Microhardness and Dislocation Identification Studies on Paracetamol Single Crystals

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Purpose. To study the mechanical behaviour of paracetamol single crystals.

Methods. Microhardness indentation techniques were used to study the hardness anisotropy of paracetamol. Solvent etching technique was used to define the range of plastic deformation and the orientation of the dislocation lines. The orientation dependence of Knoop hardness on the {001}, {110} and {20$\bar{1}$} surfaces was compared with calculated values of the Effective Resolved Shear Stress (ERSS) for plastic deformation by specific dislocation types.

Results. The principal habit faces of single crystals using both Vickers and Knoop indenters showed a range of hardness from 235 to 456 MPa depending on the type of indenter used and its orientation on the surface. Solvent etching of the plastically deformed region of the crystal around the Vickers/Knoop indentations confirmed that the slip plane was (010). ERSS analysis suggested that the deformation occurred by the slip of dislocations of the types (010)[001] and (010)[100]. Crystals doped with 0.08-0.8 w/w% *p*-acetoxyacetanilide showed hardness values similar to the pure material.

Conclusions. The low number of distinct dislocation slip systems (two) is characteristic of a brittle material and is consistent with the observation that paracetamol will tolerate only deformations of 1 part in 10^6 before fracture.

KEY WORDS: paracetamol; single crystal; hardness anisotropy; dislocation etch pits; slip plane.

INTRODUCTION

A major factor in the formulation of pharmaceutical materials is their mechanical behaviour on milling to small particle sizes or on compaction either alone or with excipients (1). Fundamental to an understanding of such processes is knowledge of the plastic/elastic and fracture behaviour of the material and the role that these properties play in the deformation taking place during particle compression and breakdown. Despite the wide range of studies which have been made on the mechanical behaviour of materials in general, relatively little has been done with well-defined single crystals of organic materials including pharmaceutical materials; most work having involved the study of compacted, powdered solids (2). There is therefore little direct evidence on which to base predictive theories of these properties in a wider range of drug materials.

For organic materials, single crystal studies have concentrated predominantly on aromatic solids because of their potential as luminescent devices (3,4), plastic crystals because of their unique mechanical behaviour (5), and organic energetic materials because of an interest in the role of dislocations in energetic decomposition processes (6). These studies comprised a combination of stress-strain analysis to define the limit of elastic behaviour and initiation of plastic flow and dislocation migration, coupled with dislocation and point defect identification and characterisation.

The studies have led to the realisation that deformation processes in molecular materials cannot be described in as simple terms as for inorganic materials. The nature and anisotropy of the molecular unit results in a major contribution from stress-induced conformational changes of the molecule to both elastic deformation and to plastic deformation by slip. Whereas all ionic materials with fcc, bcc, and hcp structures show similar dislocation slip processes, organic materials can show unique variations within the same structural class. Thus each material has to be assessed independently and broadly based attempts at prediction are unlikely to be successful.

To provide a better understanding of mechanical deformation processes in pharmaceutical materials we have initiated a survey of their mechanical behaviour. In the present publication we address the case of the most commonly formed monoclinic polymorph of paracetamol (acetaminophen).

Paracetamol (acetaminophen, $CH_3CONHC_6H_4OH$) exists in two known stable crystallographic modifications; monoclinic (7,8) and orthorhombic (9–11) and an uncharacterised unstable third form (11). For the monoclinic form a = 1.293 (4)nm, b = 0.940 (1)nm, and c = 0.710 (2)nm, β = 115.9° (7). The space group is $P2_1/n$. There are 4 molecules per unit cell.

Paracetamol powder compaction both alone and in the presence of excipients has been investigated by a number of researchers (12,13). Despite the fact that difficulties are experienced due to capping and the expression of included solvent, no detailed studies on the fracture and mechanical behaviour of single crystals have been reported for this material. Ichikawa *et al.* (14) first reported hardness values in the range 297–358MPa, for paracetamol crystals under various loads using a Vickers indenter. Duncan-Hewitt and Weatherly (15) have reported the hardness, Young's modulus, and fracture toughness values as 421MPa, 8.3Gpa, and 0.05MPam$^{1/2}$ respectively for paracetamol single crystals. Duncan-Hewitt, Mount, and Yu (16) have reported the hardness anisotropy of paracetamol single crystals of uncharacteristic morphology, using both Vickers and Knoop indentation hardness measurements. They compared their results with a theoretical assessment based on deformation involving specific dislocation types (16). Their results enabled them to speculate that the principal dislocation slip system was (010)[001] (16). No di-

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ABBREVIATIONS: ERSS, Effective resolved shear stress; AFM, Atomic force microscopy; fcc; face centred cubic; bcc, body centred cubic; hcp, hexagonal close packed; PETN, Pentaerythritol tetranitrate; RDX, Cyclotrimethylene Trinitramine.

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rect studies of the nature of the dislocations have been made. Vasil'chenko *et al.* (17) however, have revealed the emergent ends of dislocations at surfaces of paracetamol using etching techniques and examined their involvement in dissolution.

In this paper, we report a detailed study of the mechanical behaviour of paracetamol single crystals including hardness anisotropy, effective resolved shear stress analysis and dislocation etching studies. The observation of slip lines around the hardness indentations made in the fracture experiments (18), using etching techniques, offered an opportunity to identify the nature of the dislocation slip systems active in paracetamol and their potential contribution to deformation processes.

MATERIALS AND METHODS

Crystal Growth

Large (5–10mm) single crystals of paracetamol were grown from commercially available material (Rhone Poulenc, Rhodapap) by controlled slow evaporation of a saturated solution of ethanol or water at 23°C over a period of 3–6 weeks. The crystals were harvested and dried quickly using soft tissue paper. Crystals were of either columnar habit with major {110} faces or tablet-like with major {001} faces. The predominant faces for the columnar form in order of morphological importance were {110} > {001} > {20$\bar{1}$} > {011} and for the tablet-like crystals, {001} > {110}> {011} >{20$\bar{1}$} > {100} (Fig. 1). These habits correspond to those reported in the literature and reflect growth under conditions of medium (s = 7–11%) and high (s > 11%) supersaturations respectively (19). These forms differ considerably from that of the crystals used by Duncan-Hewitt *et al.* (16) in their previous study of this material.

Crystals were also grown from aqueous solutions containing various concentrations of the impurity, *p*-acetoxyacetanilide. These crystals were of the same basic morphology as the columnar crystals noted above with the importance of the {110} face increasing with impurity content (20). Analysis of the impurity content of defined sections of the crystals was carried out by HPLC using a Technopak C-18 reversed phase column with a 27% methanol/73% water mixture as eluant. This confirmed that the impurity which lay in the range 0.08–0.8%w/w depending on the degree of contamination of the solution, was located predominantly (95%) in the {110} sectors of the crystals.

Microhardness Indentation Testing

Microhardness indentation testing was performed using a Leitz Wetzlar Miniload 2 hardness tester equipped with a Leitz digital eyepiece using both Vickers and Knoop indentations at loads ranging from 0.049–0.147N. A dwell time of 30s was used in all tests. The temperature at which the tests were carried out was usually ~23°C.

For hardness measurement samples were chosen carefully. Crystals that were deformed, cracked or had a high content of inclusions were avoided. The crystals were mounted on a glass microscope slide using a double-sided adhesive tape, so that the surface to be indented was normal to the indentation direction. This was achieved by orienting the specimen stage to maximise the intensity of light reflected from the surfaces when the crystal was viewed under the microscope attachment. The 50x objective was then used to select the indentation site. The spacing between successive indents (~150μm) was sufficient to avoid interference and the zone within 2 mm of the edges of the crystal faces was avoided. Any badly formed or asymmetric indentations were ignored.

Residual impression sizes were measured using the digital measuring eyepiece of the Miniload tester which was recalibrated daily. Each hardness value quoted is the mean of

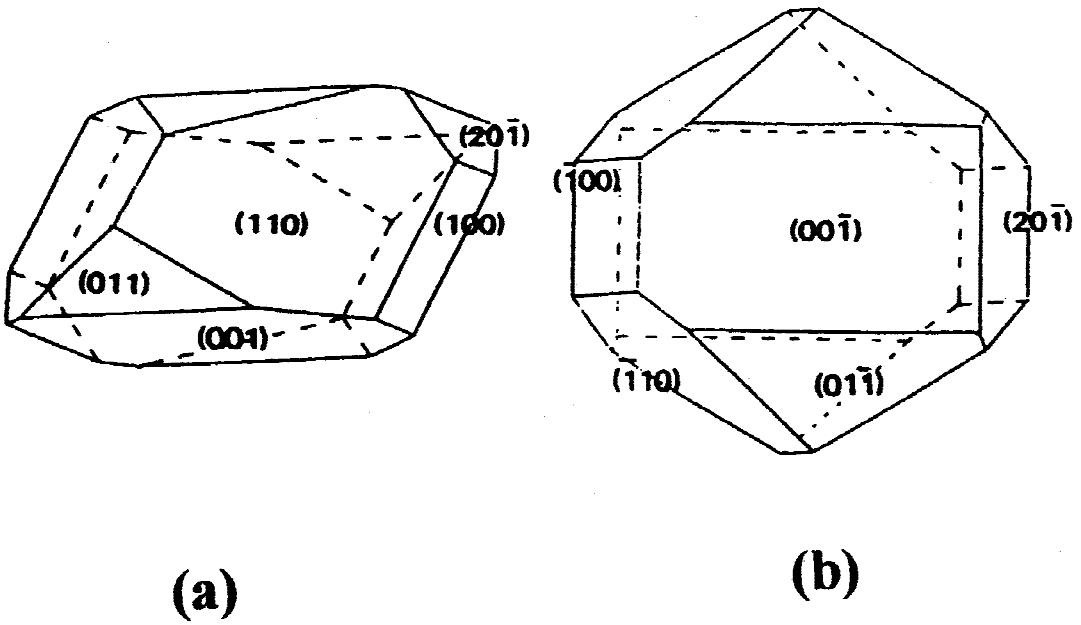

Fig. 1. Schematic morphologies of (a) columnar and (b) plate-like crystals of paracetamol grown at medium (s = 7–11%) and high (s > 11%) supersaturation respectively.

measurements made on at least 10 indentations on each face. The impressions were examined and photographed using a Leica-Reichert Polyvar 2 microscope. In carrying out the experiments and their analysis we adhered to the safeguards reported by Duncan-Hewitt *et al.* (16).

Dislocation Etching Studies

After indentation the microhardness impressions were etched using hexanol at 0°C to define the slip lines and directions. Prior to etching the mounted crystal was placed on

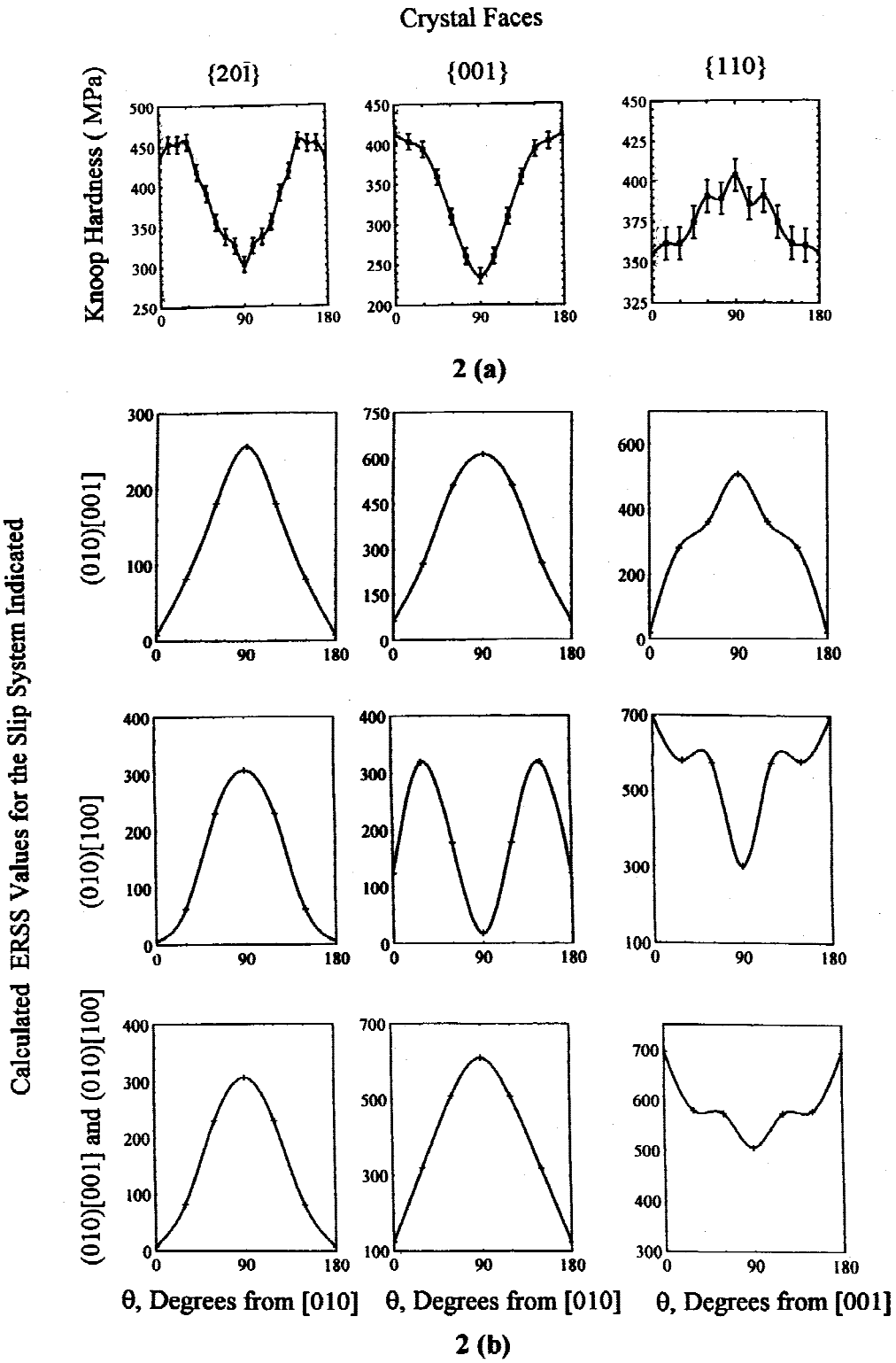

Fig. 2. (a) Experimentally observed hardness anisotropy curves for {20$\bar{1}$}, {001} and {110} surfaces. (b) The variation with orientation of the calculated ERSS values for the slip systems (010)[001], (010)[100] and (010)[001] and (010)[100].

the surface of ice to cool it slowly, so as to prevent thermal shock when the cold solvent was applied. The cooled etchant was applied by blotting a surface with soft tissue paper containing the solvent for 1–2 sec. any excess etchant was removed using soft paper. The surface was then examined and photographed under the optical microscope, concentrating on any patterns formed around indentation marks. More detailed examinations were made by atomic force microscopy (AFM) using a Quesant, Resolver 240 instrument in the z height scanning mode.

RESULTS

Vickers Indentation

Vickers indentations were made on the {001}, {110}, {011}, and {20$\bar{1}$} habit faces under loads of between 0.049N and 0.198N. The indenter diagonal was aligned parallel or perpendicular to [010] on the {001}, {011} and {20$\bar{1}$} faces and parallel to {001} on the {110} faces. The fracture discussed previously (18) caused some difficulty in assessing the size of the indentation and possibly could lead to an underestimation of the hardness. This error was minimised by using as high a load as was possible to maximise the size of the indent without causing distortion by fracture.

All faces of the pure crystals showed a similar hardness: {001}, 352–392MPa; {110}, 352–392MPa; {20$\bar{1}$}, 382–442Mpa, and {011}, 362–402MPa. This behaviour was also replicated for crystals doped with up to 0.8% (w/w) *p*-acetoxyacetanilide; ({110}, 382–442MPa). Thus we conclude that the incorporation of this impurity, which is known to concentrate in the {110} sectors (20) has no influence on the hardness.

The hardness impressions on all surfaces showed some evidence of the formation of slip lines around the impressions. On etching, those on the {110}, {001} and {20$\bar{1}$} were shown to comprise dislocation etch-pit alignments.

On all surfaces these alignments lay only along the intersection of the (010) planes with the surface. It is therefore defined that the dominant dislocation slip plane in paracetamol is (010).

Knoop Indentation

Knoop hardness was measured as a function of orientation using a Knoop indenter under a load of 0.198N. This load was found to give good indents when applied to the {001}, {20$\bar{1}$}, and {110} faces. For the {20$\bar{1}$} and {001} faces indentation orientation, $\theta_0 = 0$ corresponded to the alignment of the long axis of the indenter along the [010] direction and for {110} along the [001] direction. The results are presented in Figure 2a.

The {20 $\bar{1}$} faces showed a range of hardness between 304MPa and 456MPa with a minimum when the indenter was set at 90° to the [010] direction. The {001} faces showed a similar range of hardness with the softest direction when the indenter was parallel to [100]. The {110} face had a much narrower range of hardness, 353–402MPa with the maximum lying at 90° to [001].

Etch Pit Analysis

Besides assessing the orientational variation in hardness of the crystal surface the Knoop indentation can also be used to assess whether or not additional slip systems can be activated by the more anisotropic stress field.

Figure 3 shows indentations made at 0°, 45°, and 90° to the [001] direction on the {110} face and subsequently etched with hexanol. Despite the orientational variation in stress field the resulting slip lines and etch pit alignments again lie only along the line of intersection of the (010) plane with the surface. A similar result was obtained on other faces. This confirms this plane as the only slip plane in the system.

Further information on the nature of the dislocations, which glide on this plane, can be deduced from an examination of etch-pit geometry. Provided that the etch pits are well-defined geometrically with respect to the underlying crystal lattice, then the orientation of the point bottom of the pit relative to the surface shape defines the line direction of the emergent dislocation line (21). In the present case the extremely small size of the pits (Fig. 3) necessitated their observation and measurement by atomic force microscopy.

For each face, only one etch-pit geometry was seen. On

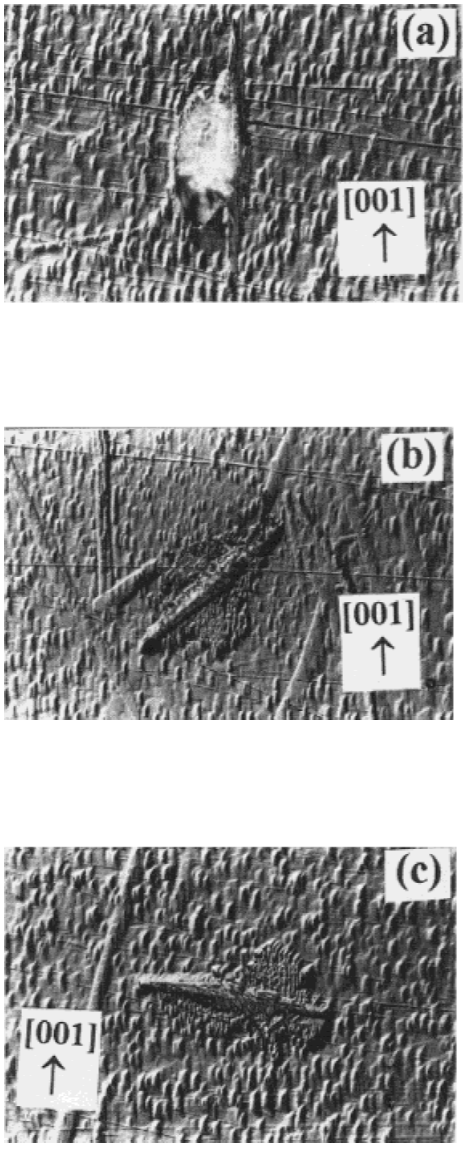

Fig. 3. Optical micrographs of etched indents made at (a) 0°, (b) 45°, and (c) 90° to the [001] direction on the {110} surfaces.

{001} it was observed that a "kite shaped" etch pit formed (Fig. 4a). The pit was elongated in the [100] direction and was seen to be symmetrical about this axis. The pit bottom was displaced slightly with respect to the "geometrical centre" of the etch pit and was coincident with its centre line. On measuring the pit with the AFM it was deduced that the line of the dislocation was [001].

On {110} faces irregular "trapezoidally" shaped etch pits were observed (Fig. 4b). There was no axis of symmetry for this etch pit and the pit bottom was displaced far from the geometric centre of the shape. Calculating the geometry, again with the aid of the AFM, it was shown that the dislocation had a line direction [100].

On {20$\bar{1}$} faces slightly elongated pentagonal shaped etch pits were observed (Fig. 4c). Once again the pit bottom was displaced along the [100] direction with respect to the geometric centre of the surface shape. The pit profile was analysed using the AFM to show that the dislocation line was directed along [001].

In summary, etch pits on the {001} and {20$\bar{1}$} faces were observed to be due to dislocations with a line direction [001] and those on the {110} face were defined to result from dislocations with [100] line directions. Since both of these line directions are in the set [h0l], they must lie in the (010) plane, giving further confirmation that the (010) is the unique slip plane.

On this basis it is most likely that the dislocation loops formed on the indentation of the {001}, {20$\bar{1}$} and {110} surfaces will have the geometry depicted in Fig. 5b.

Thus the emergent dislocations observed on these faces will be of the types (010)[001] on {001}, (010)[001] on {20$\bar{1}$}, and (010)[100] on {110}. The dislocation types (010)[100] and

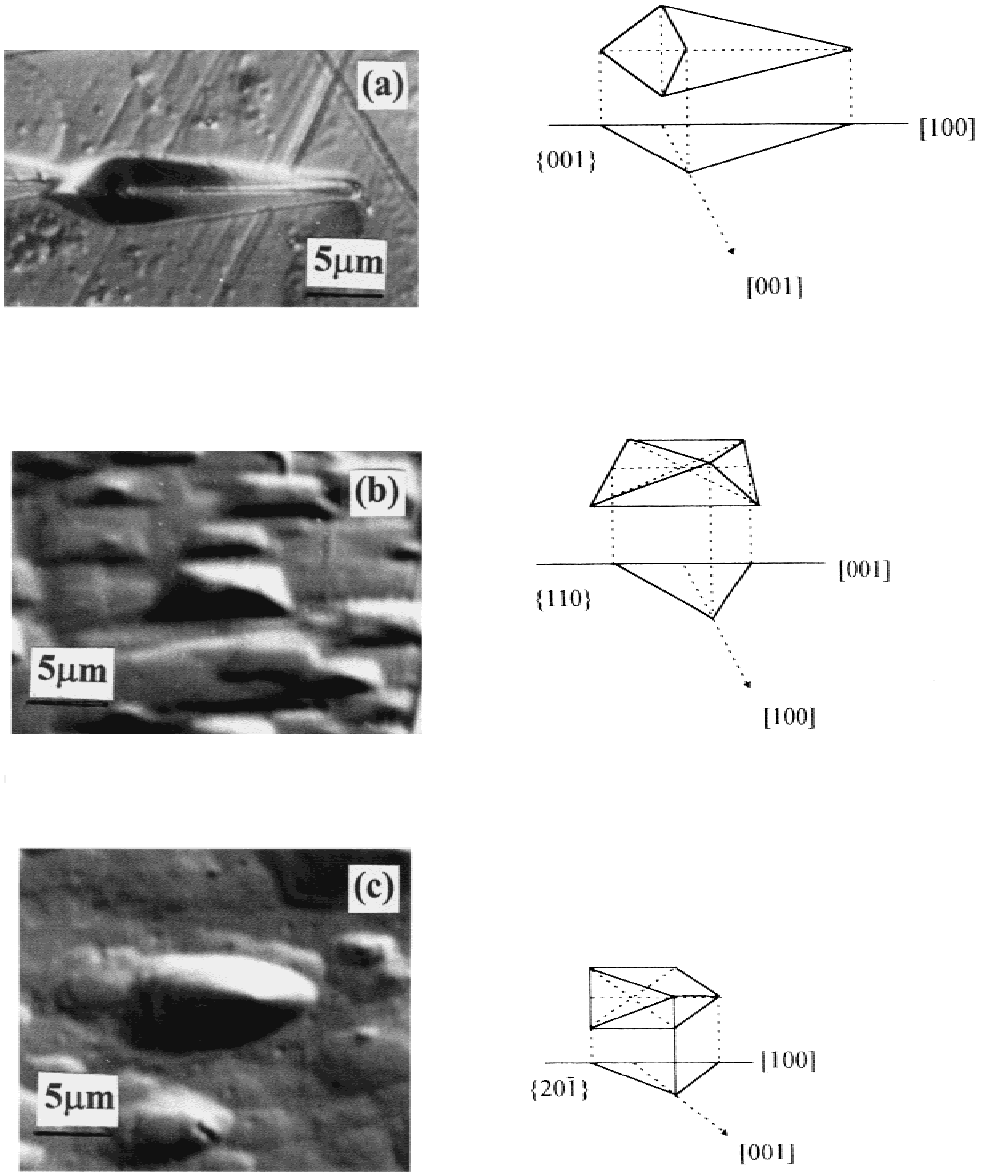

Fig. 4. Optical micrographs showing examples of the (a) "kite shaped", (b) "trapazoidally shaped" and (c) "pentagonally shaped" etch pits observed on previously indented {001}, {110} and {20$\bar{1}$} surfaces respectively. Also shown are schematic diagrams defining the dislocation direction for the three kinds of etch pits.

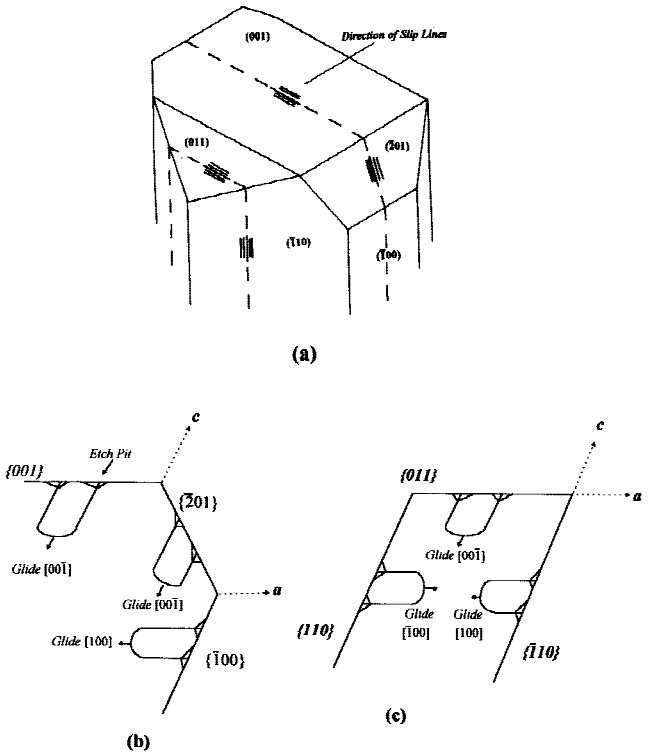

Fig. 5. (a) Schematic diagram of a paracetamol crystal showing the orientation of the slip lines on the form faces. (b) Schematic diagrams of the (010) plane with the representations of the two active slip systems.

(010)[001] would lie too close to the {001} and {110} faces respectively to be observed. Similarly, although dislocations of the type (010)[100] lie at a higher angle to the {20$\bar{1}$} face and might be observed, this angle is much less than that projected by the (010)[001] type and it is perhaps not surprising that they are not detected.

Theoretical Assessment

On the basis that the principal deformation mechanism in the indentation process is dislocation slip, Daniels and Dunn (22) have analysed the effective resolved shear stress (ERSS) developed under the Knoop indenter as a function of its orientation to the dominant slip systems. More recently, Brookes *et al.* (23) have amended and extended the theory to account for some minor discrepancies between theory and experiment in specific systems. Both analyses have been applied successfully to the orientational dependence of hardness in a range of solids, which are dominantly isotropic in character. We have extended successfully the application of the analysis to several anisotropic molecular materials of the present type and shown that the analysis can be used to confirm both the nature of the slip systems and, on this basis, the orientational dependence of the hardness of the material (24). At a later date the same correlation was attempted by Duncan-Hewitt, Mount, and Yu (16) for paracetamol. Regrettably their results were inconclusive. There was no distinct correlation between the experimental results and the theoretical prediction. To test our results we have repeated this calculation using the Brookes *et al.* analysis (23) and the two slip systems (010)[001] and (010)[100].

The results of the two calculations are presented in Figure 2b which shows the ERSS calculation as a function of orientation for the three primary faces of the paracetamol crystal assuming that deformation occurs by the given slip system. In comparing these with the experimental data it should be remembered that the ERSS is the converse of hardness and that a maximum in ERSS corresponds to a minimum in hardness and vice-versa.

It will be noted that neither prediction separately corresponds to the experimental variations. When both are considered simultaneously however, on the basis that the highest value of the applied stress corresponding to either slip system will operate at each orientation, then good agreement is found lending weight to our proposal. The calculations also predict our observation that the range of hardness on {110} should be smaller (~1/3) than on the other faces.

DISCUSSION

It is obvious from the good agreement between the experimental and theoretical approaches, that the hardness of the crystal is defined by the ease of slip of the proposed dislocation slip systems. It is of interest however to consider the geometry of the dislocations and their representation on the molecular scale.

Figure 6a and b show respectively the disposition of the paracetamol molecules on the "ab" plane viewed in the [001] direction and the "ac" plane viewed in the [010] direction. From these diagrams it will be seen that the molecules form corrugated hydrogen bonded sheets lying in the "ac" plane. These stack in the "b" direction in which they are bonded by van der Waals interactions. As a consequence of this relatively weak interplanar bonding the (010) plane should be the easiest slip plane for the same reason that it features as the cleavage and principal fracture plane (18), i.e. there are no strong bonds between the successive planes.

On this plane, slip in either the [001] or [100] direction should be easy. The orientation of the corrugation would appear to make a direct [001] translation the most favourable since this lies parallel to the corrugations. The Burgers vector would be $|\boldsymbol{b}_{[001]}| = 0.940$nm. In contrast [100] slip would proceed via a series of "partial like" motions across the corrugations to yield a Burgers vector $|\boldsymbol{b}_{[100]}| = |\boldsymbol{b}_1| + |\boldsymbol{b}_2| = 1.293$ nm. The significant difference in energy between the two $E_{[001]}/E_{[100]} \sim |\boldsymbol{b}_{[001]}|^2 / |\boldsymbol{b}_{[100]}|^2 = 88.36/167.18$ [25] coupled with the complicated nature of the slip process in the latter case means that the (010)[001] slip system should be more favourable. Both could however be easily activated as we observe. This of course is a simplistic view of the process of dislocation motion and the potential for more complex and perhaps even less energetic processes involving motion by partial dislocations should not be ignored.

We conclude that the weight of evidence points to the existence of two dislocation slip systems in paracetamol crystals, which will confer on the material a very low and anisotropic plasticity. As pointed out previously, highly ductile materials possess up to twelve equivalent slip systems (25).

The relatively low position of paracetamol amongst similar molecular materials can be defined in terms of the degree of development of the plastic region around the indentation, i.e. the extent of the dislocation distribution around the indentation and the load applied to cause this distribution. The

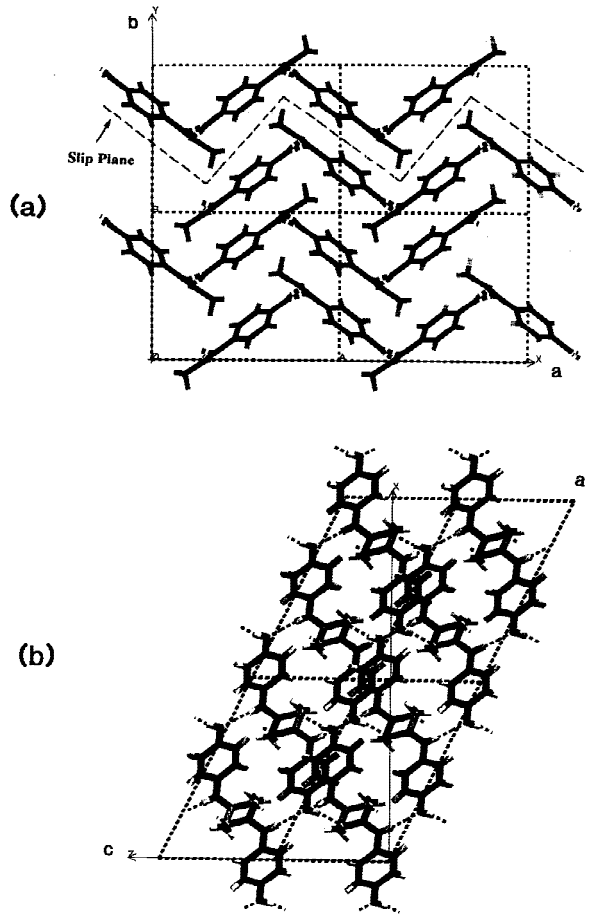

Fig. 6. Projection of the molecular packing of paracetamol on (a) the **ab** plane and (b) the **ac** plane. The sheet of molecules connected by hydrogen bonds is elongated along the [001] direction. The dotted line in (a) shows the cleavage plane, (010).

current range of data presented in Tables I and II show the general limited range of plasticity of these materials and the identified slip systems respectively. The position of paracetamol is consistent with its relative hardness and with the observation that, under tension, crystals can only be extended by $1/10^6$ before fracture (26). This value is considerably lower than a value of $1/10^2$ quoted by Shekunov *et al.*. (27) in a recent publication on paracetamol and which would be more characteristic of a ductile metal such as copper.

Table I. Comparison of the Mechanical Properties of Paracetamol with Those of Other Organic Solids

Material	Face	Range of H_V (MPa)	Range of H_K (MPa)	Extent of deformation μm (load, g)
Paracetamol	{001}	352–392	235–412	50 μm (50 g)
	{20$\bar{1}$}	382–442	304–456	45 μm (50 g)
	{110}	352–392	353–402	55 μm (50 g)
	{011}	362–402		40 μg (50 g)
RDX (24)	{210}	372–382	314–431	91 μm (50 g)
PETN (24)	{110}	147–167	127–245	160 μg (20 g)
	{101}	157–167	137–176	160 μg (20 g)
Adamantane (28)	{222}	40–50	40–60	100 μg (1 g)

Table II. The Geometry of Dislocation Slip Systems in Several Organic Solids

Material	Crystal system	Dislocation geometry	Number of distinct slip systems
Paracetamol	Monoclinic	(010) [001]	
		(010) [100]	2
RDX (24)	Monoclinic	(010) [001]	
		{021} [100]	3
PETN (24)	Orthorhombic	{110} ⟨111⟩	4
Adamantane (28)	FCC	{111} ⟨101⟩	12
dl Camphor (29)	FCC	{111} ⟨101⟩	12

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