent, thereby making such crystals brittle.[30] Saccharin (free acid) is a typical example. The observed mechanical behavior upon nanoindentation was analyzed in terms of the crystal packing and nature of the relevant intermolecular interactions.[56] The use of saccharin as an acid co-former in the pharmaceutical industry makes the study relevant.[57,58] Crystals of saccharin have major faces of (100) and (011). The molecules make centrosymmetric NH···O dimers, which stack down [100] and make an oblique angle to (100). Within a stack, the molecules are stabilized through van der Waals (π···π) interactions, while CH···O hydrogen bonds bind adjacent stacks. The molecular stacks are arranged as bilayers with a dimension of 0.9 nm with respect to (100); only weak interactions persist between bilayers (Figure 7a). In (011), stacked dimers make a criss-cross arrangement and CH···O hydrogen bonds exist normal to the plane. Thus, there is a significant overlap between interactions along both directions, although the vector of two adjacent dimers is effectively the indentation direction on (011).

The measured *P*–*h* responses suggest a major difference in the possible mechanism of plastic deformation for (100) and (011). The loading part of the *P*–*h* curve obtained on (011) is smooth, while several distinct displacement bursts (pop-ins) are observed in the *P*–*h* curve corresponding to (100) (Figure 7c). Indenting (100), results in the stacked columns becoming compressed through weak π···π interactions. The nondirectional nature of the interactions allows the layers to rearrange themselves so as to release some of the stored elastic strain energy. The extended compression disrupts the CH···O hydrogen bonds, thus forcing the columns to break away.

The structural information taken together with the calculated attachment energies indicates a possible slip system that is energetically favorable. The attachment energy and interplanar *d* spacing for (100) and (011) are $-15.9\ kJ\,mol^{-1}$, 9.2 Å and $-27.8\ kJ\,mol^{-1}$, 5.9 Å, respectively. Thus, the expected slip system in the saccharin crystal is (100)[011] (Figure 7b). The breaking of the molecular stack results in a sudden penetration of the indenter deeper into the sample; this is reflected by a pop-in. The discrete displacements associated with the pop-ins are multiples of 18 nm; this is an integral multiple of 0.9 nm, the distance between the bilayers. This observation corroborates the proposed mechanism.

For [011], the indentation is along the vector of adjacent dimers. The stacked dimers run down this face and hence provide multiple gliding paths for unhindered movement of the layers, thereby making the plastic deformation homogeneous in nature. The criss-crossing of saccharin dimers results in an overlapping of interactions with different energies and directionality. This reduces the anisotropy of *E* with respect to the different crystallographic orientations. The close-packed structure together with the marginal anisotropy of *E* is the reason for the brittleness of saccharin crystals. As a consequence of the pyramidal geometry of the indenter tip, the quantity and shape of the profiles of the material pile-up strongly depend on the crystallographic orientation, thus providing information on the anisotropy within a single face.

3.2.2. Long-Range Molecular/Layer Migration

Although classical topochemistry envisages minimum atomic or molecular movement within crystalline solids,[59,60] several phenomena such as solid-state reactivity, cocrystal formation, and defect transport can be explained in terms of molecular migration.[61–64] In 1968, Rastogi and Singh explained the solid-state reactivity of picric acid with substituted hydrocarbons on the basis of diffusion controlled by surface migration.[65] In 2005, Kaupp and Naimi-Jamal proposed long-range molecular migrations as the reason for the nearly 100% yields achieved in many solid-state topochemically governed reactions.[66] Kaupp used nanoindentation and scratch experiments to demonstrate that three-dimensionally interlocked packing, as seen in 2-benzylidenecyclopentanone or *cis*-1,2-dibenzoylethene, prohibits molecular migration.[67] Conversely, long-range migration is detected in compounds such as anthracene, ninhydrin, tetraphenylethene, thiohydantoin, and thiourea that have cleavage planes, or in other words anisotropic molecular packing.[68] The observed molecular movement is a function of the orientation of the layer arrangement and the direction of the tip movement.

We have studied the layer migration in two charge-transfer complexes of 1,2,4,5-tetracyanobenzene (TCNB) with pyrene and phenanthrene.[69] 1:1 TCNB–pyrene has a layered arrangement with (100) and (002) constituting the major faces of the crystals. The mean plane of the layers is approximately parallel to (100), while they are 68° skew to (002) (Figure 8a). The molecules within an individual layer are stabilized through CH···N bonds; the interlayer region (π···π) is nonspecific and, hence, will allow unhindered layer migration. The large anisotropy in the interaction characteristics and layer arrangement results in a significant difference of H (16%) and E (21%). Indenting on (002) results in the molecular layers and the half angle of the indenter tip becoming closely aligned, which enables the layers to slide over the edge of the indenter tip. The molecules in other orientations get compressed because of the slant arrangement of the layers; this appears as material pile-up along one of the indenter faces (Figure 8b).

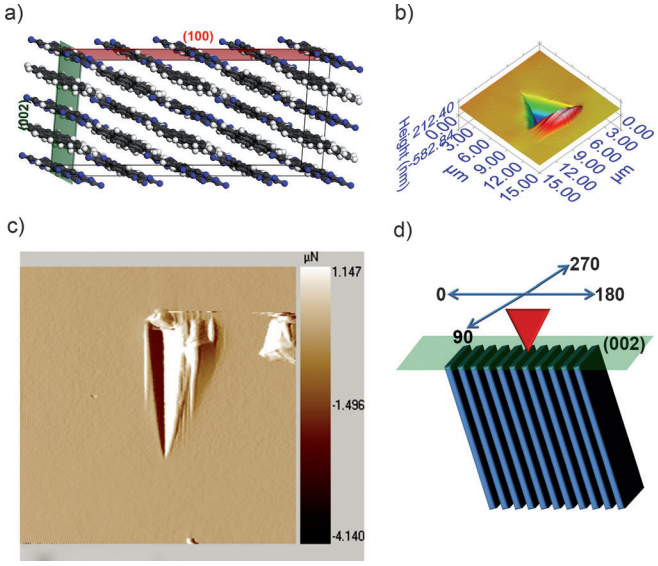


Figure 8. TCNB–pyrene complex. a) Crystal packing. b) Residual indent impression on (002). c) AFM scan image showing layer migration upon nanoscratching. Image scan size: 25 µm. d) Schematic representation of the indenter movement and layer arrangement. Reproduced with permission from Wiley-VCH.

As the structure is layered, the intra- and interlayer interactions are quite distinct and, therefore, the crystal can be cleaved along the layers. Scratch experiments on (002) together with the scratch profile analyses and the measured coefficients of friction reveal distinct molecular migration events in various orientations (Figure 8d). Scratching along the skew direction of the layers results in molecular migration becoming visible on both sides as well as a small material pile-up at the end of the scratch. However, in the opposite direction, the tip traverses against the skew direction and so experiences larger friction which results in a significant pile-up of material on both sides as well as at the end of the scratch. In the orthogonal directions, the tip moves along the cleavage plane; the skew nature of the layers results in material pile-up either on the right-hand side or left-hand side, depending on the direction of the tip movement (Figure 8c).

Unlike the TCNB–pyrene complex, the 1:1 TCNB–phenanthrene complex does not have a layer arrangement; instead, trimer units consisting of a TCNB and two phenanthrene molecules result in a staggered arrangement. The crystals consist of two major faces: (001) and (020). The trimers stack down [001], with CH···N hydrogen bonds connecting adjacent stacks. The molecular stacks are approximately parallel to (001) and perpendicular to (020). As a consequence of this staggered arrangement, the CH···N hydrogen bonds are inclined at an angle to the molecular layer, and together with the π···π interactions contribute to the stabilization of the stack (Figure 9a). Nanoscratch experiments yield entirely different results because of the difference in the molecular arrangement, the orientation of the molecular stacks, and the nature of the interactions in the intermolecular region.

When scratched along the cleavage plane, AFM scan images provide evidence of a limited layer movement. As a consequence of the presence of hydrogen bonds in the interlayer region, the indenter tip experiences a higher friction coefficient than does the pyrene complex, even in the cleavage direction. The tip traverses the cleavage plane in the orthogonal directions (Figure 9b). As a result of the vertical layer arrangement, the tip experiences friction and material pile-up at the end of the scratch (Figure 9c). The friction coefficient observed in the orthogonal directions demonstrates several uneven events; the distance between two consecutive troughs (210, 260 and 340 nm) are closely related to multiples of $d_{(020)}$ (6.517 Å, Figure 9d). The study illustrates that molecular features such as layer movement and interaction characteristics as well as the anisotropy in them can be examined in detail through nanoscratch experiments.

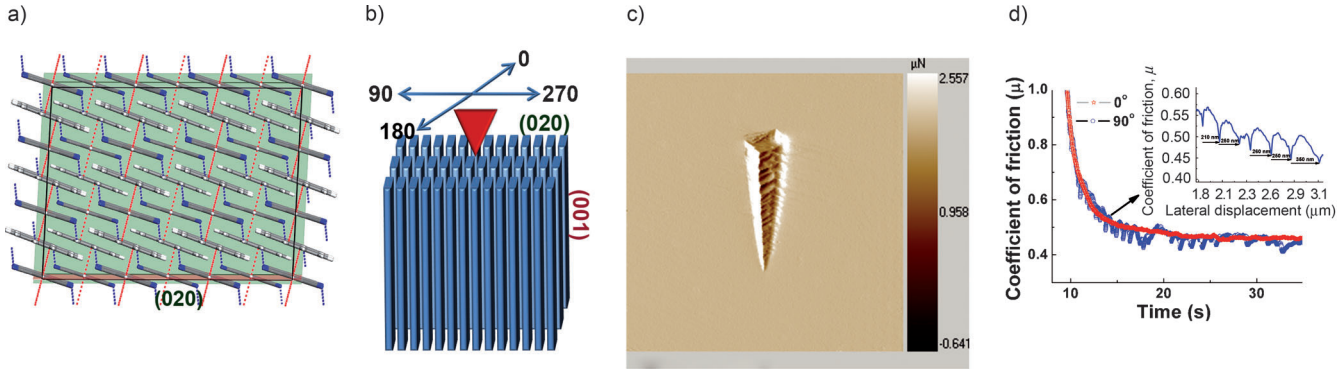


Figure 9. TCNB–phenanthrene complex. a) Crystal packing. b) Schematic representation of the indenter movement and layer arrangement. c) AFM image showing layer resistance towards indenter movement. Image scan size: 25 μm. d) The coefficient of friction at 0° and 90°. The inset shows the analysis of the distance between the two consecutive troughs, where the friction coefficient falls sharply. Reproduced with permission from Wiley-VCH.

3.2.3. Polymorphism, Phase Stability, Crystal Homogeneity

Polymorphism in molecular crystals is a well-studied phenomenon.[70] Its practical importance arises from the fact that different crystalline phases of the same compound can exhibit distinct properties.[71,72] This has particular implications in the pharmaceutical industry where polymorphism must be rigorously monitored at all stages of the production process because of chemical, regulatory, and legal issues. Since polymorphs usually have different molecular arrangements, conformations, and interactions, they can vary in their mechanical properties, which affect their ability to form tablets.[19,73] Thus, quantitative mechanical evaluation of polymorphs is of fundamental and practical importance.

In addition to its chemical and pharmaceutical importance, aspirin is important in crystal engineering because of its fascinating structural chemistry. Although the possible occurrence of aspirin polymorphs has been debated since the 1960s,[74] the topic remained dormant for many years. The prediction of a new form by Ouvrard and Price[75] in 2004 resulted in renewed interest in the polymorphism of aspirin. Vishweshwar et al. reported single-crystal XRD data which indicates the existence of the second form in some samples.[76] Bond et al. analyzed the Bragg reflections and explained that such aspirin crystals exist as intergrowths containing domains of the two structure types.[77,78] This was further corroborated by crystallographic investigations based on diffuse X-ray scattering.[79] We employed nanoindentation to examine the mechanical properties of the two aspirin polymorphs with regard to the differences in their macroscopic properties and to rationalize this on the basis of interactions.[80]

Polymorph I of aspirin exists as well-formed crystals, with (100) and (001) as major faces. The crystals of polymorph II are small; (100) and (102) constitute the major faces. In both I and II, the carboxy groups form centrosymmetric OH···O dimers and the dimers are arranged as two-dimensional layers parallel to (100). Although the structures of the two polymorphs are closely related, a clear difference exists in the intermolecular interactions across the expected slip planes, specifically in the positions of the symmetry elements relative to molecules involved in significantly stabilizing interactions (Figure 10a,b). Two distinct stabilizing CH···O interactions exist in I: 1) contacts between the aromatic ring and the acetyl carbonyl group; and 2) interactions between

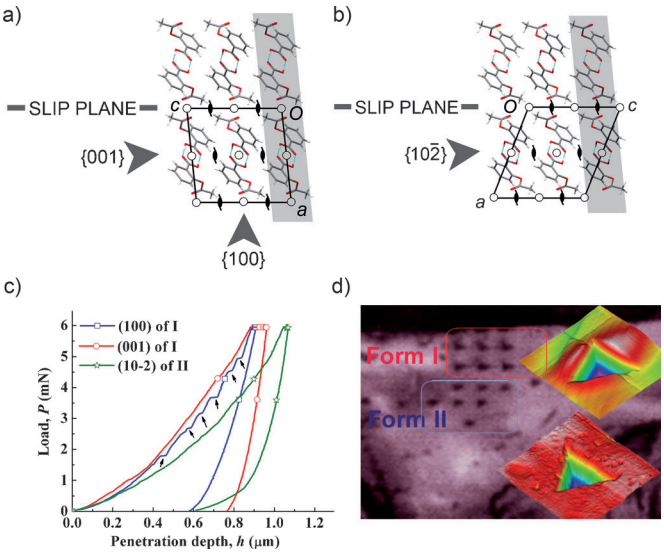


Figure 10. Aspirin. Crystal packing showing a representation of the slip planes in a) polymorph I and b) polymorph II. The gray slab represents the molecules that are involved in stabilizing interactions across the slip plane. c) Representative *P*–*h* curves of aspirin polymorphs. d) Optical micrograph and AFM images show domain coexistence in polymorph II crystals.

the methyl group and ester carbonyl group. In contrast, the significant stabilizing interactions across the slip plane in II are all of the same type, namely CH···O contacts between acetyl substituents of molecules related by a crystallographic 2_1 screw axis. The structure of form I is related to that of II by a relative shift of adjacent layers parallel to one of the crystallographic axes (specifically $^1/_2c$).[78]

Since the two forms are related along the *c*-axis, indentation experiments were carried out on (001) of I and the structurally equivalent (10$\bar{2}$) of II. {001} of I was found to be stiffer and harder than {10$\bar{2}$} of II. This softer nature of II

along the potential shearing directions provides a mechanistic rationale for the observed solid-state II→I transformation in aspirin. Although such transformations take place over months under ambient conditions, mechanical deformation such as that occurring during grinding can accelerate the kinetics. The crystal cracked upon indenting {100} of I; distinct pop-ins were observed on the *P–h* curves, because the applied stress is normal to the slip planes (Figure 10c).

The mechanical responses of the aspirin polymorphs can be correlated with their crystal structures. Since the carboxylic acid dimers in the two forms are similar, the observed mechanical differences can be attributed to the interactions existing in the interlayer region and the relative movement of the layers. The existence of two types of interactions across the slip plane with distinct potential energy profiles as well as their unsynchronized elongation and compression makes the relative movement of molecules in I more demanding. However, equivalent interactions in the interlayer region in II render the relative movement of molecules unhindered. The observed soft nature of II can be attributed to slip, which is akin to possible stress-induced phase transformation. The small activation energy barrier for the II→I transformation together with the soft nature of the crystals make it quite difficult to obtain polymorph II of aspirin.

The intergrowth of crystalline domains is a relatively rare phenomenon, and these crystals can be viewed as snapshots along the pathway of the polymorph transformation process.[81] Similar structural arrangements in polymorphs with comparable energies could be a possible reason for the intergrowth. In aspirin, single crystals of II contain domains with a nanoindentation signature corresponding to I (Figure 10d). This is despite the fact that single-crystal XRD data suggest the crystals to be structurally pure form II. The indent impressions as well as the *P–h* curves support the coexistence of crystalline domains.

Intergrown crystalline phases could be a challenge particularly in the pharmaceutical industry, wherein the phase purity of polymorphs is essential to claim intellectual property rights on the basis of non-infringement. Bond has recently reported intergrowth crystal domains in felodipine and has suggested a possible disordered layer stacking sequence in amlodipine besylate. Thus, the phenomenon of intergrown domains has been extended beyond aspirin.[81] Phase purity is usually confirmed using X-ray crystallography. However, in some cases where there is an intergrowth of crystalline domains, such characterization can be misleading. This is because crystal structures as determined from single-crystal diffractometer data are only space-averaged structures. Thus, nanoindentation, being a local probe, allows for discrimination between different forms in an intergrown sample.

3.2.4. Desolvation Processes

Numerous pharmaceuticals exist as hydrates or solvates.[82,83] Knowledge of the hydration and dehydration behavior of the drug and filler is essential to develop stable pharmaceutical formulations. This is because the physicochemical and mechanical properties of hydrates could be distinct from those of the anhydrates.[84–86] Berberine chloride dihydrate transforms to the tetrahydrate in a tablet formulation, thereby resulting in major changes in the tablet properties such as hardness, disintegration time, and dissolution behavior.[87] In the cases of phenobarbital calcium and calcium pyruvate isoniasone,[88,89] the disintegration time and appearance of tablets of hydrates differ from those of the anhydrates. Phase transitions arising from hydration or dehydration are generally accompanied by changes in the physicochemical properties, and thus understanding the mechanisms of these events under different conditions can be useful. Such properties are generally studied by using kinetic equations and physical models together with thermal analysis, powder diffraction, and mechanical analysis of compacts. Nanoindentation provides an additional means to study this phenomenon in small particles and single crystals.

To illustrate this, we conducted nanoindentation on sodium saccharin dihydrate ($Na(sac)\cdot 15/8H_2O$) which is identical to the commercially available sweetener.[94] This is an excellent example of a hydrated system in that it has a copious amount of structural water included in the freshly grown crystals.[90–93] The compound crystallizes in a large unit cell, with several structurally distinct units. (011) and (101) constitute the major faces of the crystal. The structure is unusual with "regular" and "irregular" regions separated by a clear boundary within the unit cell (Figure 11a). The regular region consists of sac^- ions arranged in a stack of water-bridged hydrogen-bonded pairs parallel to the *b*-axis. The stack is stabilized through an elaborate network of $OH\cdots N^-$ hydrogen bonds and $Na^+\cdots O$ interactions. In the irregular region, sac^-, water, and Na^+ are positionally and orientationally disordered and one can anticipate appreciable mobility of the water and the other components, caused by the abundance of the water resulting in "fluidity".

The sac^- units stack down [011], with the water columns diagonal to (011). Within a stack, weak π···π interactions exist

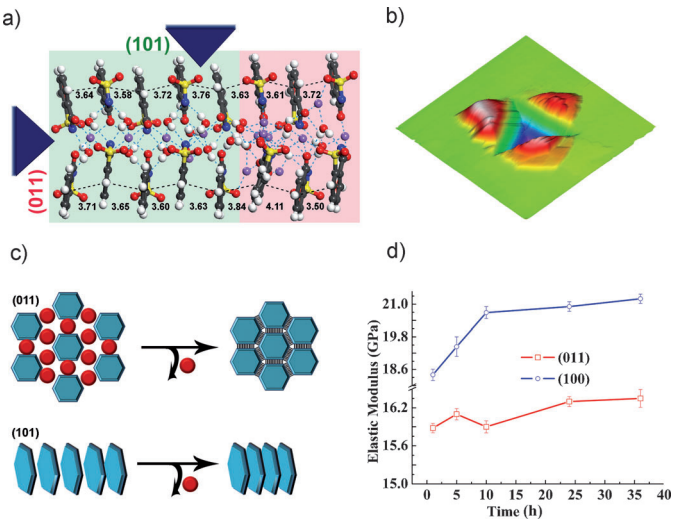


Figure 11. Sodium saccharin dihydrate. a) Crystal packing. The green and pink regions represent the regular and irregular packing, respectively. b) Indent impression show fluidlike flow on the crystal surface. c) Schematic representation of possible structural variations arising from dehydration. d) Variation in the elastic modulus with time. Reproduced with permission from the Royal Society of Chemistry.

between sac$^-$ molecules. The *P*–*h* curves obtained for (011) exhibit a higher penetration depth than for (101), thus indicating that plastic flow occurs more readily in [011].[94] Although the indentation direction is normal to the slip plane, loosely bound water acts as a hydraulic cushion for the indentation stresses and makes the layer movement more viable. In contrast, the stacking direction of sac$^-$ ions is approximately perpendicular to (101). Molecular sliding in this direction is sustained by the weak and nondirectional nature of the interactions within the stack. The stacking arrangement of sac$^-$ and the water channels together with the intricate network of interactions lead to mechanical anisotropy.

Exposing the material to the atmosphere results in the crystals efflorescing, with possible molecular rearrangements that result in a more compact structure (Figure 11c). The overall increase in *E* is appreciable (14%) for (011), whereas the change is minimal (3%) for (101) (Figure 11d). After exposure for 35 h, the *H* value of both faces becomes comparable. With the loss of intervening water columns, the sac$^-$ stacks come closer and make direct interactions with the adjacent stacks; this results in an increase in the *E* value of (011). In contrast, the *E* value of (101) is dominated by π···π interactions, and the structural change within a stack arising from the water loss is minimal. Furthermore, the energies of the π···π interactions are far less than those of the hydrogen bonds, and hence *E* remains invariant. Since the water columns open onto (011), indenting this face induces a fluid-like flow (Figure 11b). This may be attributed to the outward flow of lattice water together with dissolved sodium saccharin resulting from the disruption of the delicate equilibrium that is triggered by the applied stress. This study shows the potential utility of nanoindentation in evaluating the mechanical properties of pharmaceutical formulations at various stages of the dehydration process.

3.2.5. Organic–Inorganic Hybrid Materials

A plethora of hybrid framework materials with fascinating properties are now being synthesized and reported on a regular basis.[95] Compared to the weak noncovalent interactions present in organic crystals, hybrid systems often incorporate infinite inorganic connectivity, such as metal–oxygen–metal (M-O-M) arrays. The high mechanical performance of these hybrid materials is important since they are used as catalysts, in storage applications, and as sensors: applications where durability and reliability are important, and which are dictated by the mechanical properties. Cheetham and co-workers studied the anisotropic mechanical behavior of ($Ce(C_2O_4)$ (HCO_2)) and two polymorphs of $Cu_{1.5}(H_2O)(O_3PCH_2CO_2)$.[96,97] Significantly higher *E* values are reported along directions dominated by inorganic chains or sheets, whereas lower *E* values are noted along directions where the organic ligands form the primary linkages. These and other related studies are summarized in a recent review by Tan and Cheetham.[98]

In addition to instrumented nanoindentation, AFM nanoindentation techniques are also widely applied in the studies of crystals of biological tissues, fibrils, and pharmaceutical solids of sub-micrometer dimensions.[99,100] However, measurements using AFM are significantly influenced by surface forces that can deform the spring cantilever prior to contact, thus making it more of an adhesion study than indentation.[101,102] Further, uncertainties associated with the tip size and geometry mandates additional instrumentation for the error-free estimation of the elasto-plastic properties. In addition to surface forces, long-range attractions such as van der Waals and electrostatic forces can mask the onset of contact between the AFM probe and the specimen, which creates uncertainty in the location of the contact point and also can give poor values, usually overestimated ones.[103,104] Thus, extreme caution has to be exercised in utilizing AFM for nanoindentation studies.

4. Conclusion and Outlook

Crystal engineering was defined in 1989 as, "the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties".[4] The subject, which originated from crystallography and crystal chemistry, stressed structure at the microscopic level, as determined by single-crystal X-ray structure determination, and attempted to correlate such structures with properties of interest. Establishing connections between the structure and macroscopic properties is a classical aspect of materials science and engineering. Nanoindentation is able to make such a link between the structure of molecular solids at the microscopic level with the mechanical properties, in other words between chemistry and engineering. Thus, it has the potential to play an important role in the further development of crystal engineering.

This Minireview has summarized the preliminary nanoindentation experiments that have been used by us and others to examine the mechanical properties of molecular crystals. There are also several stress-induced phenomena that are largely unexplored: mechanoluminescence, mechanochromism, and triboluminescence. Recent advances in the nanoindentation of molecular crystals are bringing about a change in our thinking on crystal packing, interaction characteristics, polymorphism, and topochemistry.[105] In addition to opening up these scientific vistas, nanoindentation could also be developed as a "quality-control tool" in the pharmaceutical industry, in a similar way as hardness is used for the qualification of an engineering material.

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[1] C. M. Reddy, G. R. Krishna, S. Ghosh, *CrystEngComm* **2010**, *12*, 2296 – 2314.
[2] M. R. VanLandingham, *J. Res. Natl. Inst. Stand. Technol.* **2003**, *108*, 249 – 265.
[3] G. R. Desiraju, J. J. Vittal, A. Ramanan, *Crystal Engineering*: *A Text Book*, World Scientific, Singapore, **2011**.
[4] G. R. Desiraju, *Crystal Engineering*: *The Design of Organic Solids*, Elsevier, Amsterdam **1989**.
[5] J. O. Williams, J. M. Thomas, *Trans. Faraday Soc.* **1967**, *63*, 1720 – 1729.
[6] J. M. Thomas, J. O. Williams, *Trans. Faraday Soc.* **1967**, *63*, 1922 – 1928.
[7] H. M. Hawthorne, J. N. Sherwood, *Trans. Faraday Soc.* **1969**, *65*, 1783 – 1791.
[8] A. I. Kitaigorodskii, *Molecular Crystals and Molecules*, Academic Press, London **1973**.
[9] M. E. Brown, M. D. Hollingsworth, *Nature* **1995**, *376*, 323 – 327.
[10] Y. I. Golovin, *Phys. Solid State* **2008**, *50*, 2205 – 2236.
[11] P. Kumar, M. S. R. N. Kiran, *Nanoscale Res. Lett.* **2010**, *5*, 1085 – 1092.
[12] T. Beyer, G. M. Day, S. L. Price, *J. Am. Chem. Soc.* **2001**, *123*, 5086 – 5094.
[13] S. Finnie, K. V. R. Prasad, D. B. Sheen, J. N. Sherwood, *Pharm. Res.* **2001**, *18*, 674 – 681.
[14] S. Karki, T. Friščić, L. Fabian, P. R. Laity, G. M. Day, W. Jones, *Adv. Mater.* **2009**, *21*, 3905 – 3909.
[15] C. C. Sun, *J. Adhes. Sci. Technol.* **2011**, *25*, 483 – 499.
[16] M. Butters, J. Ebbs, S. P. Green, J. MacRae, M. C. Morland, C. W. Murtiashaw, A. J. Pettman, *Org. Process Res. Dev.* **2001**, *5*, 28 – 36.
[17] D. J. Dale, P. J. Dunn, C. Golightly, M. L. Hughes, P. C. Levett, A. K. Pearce, P. M. Searle, G. Ward, A. S. Wood, *Org. Process Res. Dev.* **2000**, *4*, 17 – 22.
[18] C. C. Sun, D. J. W. Grant, *Pharm. Res.* **2004**, *21*, 382 – 386.
[19] C. Sun, D. J. W. Grant, *Pharm. Res.* **2001**, *18*, 274 – 280.
[20] M. W. Y. Wong, A. G. Mitchell, *Int. J. Pharm.* **1992**, *88*, 261 – 273.
[21] J. F. Willart, M. Descamps, *Mol. Pharm.* **2008**, *5*, 905 – 920.
[22] T. P. Shakhtshneider, V. V. Boldyrev, *Drug Dev. Ind. Pharm.* **1993**, *19*, 2055 – 2067.
[23] T. P. Shakhtshneider, V. V. Boldyrev, *Reactivity of Molecular Solids* (Eds.: E. V. Boldyreva, V. V. Boldyrev), Wiley, New York, **1999**, pp. 271 – 311.
[24] R. W. Armstrong, W. L. Elban, *Mater. Sci. Technol.* **2006**, *22*, 381 – 395.
[25] C. C. Sun, H. Hou, *Cryst. Growth Des.* **2008**, *8*, 1575 – 1579.
[26] C. C. Sun, Y.-H. Kiang, *J. Pharm. Sci.* **2008**, *97*, 3456 – 3461.
[27] R. J. Roberts, R. C. Rowe, P. York, *J. Mater. Sci.* **1994**, *29*, 2289 – 2296.
[28] L. J. Taylor, D. G. Papadopoulos, P. J. Dunn, A. C. Bentham, N. J. Dawson, J. C. Mitchell, M. J. Snowden, *Org. Process Res. Dev.* **2004**, *8*, 674 – 679.
[29] C. M. Reddy, R. C. Gundakaram, S. Basavoju, M. T. Kirchner, K. A. Padmanabhan, G. R. Desiraju, *Chem. Commun.* **2005**, 3945 – 3947.
[30] C. M. Reddy, K. A. Padmanabhan, G. R. Desiraju, *Cryst. Growth Des.* **2006**, *6*, 2720 – 2731.
[31] C. M. Reddy, M. T. Kirchner, R. C. Gundakaram, K. A. Padmanabhan, G. R. Desiraju, *Chem. Eur. J.* **2006**, *12*, 2222 – 2234.
[32] R. P. Feynman, R. B. Leighton, M. Sands, *The Feynman Lectures on Physics*, Addison-Wesley, Boston, **1964**.
[33] W. C. Oliver, G. M. Pharr, *J. Mater. Res.* **1992**, *7*, 1564 – 1583.
[34] J. Stephens, T. Gebre, A. K. Batra, M. D. Aggarwal, R. B. Lal, *J. Mater. Sci. Lett.* **2003**, *22*, 179 – 180.
[35] W. C. Duncan-Hewitt, G. C. Weatherly, *J. Mater. Sci. Lett.* **1989**, *8*, 1350 – 1352.
[36] W. C. Duncan-Hewitt, G. C. Weatherly, *Pharm. Res.* **1989**, *6*, 1060 – 1066.
[37] K. V. R. Prasad, D. B. Sheen, J. N. Sherwood, *Pharm. Res.* **2001**, *18*, 867 – 872.
[38] C. Sun, D. J. W. Grant, *Pharm. Res.* **2001**, *18*, 281 – 286.
[39] R. Bandyopadhyay, D. J. W. Grant, *Pharm. Res.* **2002**, *19*, 491 – 496.
[40] Y. Feng, D. J. W. Grant, *Pharm. Res.* **2006**, *23*, 1608 – 1616.
[41] W. C. Duncan-Hewitt, G. C. Weatherly, *Pharm. Res.* **1989**, *6*, 373 – 378.
[42] L. J. Taylor, D. G. Papadopoulos, P. J. Dunn, A. C. Bentham, J. C. Mitchell, M. J. Snowden, *Powder Technol.* **2004**, *143*, 179 – 185.
[43] R. C. Rowe, R. J. Roberts, *Adv. Pharm. Sci.* **1995**, *7*, 1 – 62.
[44] N. K. Mukhopadhyay, P. Paufler, *Int. Mater. Rev.* **2006**, *51*, 209 – 245.
[45] M. Fujikane, M. Leszczynski, S. Nagao, T. Nakayama, S. Yamanaka, K. Niihara, R. Nowak, *J. Alloys Compd.* **2008**, *450*, 405 – 411.
[46] C. A. Schuh, T. C. Hufnagel, U. Ramamurty, *Acta Mater.* **2007**, *55*, 4067 – 4109.
[47] K. W. McElhaney, J. J. Vlassak, W. D. Nix, *J. Mater. Res.* **1998**, *13*, 1300 – 1306.
[48] R. Navamathavan, S. J. Park, J. H. Hahn, C. K. Choi, *Mater. Charact.* **2008**, *59*, 359 – 364.
[49] D. Lorenz, A. Zeckzer, U. Hilpert, P. Grau, H. Johansen, H. S. Leipner, *Phys. Rev. B* **2003**, *67*, 172101.
[50] C. Tromas, J. Colin, C. Coupeau, J. C. Girard, J. Woirgard, J. Grilhé, *Eur. Phys. J. Appl. Phys.* **1999**, *8*, 123 – 128.
[51] K. J. Ramos, D. F. Bahr, *J. Mater. Res.* **2007**, *22*, 2037 – 2045.
[52] K. J. Ramos, D. E. Hookes, D. F. Bahr, *Philos. Mag.* **2009**, *89*, 2381 – 2402.
[53] J. D. Dunitz, A. Gavezzotti, *Acc. Chem. Res.* **1999**, *32*, 677 – 684.
[54] R. Paulini, K. Müller, F. Diederich, *Angew. Chem.* **2005**, *117*, 1820 – 1839; *Angew. Chem. Int. Ed.* **2005**, *44*, 1788 – 1805.
[55] P. Metrangolo, H. Neukirch, T. Pilati, G. Resnati, *Acc. Chem. Res.* **2005**, *38*, 386 – 395.
[56] M. S. R. N. Kiran, S. Varughese, U. Ramamurty, G. R. Desiraju, *Cryst. Growth Des.* **2010**, *10*, 4650 – 4655.
[57] R. Banerjee, P. M. Bhatt, N. V. Ravindra, G. R. Desiraju, *Cryst. Growth Des.* **2005**, *5*, 2299 – 2309.
[58] P. M. Bhatt, N. V. Ravindra, R. Banerjee, G. R. Desiraju, *Chem. Commun.* **2005**, 1073 – 1075.
[59] G. M. J. Schmidt, *J. Chem. Soc.* **1964**, 2014 – 2021.
[60] G. M. J. Schmidt, *Pure Appl. Chem.* **1971**, *27*, 647 – 678.
[61] K. Chadwick, R. Davey, W. Cross, *CrystEngComm* **2007**, *9*, 732 – 734.
[62] R. Kuroda, K. Higashiguchi, S. Hasebe, Y. Imai, *CrystEngComm* **2004**, *6*, 463 – 468.
[63] G. Kaupp, J. Schmeyers, *Angew. Chem.* **1993**, *105*, 1656 – 1658; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1587 – 1589.
[64] R. B. Godiksen, Z. T. Trautt, M. Upmanyu, J. Schiotz, D. J. Jensen, S. Schmidt, *Acta Mater.* **2007**, *55*, 6383 – 6391.
[65] R. P. Rastogi, R. N. B. Singh, *J. Phys. Chem.* **1968**, *72*, 4446 – 4449.
[66] G. Kaupp, M. R. Naimi-Jamal, *CrystEngComm* **2005**, *7*, 402 – 410.
[67] G. Kaupp, *Top. Curr. Chem.* **2005**, *254*, 95 – 183.
[68] G. Kaupp, J. Schmeyers, U. D. Hangen, *J. Phys. Org. Chem.* **2002**, *15*, 307 – 313.
[69] S. Varughese, M. S. R. N. Kiran, U. Ramamurty, G. R. Desiraju, *Chem. Asian J.* **2012**, *7*, 2118 – 2125.
[70] J. Bernstein, *Polymorphism in Molecular Crystals*, Oxford University Press, New York, **2002**.
[71] H. G. Brittain, S. R. Byrn, *Polymorphism in Pharmaceutical Solids*, *Vol. 95* (Ed.: H. G. Brittain), Marcel Dekker, New York **1999**, pp. 73 – 124.

[72] *Polymorphism in the Pharmaceutical Industry* (Ed.: R. Hilfiker), Wiley-VCH, Weinheim, **2006**.
[73] P. P. Bag, M. Chen, C. C. Sun, C. M. Reddy, *CrystEngComm* **2012**, *14*, 3865 – 3867.
[74] R. Tawashi, *Science* **1968**, *160*, 76 – 76.
[75] C. Ouvrard, S. L. Price, *Cryst. Growth Des.* **2004**, *4*, 1119 – 1127.
[76] P. Vishweshwar, J. A. McMohan, M. Oliveira, M. L. Peterson, M. J. Zaworotko, *J. Am. Chem. Soc.* **2005**, *127*, 16802 – 16803.
[77] A. D. Bond, R. Boese, G. R. Desiraju, *Angew. Chem.* **2007**, *119*, 621 – 624; *Angew. Chem. Int. Ed.* **2007**, *46*, 615 – 617.
[78] A. D. Bond, R. Boese, G. R. Desiraju, *Angew. Chem.* **2007**, *119*, 625 – 630; *Angew. Chem. Int. Ed.* **2007**, *46*, 618 – 622.
[79] E. J. Chan, T. R. Welberry, A. P. Heerdegen, D. J. Goossens, *Acta Crystallogr. Sect. B* **2010**, *66*, 696 – 707.
[80] S. Varughese, M. S. R. N. Kiran, K. A. Solanko, A. D. Bond, U. Ramamurty, G. R. Desiraju, *Chem. Sci.* **2011**, *2*, 2236 – 2242.
[81] A. D. Bond, *CrystEngComm* **2012**, *14*, 2363 – 2366.
[82] S. R. Vippagunta, H. G. Brittain, D. J. W. Grant, *Adv. Drug Delivery Rev.* **2001**, *48*, 3 – 26.
[83] J. K. Haleblian, *J. Pharm. Sci.* **1975**, *64*, 1269 – 1288.
[84] P. R. Perrier, S. R. Byrn, *J. Org. Chem.* **1982**, *47*, 4671 – 4676.
[85] Y. Sakata, S. Shiraishi, K. Takayama, M. Otsuka, *Colloids Surf. B* **2006**, *51*, 149 – 156.
[86] E. Joiris, P. D. Martino, L. Malaj, R. Censi, C. Barthélémy, P. Odou, *Eur. J. Pharm. Biopharm.* **2008**, *70*, 345 – 356.
[87] H. H. Tong, A. S. Chow, H. M. Chan, A. H. Chow, Y. K. Wan, I. D. Williams, F. L. Shek, C. K. Chan, *J. Pharm. Sci.* **2010**, *99*, 1942 – 1954.
[88] I. Utsumi, N. Tanaka, S. Nagao, *Yakugaku Zasshi* **1961**, *81*, 1554 – 1559.
[89] I. Utsumi, N. Tanaka, S. Nagao, *Yakugaku Zasshi* **1962**, *82*, 32 – 36.
[90] R. Banerjee, P. M. Bhatt, M. T. Kirchner, G. R. Desiraju, *Angew. Chem.* **2005**, *117*, 2571 – 2576; *Angew. Chem. Int. Ed.* **2005**, *44*, 2515 – 2520.
[91] P. Naumov, G. Jovanovski, O. Grupce, B. Kaitner, A. D. Rae, S. W. Ng, *Angew. Chem.* **2005**, *117*, 1277 – 1280; *Angew. Chem. Int. Ed.* **2005**, *44*, 1251 – 1254.
[92] S. G. Fleischman, S. S. Kuduva, J. A. McMohan, B. Moulton, R. D. B. Walsh, N. Rodriguez-Hornedo, M. J. Zaworotko, *Cryst. Growth Des.* **2003**, *3*, 909 – 919.
[93] S. Velaga, S. Basavoju, D. Boström, *J. Mol. Struct.* **2008**, *889*, 150 – 153.
[94] M. S. R. N. Kiran, S. Varughese, U. Ramamurty, G. R. Desiraju, *CrystEngComm* **2012**, *14*, 2489 – 2493.
[95] Themed issue on "hybrid materials" *Chem. Soc. Rev.* **2011**, *40*, 453 – 1150 (38 articles and the references therein).
[96] J. C. Tan, J. D. Furman, A. K. Cheetham, *J. Am. Chem. Soc.* **2009**, *131*, 14252 – 14254.
[97] J. C. Tan, C. A. Merrill, J. B. Orton, A. K. Cheetham, *Acta Mater.* **2009**, *57*, 3481 – 3496.
[98] J. C. Tan, A. K. Cheetham, *Chem. Soc. Rev.* **2011**, *40*, 1059 – 1080.
[99] V. M. Masterson, X. Cao, *Int. J. Pharm.* **2008**, *362*, 163 – 171.
[100] C. Karunatilaka, D. K. Bucar, L. R. Ditzler, T. FriŠčić, D. C. Swenson, L. R. MacGillivray, A. V. Tivanski, *Angew. Chem.* **2011**, *123*, 8801 – 8805; *Angew. Chem. Int. Ed.* **2011**, *50*, 8642 – 8646.
[101] C. Picart, B. Senger, K. Sengupta, F. Dubreuil, A. Fery, *Colloids Surf. A* **2007**, *303*, 30 – 36.
[102] J. Notbohm, B. Poon, G. Ravichandran, *J. Mater. Res.* **2012**, *27*, 229 – 237.
[103] E. H. H. Chow, D. K. Bučar, W. Jones, *Chem. Commun.* **2012**, *48*, 9210 – 9226.
[104] B. P. Chandra, M. Elyas, K. K. Shrivastava, R. D. Verma, *Solid State Commun.* **1980**, *36*, 931 – 933.
[105] S. Ghosh, C. M. Reddy, *Angew. Chem.* **2012**, *124*, 10465 – 10469; *Angew. Chem. Int. Ed.* **2012**, *51*, 10319 – 10323.

