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RESEARCH PAPER

Prediction of the Mechanical Behaviour of Crystalline Solids

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ABSTRACT

Purpose To explore the use of crystal inter-planar d-spacings and slip-plane interaction energies for predicting and characterising mechanical properties of crystalline solids.

Methods Potential relationships were evaluated between mechanical properties and inter-planar d-spacing, inter-planar interaction energy, and dispersive surface energy as determined using inverse gas chromatography (IGC) for a set of pharmaceutical materials. Inter-planar interaction energies were determined by molecular modelling.

Results General trends were observed between mechanical properties and the largest inter-planar d-spacing, inter-planar interaction energies, and IGC dispersive surface energy. A number of materials showed significant deviations from general trends. Weak correlations and outliers were rationalised.

Conclusions Results suggest that the highest d-spacing of a material could serve as a first-order indicator for ranking mechanical behaviour of pharmaceutical powders, but with some reservation. Inter-planar interaction energy normalised for surface area shows only a weak link with mechanical properties and does not appear to capture essential physics of deformation. A novel framework linking mechanical properties of crystals to the distinct quantities, slip-plane energy barrier and inter-planar interaction (detachment) energy is proposed.

KEY WORDS mechanical properties · particle deformation · slip plane · molecular modelling · inter-planar interaction energy

INTRODUCTION

Crystal structure and morphology play an important role in determining the physical and mechanical properties of pharmaceutical powders, and hence determine the processing behaviour (1). On a fundamental level, the key determinants of mechanical behaviour are the strength and directionality of the intermolecular interactions within the crystal lattice and their reaction to mechanical stress. Particles can respond to stress by exhibiting deformation which may be elastic, plastic, or brittle fracture, or a combination of these depending on the crystalline structure of the material and the nature of the applied stress (magnitude, rate of application, and whether sustained) (2,3). How materials respond to stress can affect product performance. For instance, materials that exhibit enhanced plasticity can yield tablets with a high tensile strength resulting from consolidation and densification of such materials during compression (4). Deformation via shearing is considered to occur along slip planes between molecules resulting in plastic flow when intermolecular forces are exceeded (5). The slip planes therefore are thought to be the crystal planes with the weakest intermolecular interactions. Planes with weak interactions are also considered to be prone to cleavage when crystals do fragment (6). The slip planes are not considered to be solely responsible for the response of the crystal to mechanical stress, as flaws (e.g.

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cracks) and defects (vacancies, edge or screw dislocations) in the crystal are also thought to impact on the crystal's propensity to deform or fragment under pressure (7,8).

As the molecules in organic crystals can often form a range of different hydrogen bonding frameworks (chains, ribbons, sheets or 3-dimensional), hydrogen bonding has attracted a particular focus due to its directional nature as being the main cause of anisotropy in the mechanical properties of molecular crystals (9). The number and types of hydrogen bond donors and acceptors and the directionality of the interactions in any crystal is therefore expected to impact on the interaction energy between planes. For example, for adipic acid and salicylamide, molecular slip is known to take place through the main network of hydrogen bonds, while in sucrose and lactose monohydrate, deformation occurs through the cleavage of the weakest hydrogen bonds (10).

The deformation behaviour of a material dictates the success or otherwise of a number of pharmaceutical processes including tabletting, where a predominant elastic response can give rise to capping and/or lamination of the tablets, and micronisation in which the deformation behaviour can determine the lowest attainable particle size. As challenging mechanical properties can enhance the risk to the development of a robust drug product, an ability to predict and rank materials in terms of their mechanical behavior (by experiment or modelling) would be highly desirable.

There are three distinct approaches that have the potential to predict the mechanical behaviour of a material given either its crystal lattice constants or the crystal structure: the use of inter-planar d-spacings, the calculation of elastic constants for the crystal (9,11), and the use of attachment energies (12). The basis for the inter-planar d-spacings is the link between the d-spacing and the relative strength of interaction between planes characterised by the d-spacing. This forms the basis of the BFDH method for predicting morphology, where it is assumed that the rate of growth of a particular surface is inversely proportional to the inter-planar d-spacing (13). As molecular interactions are not considered, the method is applicable only to crystals with isotropic interactions. The elastic constant calculations involve the evaluation of inter-molecular interactions to determine the force constants that characterise both axial and shear deformations in the harmonic approximation (9,11). The force constants however characterise only miniscule displacements of the lattice planes about the energy-minimised crystal structure i.e. the initial elastic component of the deformation, and not any subsequent stages involving additional barriers that may need to be overcome as the planes begin to displace. The attachment energy approach is also based on inter-molecular interactions and involves the calculation of the energy of attachment of a crystal slice of molecules onto a given crystal surface. This method is commonly employed to predict crystal morphologies, being based on the kinetic hypothesis that the rate of crystal growth of a given face is proportional to the attachment energy for that face (14,15). In the current context the attachment energies are employed to characterise and identify the crystal planes that are the most weakly interacting and could serve as the slip planes. Both the elastic constant and the attachment energy approaches have shown some success in linking the crystal packing and the associated molecular interactions to the mechanical behaviour of a material including mechanical behaviour during tabletting (12,16).

In this study we employ a combined approach involving both experiment and computer modelling to correlate the mechanical behaviour of organic crystals to their crystalline structures, with a particular emphasis on linking crystal planes with the weakest inter-planar interaction i.e. those that could serve as slip planes, to the crystal propensity to fracture. We revisit the use of attachment energies in identifying the slip planes (which hitherto have given variable results), extending previous studies by investigating a larger range of pharmaceutical materials. As an aspect of this study was to identify a rapid method to enable prediction of the mechanical properties of crystals, we also explore the use of the largest d-spacing of a crystal structure as a first-order indicator of the propensity for a material to exhibit fracture. The largest d-spacing may be calculated given the unit cell parameters of a crystal or can be rapidly determined from a powder X-ray diffraction scan.

MATERIALS AND METHODS

Materials

Ibuprofen was supplied by Albemarle Corporation (LA, USA) Lot No. 7050-0354, salbutamol sulphate by Cipla, India (Batch No. H80142), lactose monohydrate (Respitose-SV003 and SV010) by DMV Fonterra, Netherlands, and paracetamol by Mallinckrodt Chemicals Ltd., Staveley, U.K. (Lot No. 6088903P874).

Molecular Modelling

The crystal structure data for the range of pharmaceutical materials studied (paracetamol-monoclinic polymorph I, lactose monohydrate, ibuprofen, aspirin, adipic acid, tolbutamide, theophylline, sucrose, phenacetin, sulfadiazine, and sulfathiazole-polymorph IV) were acquired from the Cambridge Structural Database (CSD, UK) (17).

Mercury (version 2.3) (CCDC, Cambridge, UK) was used to display the crystal packing motifs, to ascertain the hydrogen bonding dimensionalities, and to generate simulated powder X-ray diffraction patterns for all materials using the single crystal structure data acquired from the CSD.

The molecular modelling software Materials Studio 4.1 (Accelrys, Inc.) was used to calculate lattice, attachment and surface energies of the materials studied (see work flow in Fig. 1). Prior to commencing the computational studies, missing hydrogen atoms were added and inappropriate bond angles and distances were set to ideal values. Geometrical optimisations of the crystal structures of the various materials were performed using the CVFF (with force field assigned charges) (18) and Dreiding (with Qeq and Gasteiger charges) (19) force fields. Morphology calculations were performed using the BFDH (20), growth morphology (attachment energy based) (13), and equilibrium morphology (surface energy based) methods as implemented in Materials Studio. The BFDH method was used to generate a list of possible dominant growth faces, associated d-spacings and percentage facet areas. The BFDH method relates relative growth rates (R_{hkl}) along crystallographic directions defined by the inter-planar distances (d_{hkl}). The growth morphology approach involving attachment energies utilises the atom-atom potential method and yields the lattice energy as well as a list of the required attachment energies of the different faces, which are then normally used to calculate the crystal habit using the Wulff construction (21). The equilibrium morphology method calculates the surface energies for the various surfaces which are then utilised to generate the crystal habit.

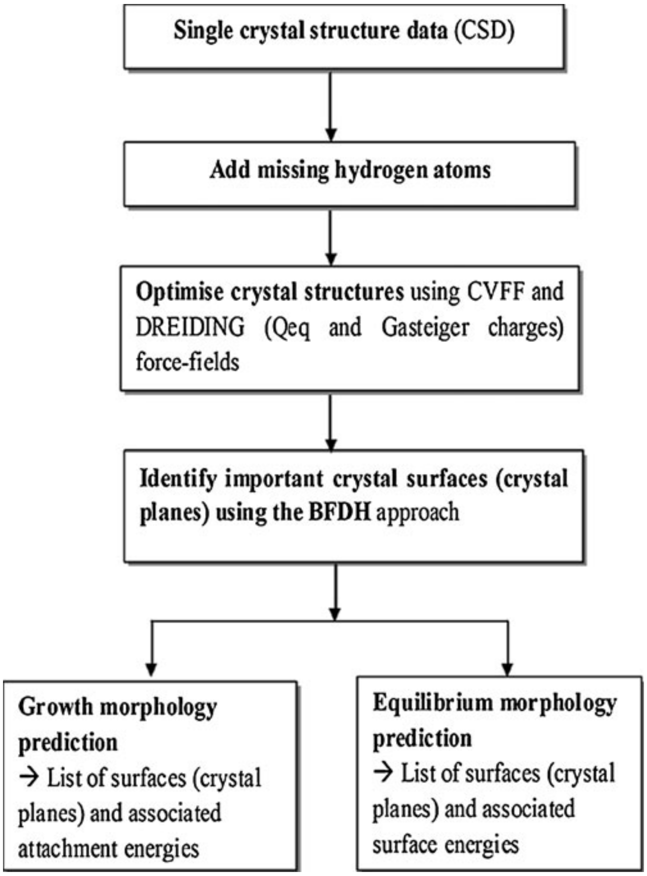


Fig. 1 Flow diagram for the identification of potential slip planes characterised with the lowest inter-planar interaction energy.

Micronisation

The micronisation behaviour of ibuprofen, lactose monohydrate, salbutamol sulphate and paracetamol (starting particle size=<40 μm) was evaluated using a small scale microniser (FPS Spiral Jetmill, FPS, Italy). Grinding pressure was kept at 5 bar, while injector pressure was kept constant at 8 bar and the feed rate was set at the highest level of the feeder.

For each micronisation experiment, 5 g samples were used. Grinding and injector pressure were set using the appropriate regulators that had been calibrated using an external pressure gauge (accuracy ±1.6%). Samples were collected from the collection vessel at the end of the experiments and stored over phosphorous pentoxide at room temperature to avoid any moisture-induced changes before characterisation. For all experiments, the moisture content of the utilised compressed air was 2–6% RH, which was measured using a hand held Testo 610 hydrometer (Testo, UK).

Particle Size Analysis

Particle size distributions were determined for ibuprofen, lactose monohydrate, salbutamol sulphate and paracetamol samples using a Sympatec laser diffraction particle size analyser with a HELOS & RODOS dry dispersion unit (Sympatec Instruments Ltd., UK). 15–20 mg samples were fed into the analyser using an air pressure of 4 bar at a rate of 30 mm/sec. Trigger conditions used for both starting and micronised batches were 5 s at an optical concentration of 1%. All samples were analysed in triplicate. The polydispersity of the powder was expressed by the polydispersity index (PDI).

$$\mathrm{PDI} = \frac{\mathrm{D}(\mathrm{v}, 90) - \mathrm{D}(\mathrm{v}, 10)}{\mathrm{D}(\mathrm{v}, 50)}$$

where D (v, 90), D (v, 10) and D (v, 50) are the equivalent volume diameters at 90, 10 and 50% cumulative volume, respectively.

Inverse Gas Chromatography

Inverse gas chromatography (IGC) measurements were carried out for ibuprofen, lactose monohydrate, salbutamol sulphate and paracetamol powder samples using an automated Perkin Elmer gas chromatograph (Perkin Elmer, USA) equipped with a flame ionisation detector. Nitrogen was used as carrier gas with hydrogen and compressed air employed for the detector. The flow rate of carrier gas at the column outlet was measured using a bubble flow meter. Details of the IGC method have been previously reported by Saxena (22). Adsorption measurements were performed at 30°C at infinite probe dilution. Hexane, heptane. octane and nonane were used as non-polar probes, while ethyl-acetate, acetone, chloroform and THF were used as polar probes in this study. The dispersive component surface free energy and specific surface free energy were determined using the method described by Schultz and Lavielle (23).

Brittleness Indices

Brittle materials show little or no plastic deformation with low energy absorption during fracture, while ductile materials exhibit greater plastic deformation with high energy absorption (24). We employ here the two brittleness indices, Brittleness Index 1 developed by Roberts (8), and Brittleness Index 2 developed by Rowe and Roberts (25).

Brittleness Index I is calculated from the ratio of the critical stress intensity factor to the *modified* yield stress of individual materials (8):

$$\text{Brittleness Index 1} = (\mathrm{K_{ICo}}/\sigma_{\mathrm{ym}})^2 \mu\mathrm{m}$$

where $\mathrm{K_{ICo}}$ is the critical stress intensity factor determined using a three point beam bending test and σ_{ym} is the modified yield stress. The latter is obtained by multiplying the yield stress (σ_y), as measured according to the Heckel method (the reciprocal of the slope of the plot of ln (1/1-D), where D is the relative compact density, as a function of pressure), by a factor of 1.37 (8). It was postulated by Roberts (8) that the measured yield stresses are typically lower than the true yield stresses of materials. In this regard a relationship between indentation hardness and yield stress was constructed and the slope determined for the straight line was 4.11, which when divided by the constraint factor (ratio of hardness to yield stress) for plastic materials, C=3, yields the factor 1.37. Note that low values of the Brittleness Index I indicate higher brittleness while high values characterise ductile materials.

Brittleness Index 2 is calculated from the ratio of the hardness to the critical stress intensity factor (25):

$$\text{Brittleness Index 2} = (\mathrm{H}/\mathrm{K_{ICo}}) \mu\mathrm{m}^{-1/2}$$

where H is the hardness and $\mathrm{K_{ICo}}$ is the critical stress intensity factor. The hardness was determined from micro-indentation (25). In contrast to Brittleness Index 1, high values for Brittleness Index 2 indicate high brittleness while low values indicate ductility.

The bulk of the data analysis in the current paper is based on the comprehensive set of Brittleness Index 1 values taken from Roberts (8). The Brittleness Index 2 data (25) is only available for just a few materials and hence has been used in a limited way.

Brittle-Ductile Transition Size, d_{crit}

An important quantity for characterising the behaviour of a material to milling is the limiting particle size that can be obtained by compressive stress alone, d_{crit} (26). This is a material dependent parameter, below which the compressive stress is accommodated entirely by plastic flow. We briefly outline the physical basis for the limiting particle size d_{crit}. When the potential slip planes have an interaction energy above some critical level, the crystal is unable to accommodate the stress by slip and instead fractures. However, since the interaction energy is a function of the contact area between the planes, whether a crystal can exhibit slip or otherwise will depend on some coherent length (a length over which the planes are structurally ordered) or the size of a crystal. In general the coherent length, being limited by defects, will be significantly smaller than the crystal size. However, as the particle size is reduced, there will come a distinct point (which will be different for each material) when the contact area and the associated overall interaction energy between the planes, being limited by the particle size, is low and all applied stress is accommodated by slip. Thus no fragmentation occurs below this particle size, and there can be no further size reduction.

The d_{crit} values employed in the data analysis were taken from Roberts (8).

Anisotropic and Isotropic Materials

The hydrogen bonding dimensionalities of the various materials were characterised using the software Mercury 2.3. Hydrogen bonding dimensionality can be classified as: (a) *3-dimensional bonding*: where every molecule in the crystal is inter-connected by hydrogen bonds; (b) *2-dimensional bonding*: where the hydrogen bonds provide linkages between molecules within a given layer, but there are no interlayer hydrogen bonds; (c) *1-dimensional bonding*: where the molecules are connected by hydrogen bonds to form chains or columns; (d) *0-dimensional bonding*: where hydrogen bonding is absent apart from connected molecular clusters such as dimers. Materials with 3-D or 0-D hydrogen bonding could to a first approximation be considered to be isotropic materials, while materials demonstrating 1D or 2D hydrogen bonding would be anisotropic.

RESULTS AND DISCUSSION

The primary objective of the study was to investigate the relationship between the mechanical properties of a range of crystalline molecular substances and the energy required to displace the most weakly interacting crystal planes in the respective lattices. To evaluate this relationship, knowledge of the crystal structure is essential. When a crystal is stressed it will respond by either fracturing or deforming. Intuitively one would expect that the deformation will invariably involve crystal planes that are the easiest to displace and hence characterised by the lowest (absolute) interaction energy. To this end we have investigated whether the interaction energy for a set of planes can be related to brittleness, the brittle-ductile transition size d_{crit}, and the hardness of the crystal. The slip-plane interaction energy was derived from either crystal layer attachment energy, as normally employed in kinetics-based crystal morphology predictions, or from the calculated surface energy as used in equilibrium morphology predictions.

For the situation when the crystal structure of a material is not available, the use of the largest inter-planar d-spacing may serve as a tool for predicting the mechanical behaviour of crystals. The d-spacing has found some application (albeit limited) in identifying the main crystal growth surfaces, and hence may serve as a first guess for characterising the strength of interaction between a given set of planes; the larger the d-spacing the weaker the interaction between the planes. The Brittleness Index 1 and the brittle-ductile transition size are plotted as a function of the largest d-spacing for each of the materials in Figs. 2 and 3 respectively. Materials with low values for the largest d-spacing are expected to be more brittle, as these planes are more strongly interacting. Both plots show a general trend that complies with these considerations but with some outliers. The outliers include adipic acid, sucrose, lactose monohydrate, and phenacetin. As the d-spacing approach is expected to work for crystals where the inter-molecular interactions are isotropic, the expectation is that each of the outliers is characterised by a strongly anisotropic framework of hydrogen bonding. A crystalline structure with either a lack of or a 3-D hydrogen-bonding framework is expected to be near isotropic in terms of intermolecular forces, and hence should comply with the d-spacing correlation. Crystals with hydrogen bonding which is either 1-D or 2-D will be anisotropic and hence not expected to be encapsulated by the d-spacing correlation. Examination of the dimensionalities of the hydrogen bonding in the crystal structures of the materials investigated (Table I) reveals no link with whether the mechanical properties of a material do or do not correlate with the d-spacing. Thus the outliers adipic acid (1-D), sucrose (3-D), lactose monohydrate (3-D), and phenacetin (1-D), reveal a mixed bag of hydrogen-bonding dimensionality, as do the set of molecules that do comply with the correlation.

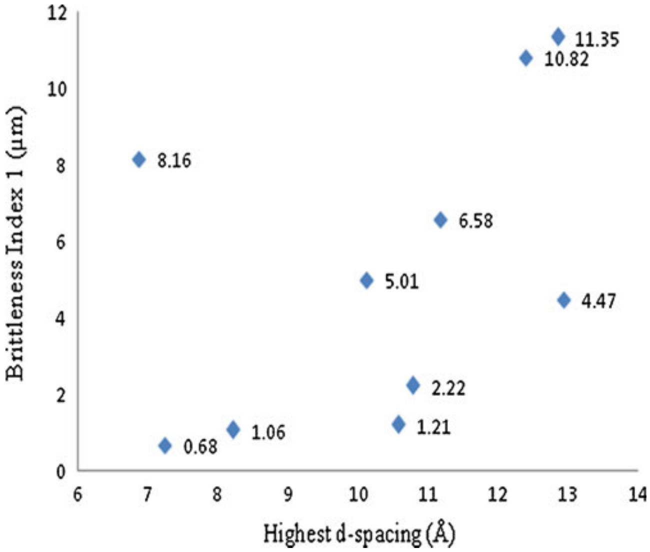


Fig. 2 Brittleness index 1 of various materials as a function of their highest d-spacing.

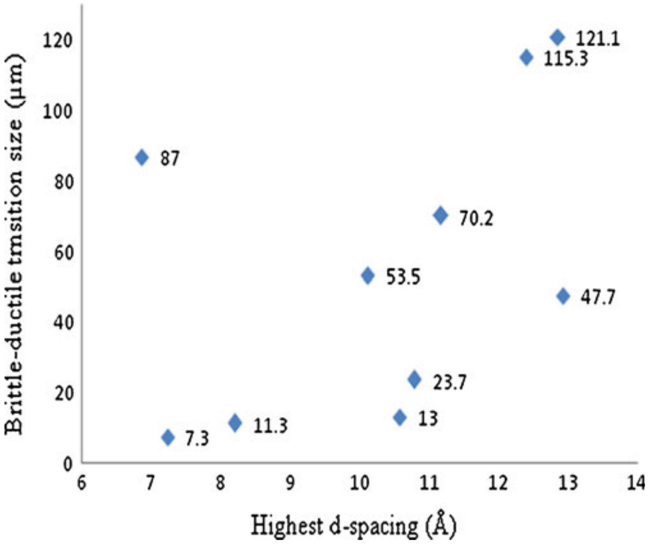


Fig. 3 Brittle-ductile transition size for various materials as a function of their highest d-spacing.

Focusing on the general trend, the data suggest that the largest d-spacing could possibly serve as a first-order indicator of the mechanical properties of a crystal, though it may fail for particular materials. Given that d-spacings can be readily determined from the crystal lattice constants, or if these are not available, from a quick powder X-ray diffraction scan, this approach is worth incorporating into a product development workflow.

The attachment energy calculations are a step up from the d-spacing approach, and explicitly take into account the intermolecular interactions. These calculations can however

Table I Crystal and Mechanical Properties for a Range of Pharmaceutical Materials, Associated Crystal Planes Given in Brackets

Material	Highest d-spacing (Å)	Attachment energy (kcal/mol)	Number of molecules in unit cell, Z	Specific interaction energy (kcal/mol/ Å^2)	Surface energy (kcal/mol/ Å^2)	Brittleness Index 1 (μm)	Brittleness index 2 ($\mu m^{-1/2}$)	Brittle-ductile transition size (d_{crit}) (μm)	Hydrogen bonding dimension
Adipic acid	6.93 / (10-1)	−14.12 / (110)	2	0.16 / (110)	0.18 / (110)	8.16	0.88	87	1 D
Paracetamol - I	7.24 / (011)	−16.46 / (011)	4	0.31 / (011)	0.26 / (011)	0.68	3.65	7	2 D
Sulfathiazole - IV	8.42 / (1-10)	−10.83 / (1-10)	4	0.17 / (1-10)	0.16 / (1-10)	1.06	–	11	3 D
Tolbutamide	10.07 / (200)	−12.37 / (200)	4	0.17 / (200)	0.18 / (200)	5.01	–	54	1 D
Sucrose	10.64 / (001)	−16.88 / (001)	2	0.25 / (001)	0.22 / (001)	1.21	2.88	13	3 D
Lactose monohydrate	10.71 / (020)	−33.27 / (020)	2	0.46 / (020)	0.29 / (020)	2.22	1.45	24	3 D
Aspirin	12.16 / (100)	−7.26 / (100)	4	0.21 / (100)	0.21 / (100)	6.58	0.56	70	0 D
Theophylline	12.85 / (200)	−8.93 / (200)	4	0.29 / (200)	0.23 / (200)	11.35	–	121	1 D
Sulfadiazine	12.96 / (100)	−10.45 / (100)	4	0.25 / (100)	0.23 / (100)	10.82	–	115	2 D
Phenacetin	13.28 / (100)	−17.85 / (100)	4	0.30 / (100)	0.22 / (100)	4.47	–	48	1 D
Ibuprofen	14.26 / (100)	−6.23 / (100)	4	0.15 / (100)	0.26 / (100)	51.49	0.34	549	2 D

depend on the force field employed. In view of this, the two force fields considered, CVFF and Dreiding, were compared as to whether they can reproduce the crystal structure of each of the materials considered. For each material the crystal structure was optimised using both CVFF and Dreiding and the percentage deviation between the optimised structure and the experimental structure assessed (results are tabulated in the Supplementary Material). A percentage deviation in the lattice parameters of less than 5% was considered to be acceptable (9). The CVFF force field was observed in general to yield lower percentage deviations (<5%) between the optimised unit cell parameters and the experimental parameters (Supplementary Material) when compared to the Dreiding force field. Despite being generally better, the CVFF force field however did show slightly larger deviations (5.7–8.4%) for aspirin and adipic acid (Supplementary Material S1).

The kind of deviations obtained in reproducing the crystal structures with the two force fields employed is not unexpected given the broad range of materials studied, and there is now an increasing awareness of the limitations of supposedly *universal* force fields which include CVFF and Dreiding (e.g. 27). Indeed there is now a tendency towards employing force fields that are optimised for a given class of molecules or even a specific molecule (28–30). We note that the accuracy of the two force fields employed may not be sufficient to discriminate, for instance, the stability of polymorphic forms based on lattice energies (for which the accuracy needs to be better than about 1 kcal/mol). However, the situation is different with respect to the relative attachment energies for which the differences can be captured by such force fields as witnessed by the many successful morphology predictions reported in the literature (13). We present here the data using CVFF given its performance was overall superior.

Earlier studies investigated the relationship between the mechanical properties of crystals and crystal attachment energies directly (12). The attachment energy is defined as the energy *per molecule* released when one slice of thickness d_{hkl} crystallises onto a crystal face (hkl). For characterising the behaviour of lattice planes to applied stress, the required quantity is the interaction energy between the planes. This is an extensive quantity (the larger the contact area, the larger the energy) and needs to be normalised with respect to the contact surface area, suggesting that the appropriate quantity for characterising the strength of interaction between a set of planes is the *specific* interaction energy. The attachment energy, being the energy required to attach a single molecule to a given surface, is therefore not appropriate.

The specific (absolute) interaction energy γ_{hkl} (which is equivalent to the surface energy) for a set of planes characterised by the d-spacing d_{hkl} can be estimated from the attachment energy $E_{hkl}{}^{att}$ using the relationship (31)

$$\gamma_{hkl} = \mathcal{Z}.d_{hkl}.\left|E_{hkl}^{att}\right|/2V$$

where $\mathcal{Z}$ is the number of molecules in the primitive unit cell and V is the volume of the primitive cell.

For each of the materials, the lowest attachment energy and associated plane, along with the lowest specific interaction energy and associated plane, the lowest surface energy (see below) and associated plane, the highest d-spacing, the Brittleness Indices 1 and 2, and the brittle-ductile transition size (d_{crit}) are tabulated in Table I. Please note that the attachment energies that are the outputs from the Morphology Module in Materials Studio are for the unit cell of the material being investigated and hence cannot be compared between materials as the number of molecules within the unit cell, $\mathcal{Z}$, may differ between materials. Here we have normalised the attachment energies to per molecule i.e the energies have been divided by the respective $\mathcal{Z}$ values.

The Brittleness Index 1 and the brittle-ductile transition size are plotted as a function of the lowest (absolute) attachment energy for a set of planes for each of the examined materials in Figs. 4 and 5 respectively. Both plots show no correlation, indicating that as expected the attachment energy as defined is an inappropriate quantity for characterising the relative strength of interaction between planes. This explains the variable results reported earlier, for example, by Sun and Kiang (12) who reported a success rate of less than 50% for slip plane prediction using attachment energy calculations.

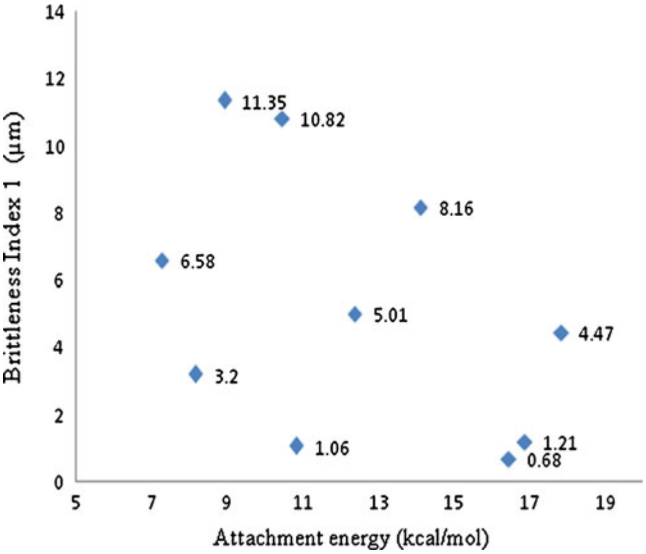


Fig. 4 Brittleness index 1 for various materials as a function of their lowest crystal layer attachment energy.

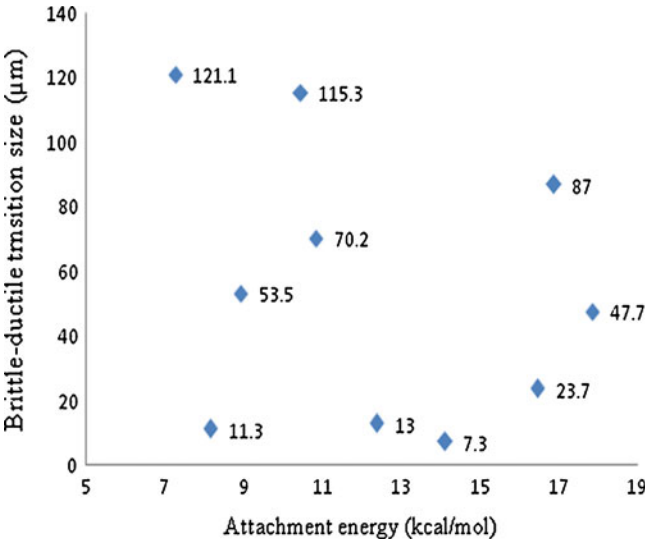


Fig. 5 Brittle-ductile transition size for various materials as a function of their lowest crystal layer attachment energy.

Plots of the Brittleness Index 1 and of the brittle-ductile transition size (d_{crit}) as a function of the lowest, specific inter-planar interaction energy (i.e. attachment energy normalised with respect to contact area) for the various materials are shown in Figs. 6 and 7 respectively. These figures also show considerable scatter. The expectations are that materials with potential slip planes with a higher specific interaction energy (corresponding to a stronger interaction) should exhibit increasing brittleness. On this basis one can broadly categorise the behaviour of the materials in Figs. 6 and 7 into two groups: those that follow the expected general trend (albeit not so strong) and the outliers.

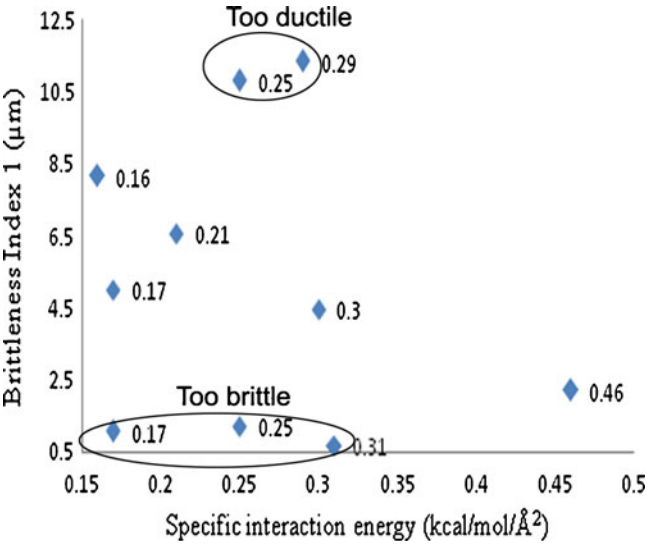


Fig. 6 Brittleness index 1 for the set of materials examined as a function of their lowest, specific inter-planar interaction energy. 'Too brittle' = sucrose, sulfathiazole and paracetamol. 'Too ductile' = sulfadiazine and theophylline.

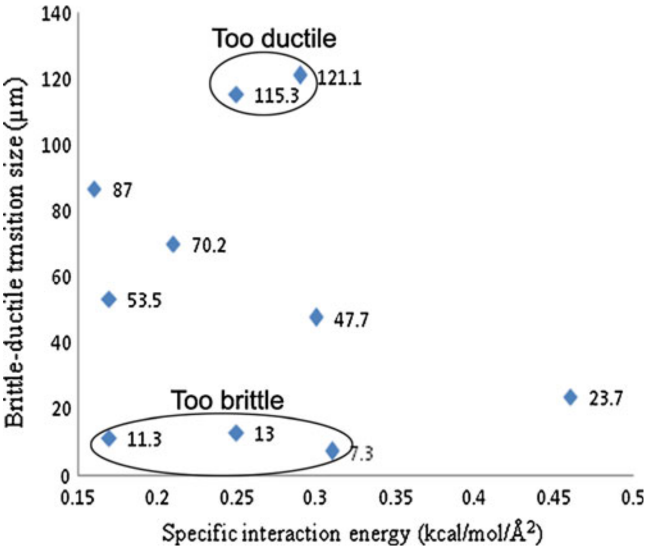


Fig. 7 Brittle-ductile transition size for the set of materials examined as a function of their lowest, specific inter-planar interaction energy. 'Too brittle' = sucrose, sulfathiazole and paracetamol. 'Too ductile' = sulfadiazine and theophylline.

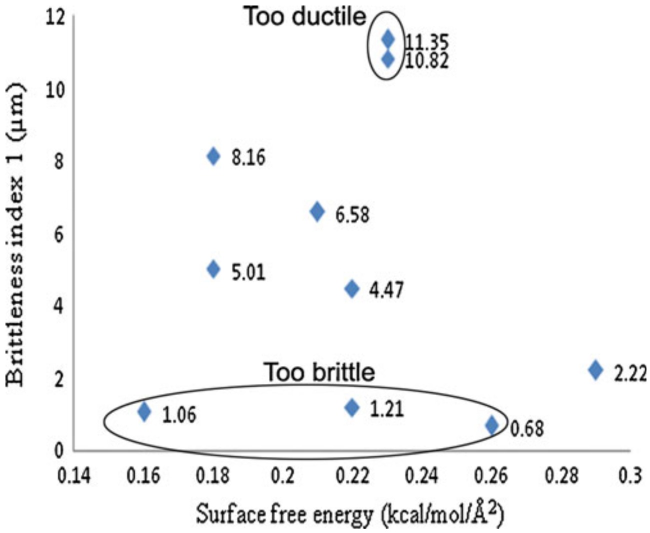


Fig. 8 Brittleness index 1 for the set of materials examined as a function of their lowest, specific surface energy characterising a set of planes. 'Too brittle' = sucrose, sulfathiazole and paracetamol. 'Too ductile' = sulfadiazine and theophylline.

In turn the outliers can be classified into two groups: those whose potential slip planes are characterised by a low interaction energy and yet are 'too brittle', which include paracetamol (monoclinic form I), sucrose, and sulfathiazole (form IV); and those that have a high slip-plane interaction energy and yet are 'too ductile' and include sulfadiazine and theophylline. We address possible causes for these outliers later in the discussion.

The specific interaction energies for the sets of planes were obtained by normalising the attachment energies with respect to the surface area, hence they are an approximation to the required interaction energies. In contrast, the equilibrium morphology calculation is based on surface energies (rather than attachment energies) and yields the surface energies for the set of planes using a more rigorous approach. The surface energy of a plane is obtained from the difference between the results of two calculations involving the crystal structure: (a) a calculation with periodic boundary conditions in all 3 dimensions; (b) a separate calculation with 2-D periodicity exposing the given surface to vacuum. As two surfaces are created the difference in energy is divided by 2 (Materials Studio manual, Accelrys, Inc.).

The Brittleness Index 1 and the brittle-ductile transition size d_{crit} are plotted as a function of the lowest surface energy for a set of planes in Figs. 8 and 9. These plots show a behaviour very similar to that obtained for the specific interaction energies estimated from attachment energies (Figs. 6 and 7). There is a weak general trend; materials with high surface energy have a greater propensity for size reduction, and there are two groups of outliers. The outliers comprise the same set of molecules as those observed for the specific interaction energies derived from attachment energies.

The experimental hardness (resistance of a material to local deformation) using the data from Rowe and Roberts (25) is plotted as a function of the specific interaction energy (surface energy calculation) for the weakest interacting sets of planes in Fig. 10. The available experimental hardness data is limited and we do not have respective values for all the materials that we have studied. The plot in Fig. 10 reveals a general trend, linking higher interaction-energy

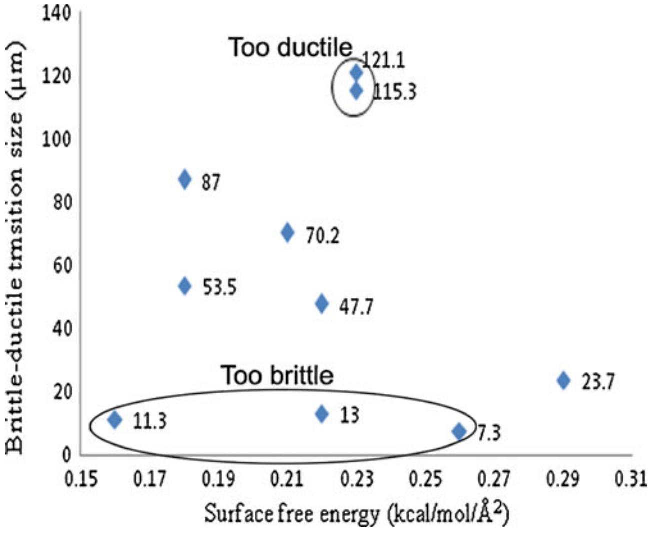


Fig. 9 Brittle-ductile transition size for the set of materials examined as a function of their lowest, specific surface energy characterising a set of planes. 'Too brittle' = sucrose, sulfathiazole and paracetamol. 'Too ductile' = sulfadiazine and theophylline.

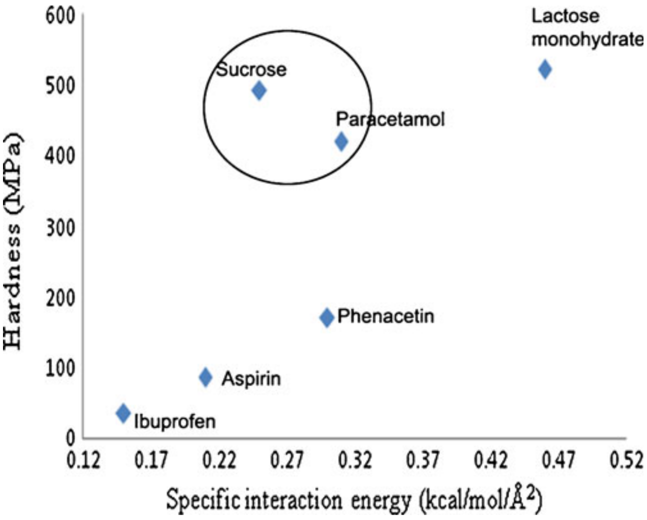


Fig. 10 Hardness of various materials as a function of their specific inter-planar interaction energy (surface energy calculation).

planes with greater hardness, but also shows outliers. This correlation is intuitive and expected, higher barriers to deformation defining greater hardness. The outliers again are paracetomol and sucrose.

In Fig. 11 we plot the Brittleness Index 2 as a function of the experimentally determined (using IGC) dispersive surface free energies for powdered samples. The data set here is also limited comprising only four materials. The plot shows an excellent correlation. What might be the basis for this correlation? From thermodynamics, crystals attempt to minimise their overall surface energy leading to crystal habits dominated by facets that have the lowest surface energy. These facets are therefore parallel to sets of planes with the lowest interaction energy i.e. the potential slip planes. The IGC method in measuring the surface energies of powdered samples is in fact characterising the interaction energy of the associated potential slip planes. We note that this limited data set does not include any of the molecules that are outliers in the correlation between mechanical properties and inter-planar interaction energies.

Finally we investigated whether a direct assessment of the inclination of a material to comminution, defined here as the lowest particle size obtained using a defined micronisation protocol, could be linked with the experimentally (PXRD) determined highest d-spacing value (Fig. 12). This too reveals a good correlation, but we are unable to assess its general application as this data set is limited and does not include the outlier materials.

An issue that could have a significant effect on the variation observed in the various tested correlations is the variability in the experimental values of the material indices, Brittleness Index 1 & 2 and d_{crit}, which may be responsible for some of the scatter. The key components of these indices such as the critical stress intensity factor (measure of the resistance of material to cracking) can show a rather large variation depending on whether the mechanical properties are determined using single crystals or compacts prepared from a powdered sample, as well as the crystal size and quality (25). Since crystallisation conditions may differ between materials, yielding crystals of differing quality, a comparison between materials may be an issue.

What can we infer from the various results presented? Firstly, the use of attachment energies directly is inappropriate; these energies need to be normalised with respect to the surface area to yield specific interaction energies for the sets of planes. The second point is that it appears that there is little to choose between the inter-planar interactions

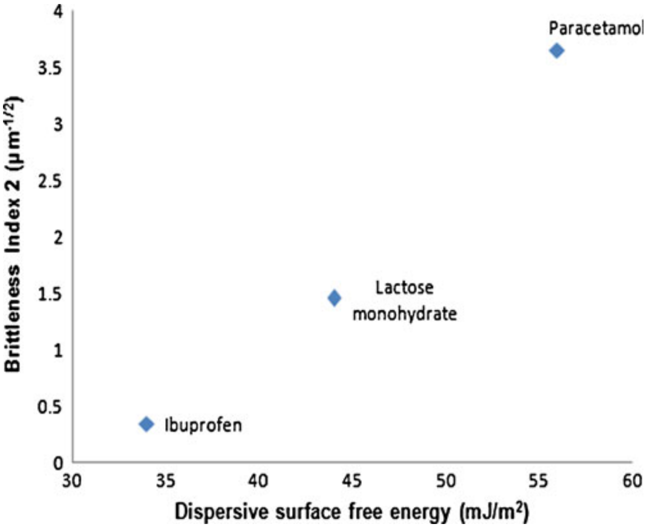


Fig. 11 Brittleness index 2 for three materials as a function of their specific dispersive surface energy determined using IGC.

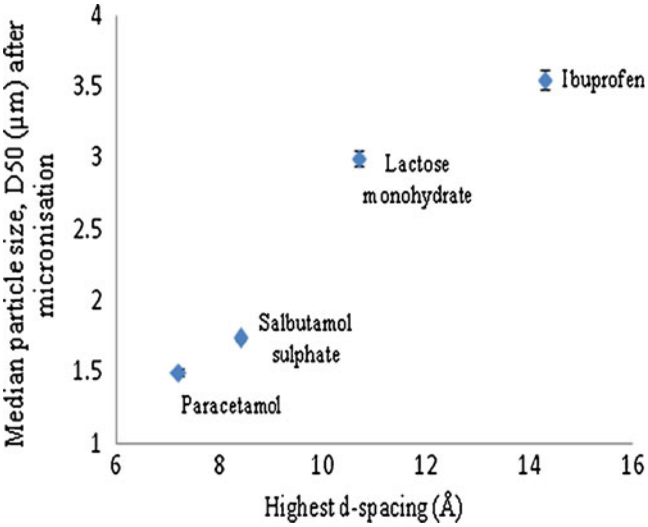


Fig. 12 Median particle size after comminution for four materials as a function of their highest d-spacing.

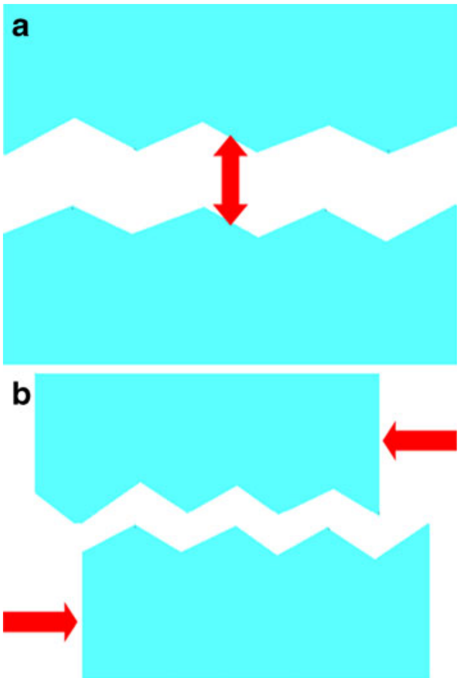


Fig. 13 Schematic indicating the distinction between (**a**) detachment energy and (**b**) the energy barrier to lateral displacement.

estimated from the attachment energies or the directly determined surface energies. With respect to the correlations the general trends in correlating brittleness, brittle-ductile transition size (d_{crit}), and hardness to the interaction energy of the weakest interacting set of planes are weak and there are significant outliers. Clearly, the mechanical behaviour of the crystals is not entirely captured by the slip-plane interaction energies. What essential physics might be missing? Slip by definition is the *lateral* displacement of a layer of molecules relative to another layer. The inter-planar interaction energies calculated here however reflect the work required to detach a layer in a direction *perpendicular* to the slip plane. This distinction is illustrated in Fig. 13. The implication is that whilst low inter-planar interaction energies may be indicative of slip for surfaces that are relatively flat, the interaction energies cannot be expected to predict slip planes when the surfaces are corrugated. Indeed, conceptually one could have a set of planes with inter-twined corrugated surfaces and zero interaction energy, but for which the interaction energy hypothesis would falsely predict high slip tendency. In practice this set of planes is unlikely to exhibit slip as the required lateral displacement will be restricted by the inter-twined corrugations. Corrugated inter-planar surfaces therefore would explain materials that have a low interaction energy and yet do not show ductile behaviour. At the other extreme, a material could have high interaction energy planes and yet be very ductile, provided the surface is flat. This could happen if the potential energy landscape for the relative displacement of the layers is equi- or near equi-potential. Here, although the interaction energy between the planes may be high or low, it does not change (much) as the layers are translated, and the force to displace the layers is low or zero. For instance, a group of hydrogen bonds could break at one location whilst another group forms elsewhere as the plane is translated, keeping the interaction energy more or less the same. A macroscopic analog would be the transport of a large stone on log rollers.

With a view to identifying whether the outlier materials can be linked to inter-twined corrugated surfaces which are not being captured in the interaction energies, we attempted a qualitative visual assessment of the extent of corrugation for each of the materials. It is tempting to bring in the extent and nature of the hydrogen bonding (i.e. whether within the layers or between the layers, or both) in

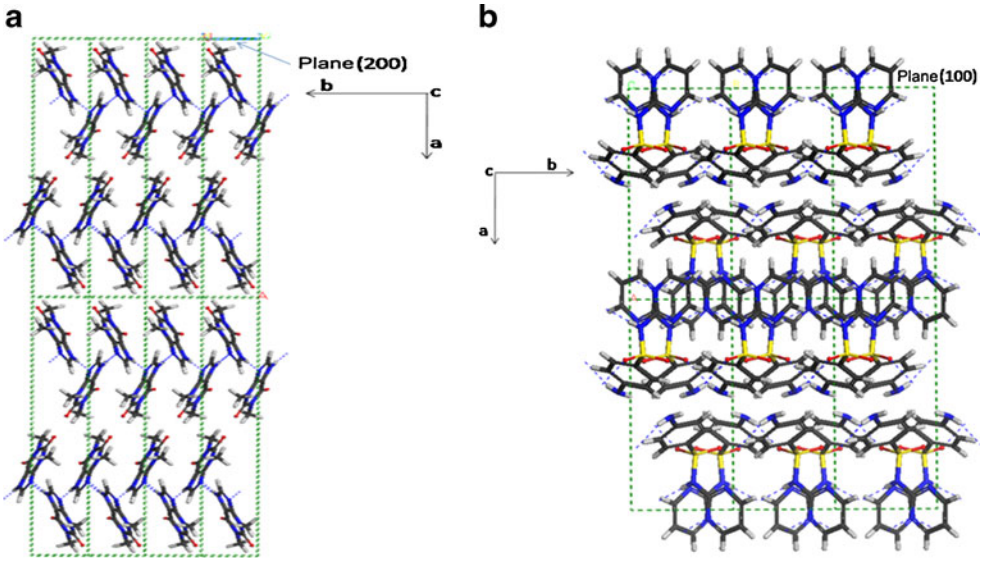


Fig. 14 Crystal structures of (**a**) theophylline and (**b**) sulfadiazine revealing potential slip-plane surfaces that are relatively flat and which could be responsible for the high ductility of the materials. For sulfadiazine, the flat slip plane appears to be the (200), which is half-way down the unit cell along the *a*-axis, and not the (100) as predicted by the interaction energy calculations.

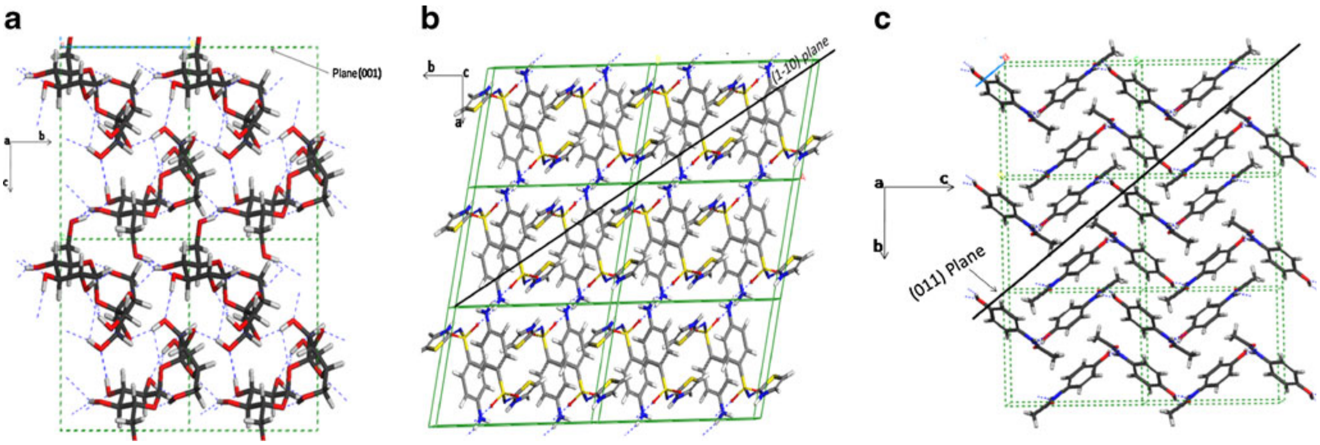
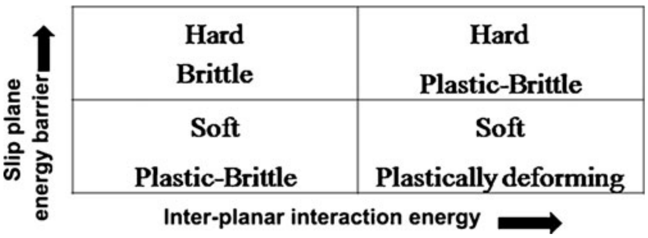


Fig. 15 Crystal structures of (**a**) sucrose, (**b**) sulfathiazole (form IV), and (**c**) paracetamol (form I), revealing corrugated and interpenetrating planes in the lattice that may be the cause of brittleness of these materials.

the discussion as a potential cause for the outliers. Hydrogen bonding would in fact be captured by the interaction energies, and hence is not expected to explain the outliers. Indeed lactose monohydrate, despite a strong three-dimensional hydrogen bonding network that links molecules within and between layers, complies with the overall trend and is not an outlier.

Accepting that a visual assessment of the crystal structures can only yield qualitative inferences, we were able to categorise the structures into three broad categories: crystals that comply with the relationship between brittleness and interaction energy, those that are 'too brittle', and those that are 'too ductile'. We focus on the outliers i.e. the latter two categories. The materials that are too ductile relative to their slip-plane interaction energies are theophylline and sulfadiazine. Both as expected reveal slip-plane surfaces that are relatively flat (Fig. 14). Although the slip-plane interaction energies are high, it is most likely that the inter-planar surfaces are near equi-potential with a relatively low force being required to induce displacement. The crystal structures of the materials that are too brittle are shown in Fig. 15. For all three, we note that the potential slip planes are characterised by inter-planar surfaces that are highly corrugated and integrated, making displacement of the planes difficult. So while the inter-planar interaction energy (the detachment energy in the vertical direction) is low, the lateral displacement of the planes is difficult, encouraging brittle behaviour. This rationalisation of the data clearly strengthens the assertion that the interaction energy between the surfaces of sets of planes does not capture the mechanical behaviour, and we also need to focus on the energy barrier to lateral displacement of the planes.

We therefore have two distinct processes, slip and fragmentation, with slip being characterised by the energy barrier to lateral layer displacement, and fragmentation by the detachment energy i.e. the inter-planar interaction energy. Neither of these energies alone can characterise whether the response of a material is predominantly plastic deformation or brittle fracture. When a material is subjected to impact stress, it has essentially two choices: either to accommodate the stress by exhibiting slip along the planes with the lowest energy barrier, or to fragment at an interface with the lowest detachment energy. If the lowest detachment energy is less than the slip-plane energy barrier, then the material is expected to exhibit mostly fracture and fragmentation. If on the other hand the slip-plane energy barrier is lower, then the material is expected to show predominantly plastic behaviour. Based on these considerations the behaviour of a material given its slip-plane energy barrier and lowest detachment energy is summarised in the matrix of mechanical behaviours shown in Fig. 16. For highly anisotropic materials, the mechanical behaviour of the material will of course depend on the orientation of the crystal to the applied stress. Clearly, to characterise the mechanical properties of a crystalline material we need both quantities, the lowest inter-planar detachment energy as well as the slip-plane energy barrier. How might the latter be determined? A possible approach is the use of molecular dynamics simulations to simulate the relative lateral displacement of the planes and to monitor the energy barrier. Such simulations have in fact been



Hard Brittle	Hard Plastic-Brittle
Soft Plastic-Brittle	Soft Plastically deforming

Fig. 16 Matrix summarising the mechanical behaviour of a material based on its slip-plane and lowest inter-planar interaction (detachment) energies.

carried out for crystals of the amino acid DL-norleucine albeit in another context (32).

CONCLUSION

We have investigated the use of inter-planar d-spacing and revisited the use of attachment energies to predict mechanical properties of crystalline materials. The results suggest that the maximum inter-planar d-spacing could serve as a first-order indicator of whether a material exhibits predominantly brittle fracture or plastic deformation, though it may fail for some specific materials. The advantage is the d-spacing can be readily calculated given the crystal lattice constants or may be determined experimentally from a rapid powder X-ray diffraction scan.

The direct use of attachment energies to identify the potential slip planes has been shown to be inappropriate. The inter-planar interaction energy is intensive i.e. it depends on contact area and therefore it is necessary to normalise the attachment energies with respect to the contact area. An alternative is to use surface energy which is essentially identical to the required inter-planar interaction energy. The results reveal that the correlations between the brittleness indices or the brittle-ductile transition size and the inter-planar interaction energies (whether determined from attachment or surface energies) are rather weak, with a number of materials showing significant departure from the overall trend. It appears that the inter-planar interaction energy does not capture the essential physics of deformation. The inter-planar interaction energy reflects the work required to detach a layer in a direction perpendicular to the slip plane, while slip by definition is the lateral displacement of the planes relative to each other. This approach therefore fails for inter-planar surfaces that are corrugated and which interpenetrate and are difficult to displace. Such materials show up as being 'too brittle' relative to their inter-planar interaction energies. The approach also fails for materials that have high inter-planar interaction energies but are characterised by relatively flat inter-planar surfaces if the surfaces are near equi-potential. In this case the materials appear to be 'too ductile' relative to their inter-planar interaction energies. To capture the essential physics of the problem the characterisation of both the detachment energy and the barrier to lateral displacement of crystal planes are required. The latter can be determined using molecular dynamics simulations.

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