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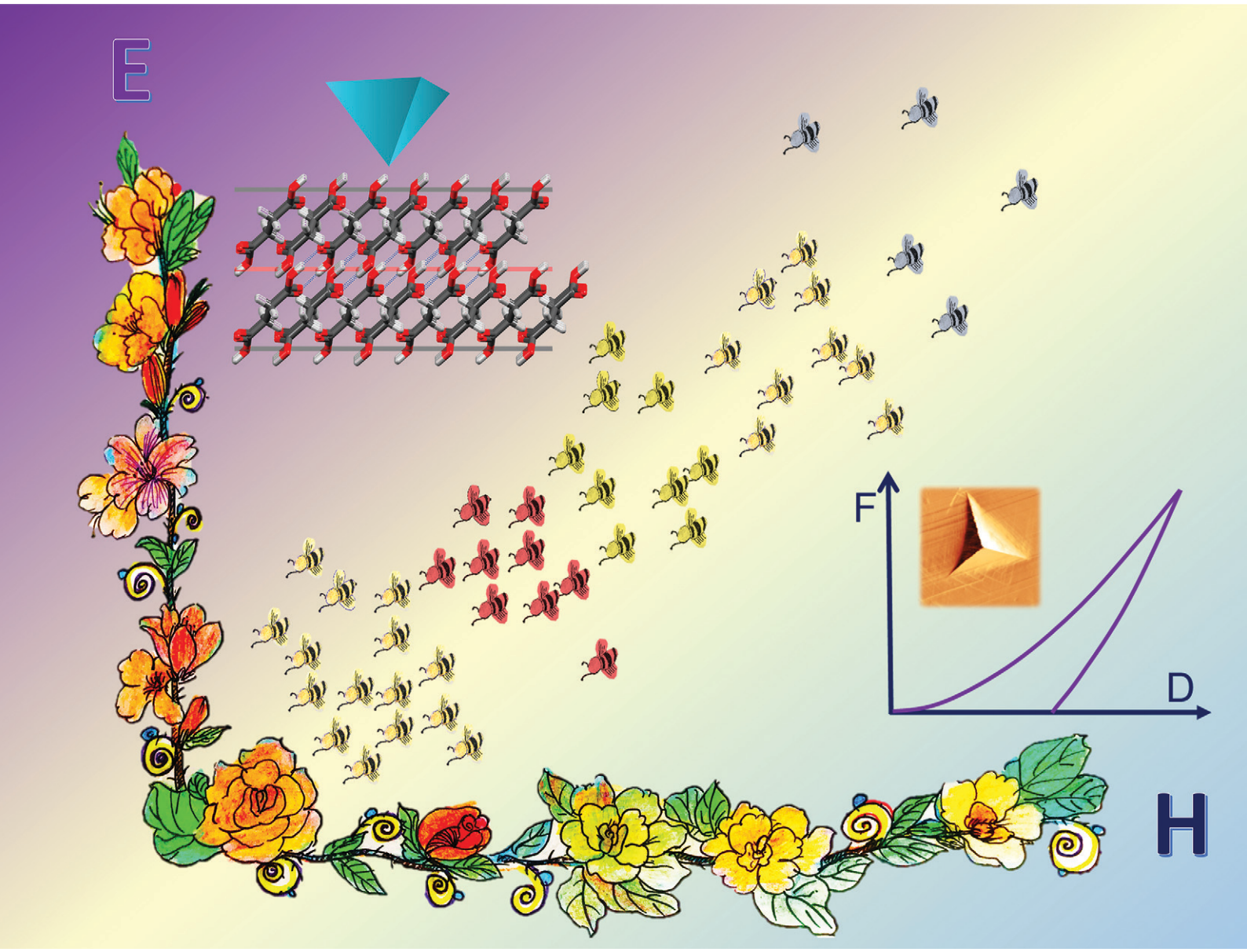

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The landscape of mechanical properties of molecular crystals†

Chenguang Wang and Changquan Calvin Sun *

An analysis of compiled literature nanoindentation hardness (H_c) and elastic modulus (E) values of molecular crystals revealed a wide range of mechanical properties (0.001–1.80 GPa for H_c and 0.27–46.8 GPa for E). A global approximately linear relationship between E and H_c is observed and possible reasons for deviation from the line are discussed. A classification scheme for molecular crystals based on E and H_c is proposed. In addition, results suggest that the effectiveness of crystal engineering strategies in modifying both E and H_c follows the order cocrystallization/salt formation > polymorph formation > anisotropy. A clear understanding of the E and H_c landscape lays a foundation for effective optimization of the mechanical properties of molecular crystals through crystal engineering.

Owing to their importance to materials function and performance, the mechanical properties of metal, polymer and inorganic crystals have been extensively and systematically investigated for a long time.[1–3] In contrast, systematic investigation of the mechanical properties of molecular crystals was lacking until modern nanoindenters became commercially available.[4,5] Knowledge of the crystal structure–mechanical property relationships for molecular crystals is of great importance for designing functional pharmaceutical materials and nonlinear optical materials.[6]

The mechanical properties of molecular crystals can be qualitatively assessed from their response to external stresses, such as bending, twisting, and shearing, where elastic, plastic, and brittle behaviors have been amply documented.[4,7–15] The response to external stresses often depends on the direction of the applied stress because of the relatively low structural symmetry of molecular crystals.[16] It has been recognized that plastically bending crystals are characterized by structural anisotropy, with drastically different intermolecular interactions in orthogonal directions,[9] shearing crystals show layered structures without specific interlayer interactions,[4] elastic crystals are highly isotropic with comparable intermolecular interactions in orthogonal directions,[17,18] brittle crystals have either rigid hydrogen-bonded 3D structures or stacking hydrogen-bonded 2D zigzag layers,[7] and twisting crystals are plastic and bendable in two dimensions.[19,20] Such qualitative studies of crystal mechanical properties, although useful, require well-formed crystals with adequate size, usually >500 μm, to allow easy manual manipulation.

The nanoindentation test can be performed on small crystals to quickly quantify their mechanical properties by measuring contact hardness (H_c, see the ESI†),[21] elastic modulus (E), fracture toughness, and contact stiffness.[22–24] Consequently, nanoindentation has been widely utilized to probe crystal structure–mechanical property relationships in the field of crystal engineering, including the effects of crystal anisotropy and crystal structural modifications attained by polymorph formation, hydration or dehydration, and salt and cocrystal formation.[5,25–29]

H_c and E are the most commonly reported parameters from nanoindentation experiments. The availability of a large number (256 for E and 257 for H_c as of November 15, 2019, see the ESI†) of nanoindentation results (all were collected using a Berkovich tip except for 6 measurements where a cube corner tip was used and 4 measurements where a spherical tip was used) makes it possible to map and explore the landscape of mechanical properties of molecular crystals. Performing a systematic analysis of the available E and H_c values to gain insights into the mechanical properties of molecular crystals helps answer the following questions: 1) What are the distributions of E and H_c? 2) How does the crystal structure affect E or H_c? 3) How are H_c and E related? 4) How sensitive are E and H_c to crystal anisotropy and solid form modification (polymorphs, salts and cocrystals)?

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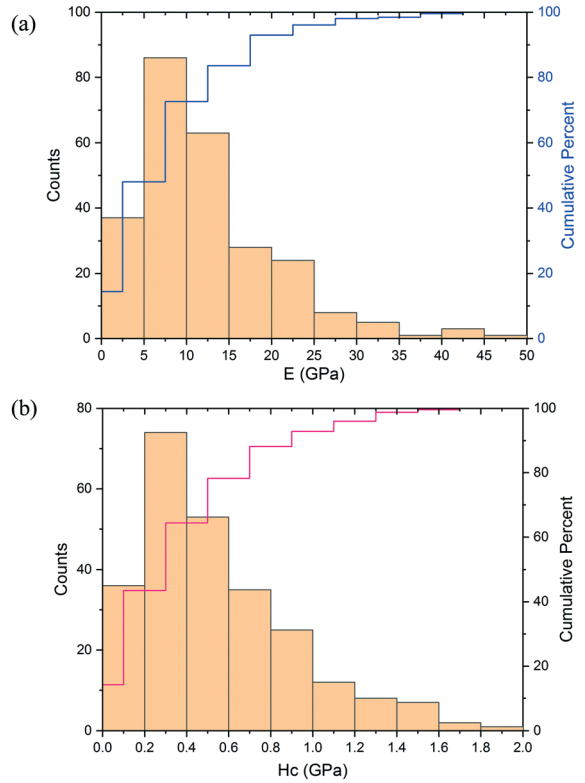

Fig. 1 Distributions of mechanical properties of molecular crystals: a) elastic modulus (n = 256) and b) contact hardness (n = 257).

From the distributions (Fig. 1), the H_c (mean = 0.55 GPa, median = 0.43 GPa, 0.001–1.80 GPa range) and E (mean = 12.4 GPa, median = 10.5 GPa, range 0.27–46.8 GPa) of molecular crystals are lower than those of metals and ceramics (Fig. 2). This is consistent with the weaker intermolecular interactions in molecular crystals, such as hydrogen bonds, halogen bonds, and van der Waals forces, than metallic, ionic or covalent bonds in other classes of materials.

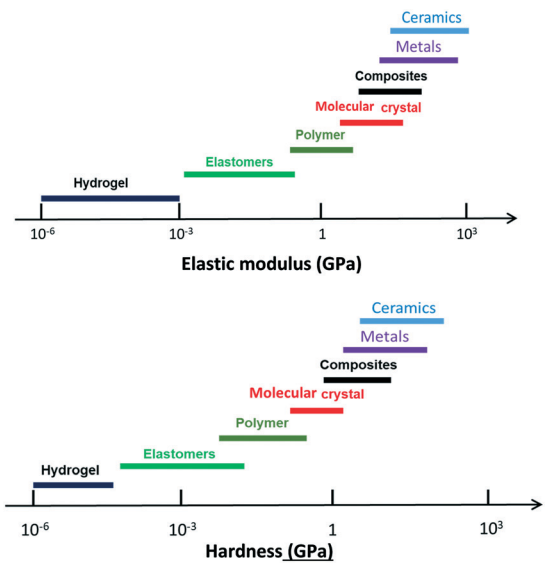

Fig. 2 The distributions of typical elastic moduli and hardness of molecular crystals in relation to other common classes of materials.[30]

Based on the overall distributions of E and H_c, we can classify molecular crystals based on their mechanical properties. Qualitative descriptions of mechanical properties based on the E and H_c values, corresponding to the top 10%, 10–25%, 25–75%, 75–90%, and bottom 10% of the overall distribution, may be proposed (Table 1).

The wide ranges of both E and H_c (Fig. 1) affirm diversity in the mechanical properties of molecular crystals, which also validates the strategy of property enhancement through crystal engineering. A high E usually corresponds to the presence of strong and dense hydrogen-bond networks along the loading direction, high packing density, and crystallinity.[25] A low E is usually accompanied by the presence of large voids, with weak interactions between adjacent molecule layers perpendicular to the loading direction.[5]

The E of as-grown hexachlorobenzene crystals (E = 4.82 GPa, Fig. 3a) is close to that of the widely used polymer poly(lactic) acid (E = 3.5 GPa).[31] The kink part of a bent hexachlorobenzene crystal is even more compliant (E = 0.6 GPa) and softer (H_c = 0.001 GPa), due to the decreased density, increased mosaicity and packing imperfections.[11] A bendable hydrate crystal, galactose hydrate (H_c = 0.29 GPa and E = 4.57 GPa), consists of stacking layers fortified with intralayer C–H···π interactions, whereas water interacts with the molecular layers through O–H···O and O–H···S weak hydrogen bonds (Fig. 3b).[32] Molecular crystals can also be very stiff and strong. For example, the E values of the (001) face of α-glycine (E = 44 GPa) and the (011) face of L-alanine (E = 34 GPa)[25] are close to those of binary alkali silicate glasses (E = 59–72 GPa).[33] The stiffness of those two amino acids corresponds to the presence of a dense network of charge-assisted strong hydrogen bonds between zwitterionic molecules, R–NH_3^+···O^-–R′ (Fig. 3c and d).

One observation in this work is that E and H_c are linearly related (R^2 = 0.93) with a slope (E/H_c) of 23.53 (Fig. 4a). This value is also close to that for biological materials ($E/H_c \approx$ 21.74, with 95% confidence intervals of 20–23.3).[34] For inorganic crystals, metals, and metallic glasses, although not observed between bulk modulus and the Vickers hardness (H_v), H_v did linearly correlate with the shear modulus, G, where $G = 6.62H_v$.[35,36] H_c is critical for understanding material performance, such as powder compression and cold welding.[37,38] Such a relationship may be used to estimate H_c from E, which can now be relatively accurately calculated

Table 1 Classification of molecular crystals based on E and H_c

E (GPa)		H (GPa)	
>23	Super stiff	>1.1	Super hard
16–23	Stiff	0.72–1.1	Hard
6–16	Intermediate stiffness	0.26–0.72	Intermediate hardness
4–6	Compliant	0.15–0.26	Soft
<4	Super compliant	<0.15	Super soft

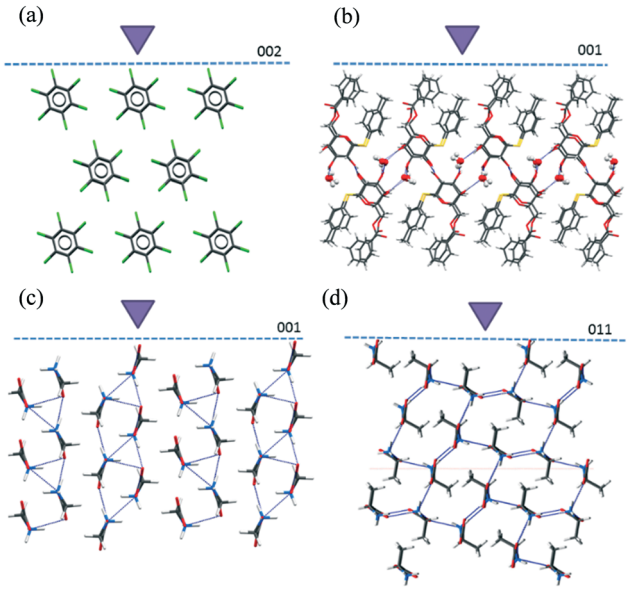

Fig. 3 Crystal packing of a) soft hexachlorobenzene (002), b) soft galactose hydrate (001), c) α-glycine (001) with a high E of 44 GPa, and d) L-alanine (011) with a high H of 1.8 GPa. The downward triangles represent indenter tips.

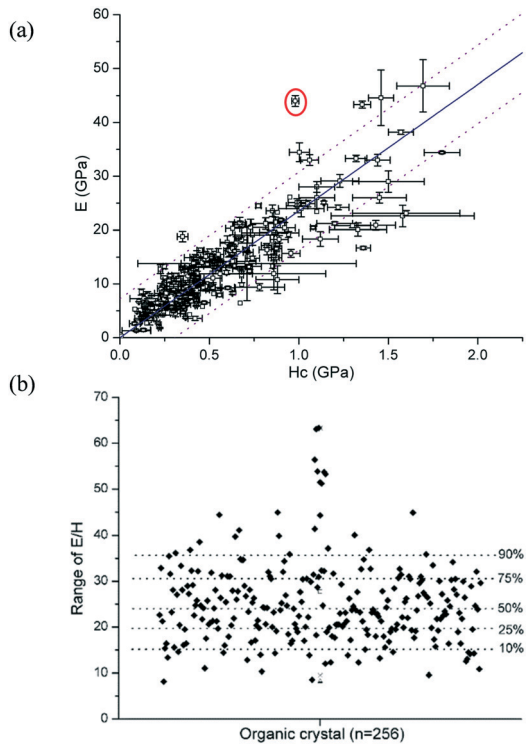

Fig. 4 a) Linear relationship between the contact hardness and elastic modulus of molecular crystals (the dashed lines indicate 90% confidence intervals with the outlier data of the α-glycine face (001) highlighted) and b) the distribution of E/H_c values.

from crystal structures.[25] Given the variability in the dataset, we caution that the global linear relationship may not be observed when only a small set of data points is analysed.[39]

The E/H_c values of a wide variety of materials (metals, ceramics, and polymers) typically fall in the range of 10–150, with brittle (*e.g.*, glasses) and plastic materials usually on the low and high ends of the range, respectively.[40] Approximately, 90% of the molecular crystals have E/H_c values below 35 (Fig. 4b), indicating the generally brittle nature of this class of materials. However, some molecular crystals can still be highly plastic with high E/H_c (Fig. 4b).

Deviations from the global linear relationship in individual cases can be expected by any factor that affects E and H_c to different extents due to different molecular mechanisms for elastic and plastic deformation. It is known that H_c depends on the ease of irreversible slip of molecular layers, but E depends on the packing efficiency, number and strength of intermolecular hydrogen bonds and the orientation of hydrogen bonds to the loading axis, as well as crystallographic voids.[25,41] The E/H_c ratio of the α-glycine (001) face is significantly higher than 23.5.[42] The high E is consistent with the strong hydrogen-bonded molecular layers running along the direction of the loading axis during nanoindentation, *i.e.*, perpendicular to (001). On the other hand, the interlayer interactions are weak, which allows easier slip of rigid layers (Fig. 3c). Consequently, its H_c is lower than that of L-alanine (011), which has both high E and H_c corresponding to its structure of a dense 3D strong hydrogen bond network (Fig. 3d). For the solid solutions, or tautomeric polymorphs, of omeprazole the presence of more 5-methoxy tautomers led to a nearly two fold increase in H_c (from 0.43 to 0.86 GPa), due to the greater hindrance to inter-layer slip, but only an ~10% increase in E (from 12.0 to 13.3 GPa).[41] Thus, the use of the global slope of 23.5 to predict H_c from E should be exercised with caution for highly anisotropic crystals because their H_c values are more sensitive to the presence of crystal defects than E. The different responses of E and H_c to crystal defects suggest that the variations in the data set summarized in Fig. 4 are at least partially caused by varying quality of crystals tested by nanoindentation. Other factors that may also affect E/H_c include 1) temperature,[43] 2) indentation size, and 3) the orientation of crystal slip planes relative to non-spherical indenters.[44] Most nanoindentation studies were performed on the major faces of crystals. Since major faces usually correspond to low attachment energy, strong intermolecular interactions tend to orient normal to the indentation direction. Minor crystal faces are usually of poor surface quality, which affects the accuracy of measured E and H_c.[45] In addition, many other factors must also be carefully controlled to ensure the accuracy of E and H_c values. These include the sample preparation, relative humidity, loading function, indentation depth, strain rate, and tip geometry, avoidance of fracture, and pile-up correction based on post indentation imaging.[24,46] Such variations among different studies are expected to contribute to the variation in the dataset. Thus, the global linear relationship ideally needs to be verified in a study where variations in experimental parameters are absent. Within the current dataset, one study

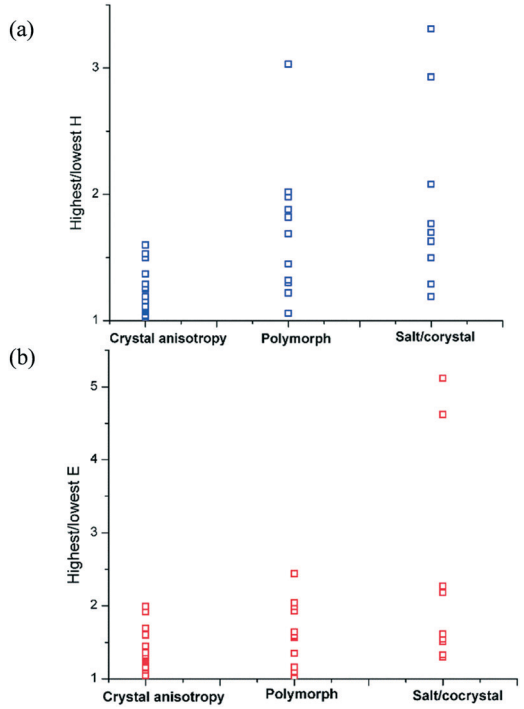

Fig. 5 a) Ratios of the highest to lowest values of a) H_c and b) E due to crystal anisotropy (n = 19), polymorph formation (n = 11), and salt formation/cocrystallization (n = 9).

of six molecular crystals under well-controlled nanoindentation conditions yielded a linear relationship over a wide range of H_c with a slope (E/H_c) of 23.4 (R^2 = 0.98, Fig. S1†). This is similar to the observed global slope in Fig. 4a.[44]

Modulating mechanical properties through crystal habit modification, polymorph crystallization, or multi-component crystallization (hydrates, salts, and cocrystals) is an active area of research. Property enhancement through modifying the crystal morphology takes advantage of the anisotropic nature of molecular crystals.[47] The potential impact of each of these crystal engineering strategies on mechanical properties may be assessed by examining the ratio of the highest to the lowest E or H_c values when those strategies are employed for a given system. Results suggest that the effectiveness of these strategies on modifying both E and H_c follows the order cocrystallization/salt formation > polymorph formation > anisotropy (Fig. 5, see Table S1† for details). The largest change in E and H_c was observed among voriconazole salts and cocrystals, where the E of the hydrochloride salt was 5.1 times that of voriconazole, and the H of the hydrochloride salt was 3.3 times that of the 4-hydroxybenzoic acid cocrystal. This observation is not surprising because, compared to polymorphs, the multicomponent salt formation and cocrystallization can survey a chemically and structurally broader and more diverse landscape. This more likely leads to observation of greater change in properties (Fig. 5).[48]

The collection and analyses of a dataset of E and H_c of molecular crystals revealed an impressively wide range of mechanical properties, which can be as soft as some very soft polymers and as stiff as binary alkali silicate glasses. Crystal engineering using the multi-component salt or cocrystal approach allows access to a wider range of mechanical properties than that by the polymorph and crystal morphology approaches. Further growth of this database and more detailed structural analyses of outliers from the global linear relationship may facilitate the quest for optimizing mechanical properties of molecular crystals for various applications through crystal engineering.

Conflicts of interest

There are no conflicts to declare.

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