High-pressure studies of pharmaceutical compounds and energetic materials

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The effects of high pressure on pharmaceutical compounds and energetic materials can have important implications for both the properties and performance of these important classes of material. Pharmaceutical compounds are frequently subjected to pressure during processing and formulation, causing interconversion between solid forms that may affect properties such as solubility and bio-availability. Energetic materials experience extremes of both pressure and temperature under conditions of detonation and deflagration, causing changes in properties such as sensitivity to shock and chemical reactivity. This *tutorial review* outlines the various methods used to study these materials at high pressure, describes how pressure can be used to explore polymorphism, and provides examples of compounds that have been studied at high pressure.

1. Introduction

Although high pressure has been used extensively to study a range of materials that include metals, semiconductors, superconductors, minerals, and ices, two classes of material that have received rather less attention are pharmaceutical compounds and energetic materials (explosives, propellants, pyrotechnics, and gas generators). Nevertheless, the responses of these important materials to high pressure are of great interest; this is especially true for explosives, which experience extremes of both pressure and temperature under detonation and deflagration conditions.

The scope of this article includes a brief outline of the importance of polymorphism in molecular materials, the various techniques used to study these materials under pressure, examples of pharmaceutical compounds and energetic materials that have been studied at high pressure, and an indication of some of the possible directions that future research in these areas could take. Included in the section on pharmaceuticals is a brief summary of how the structures of simple organic compounds such as amino acids respond to pressure.

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2. Polymorphism

Before discussing these materials in detail, it is useful to introduce the concept of polymorphism and its importance in molecular materials. This topic has been comprehensively reviewed by Bernstein.[1] Polymorphism (from the Greek meaning "existing in multiple forms") is a term that is used in many disciplines. In chemistry and materials science, it refers to a substance that can adopt more than one crystal structure in the solid state; these different crystalline forms are termed *polymorphs*. The term *pseudo-polymorphism* is sometimes applied to hydrates and solvates and has been widely used in older literature, although its use is confusing and is

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Colin R. Pulham graduated in Chemistry from the University of Oxford in 1987 and remained there to work in the group of Prof. A. J. Downs, as a graduate student and then as a postdoctoral research associate studying volatile hydrides of Group 13. In 1992 he was awarded a Royal Society University Research Fellowship and moved to the School of Chemistry at the University of Edinburgh, where he was subsequently appointed as a member of academic staff. His interest in high-pressure research was inspired by a good friend and colleague, Dr David R. Allan, and an active programme of research into the effects of pressure on molecular materials has now been established.

now discouraged. A good example of the dramatic differences between the properties of polymorphs is provided by three common forms (allotropes) of elemental carbon: diamond, graphite, and C_{60} (Buckminsterfullerene). Graphite is a black, soft, electrically conducting and chemically reactive material, whilst diamond is optically transparent, hard, electrically insulating and chemically rather inert. In contrast to both graphite and diamond, Buckminsterfullerene is soluble in aromatic solvents and can be vaporised at relatively low temperatures. These differences in properties arise entirely from the different crystal structures adopted by each of the allotropes, which are illustrated in Fig. 1. In a similar way, molecules and ions may pack together in different ways in the crystal to form polymorphs. The main properties affected by polymorphism are melting and sublimation temperature, heat capacity, conductivity, solubility, density, dissolution rate, stability (to temperature and pressure), hygroscopicity, colour, and solid-state chemistry.[1] Important techniques that are used to study polymorphism in molecular materials include infrared and Raman spectroscopy, differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), optical polarising microscopy, powder and single-crystal X-ray diffraction, and solid-state NMR spectroscopy.[1] In recent years, there have been significant developments in the use of computational methods to predict crystal structures of polymorphs although there remain substantial challenges before these techniques can be widely and routinely applied.[2]

3. Polymorphism in pharmaceutical compounds

The phenomenon of polymorphism (and solvate formation) in the pharmaceutical industry is particularly important for the following reasons:

Bio-availability

Most drugs are administered in the solid form and rely on dissolution in the gastro-intestinal tract for their action. Hence if two polymorphs of the same drug compound have very different solubilities, then the bio-availabilities of the two forms may be very different with implications for administration of the correct dosage to the patient.

Processibility and storage

Drug materials go through several stages of processing before being finally incorporated into tablets. These may include crystallisation, milling, freeze drying, wet granulation, mixing with excipients, and tabletting. Once formed, tablets may be exposed to a wide range of temperatures and humidities depending on where they are stored and used. Different polymorphs may respond very differently to these processes and so polymorph selection and control is crucial. Perhaps the most striking example of the potential impact of polymorphism in the pharmaceutical industry to date is represented by the case of Ritonavir, a protease inhibitor for HIV. This was marketed in 1996 as a semi-solid capsule in liquid formulation, but in 1998 many final product lots failed a dissolution test, caused by the sudden appearance of a new, thermodynamically more stable polymorph that was consequently much less soluble. A new formulation to accommodate the new form was designed and a controlled process was established to generate consistently the initial form, but the company lost substantial revenue during the year that the drug was withdrawn for reformulation.[1]

Regulatory authorities

On account of the potential risks to patients, regulatory authorities such as the US Food and Drug Administration (FDA) now demand detailed information about drug polymorphs (polymorph types, reproducibility of manufacturing, and purity levels) before granting licenses for product distribution.

Intellectual property

Different polymorphs of a drug compound can be patented, and so intellectual property can also become an issue for the pharmaceutical companies who develop and market new drug products. Challenges to patents on the basis of polymorphism are therefore becoming increasingly frequent and very expensive.[1]

For these reasons, pharmaceutical companies employ substantial effort in the identification and characterisation of as many polymorphs as possible, and in the control of the processes used for their manufacture.

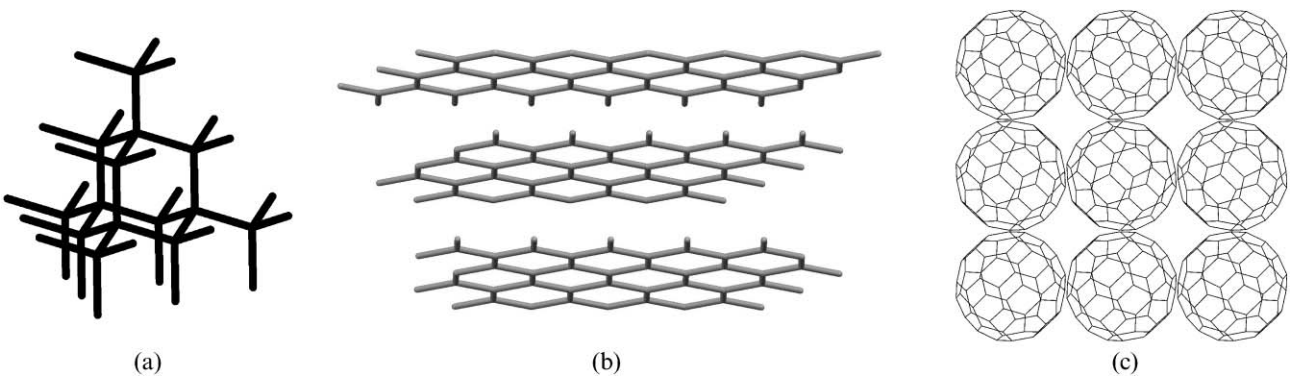

Fig. 1 Crystal structures of (a) diamond, (b) graphite, and (c) C_{60}.

4. Effects of pressure on pharmaceutical compounds

4.1 Milling and tabletting

Given the unrivalled ability of pressure to modify the structures and properties of metals, minerals, and ices, it should be anticipated that molecular compounds such as pharmaceuticals should also be susceptible to the effects of pressure. This section focuses first on the effects of two types of processing commonly used within the pharmaceutical industry, namely milling (or mechanical grinding) and tabletting.[3] Milling is used to reduce particle size and to ensure homogeneity of the formulation. Under these conditions the material can experience significant localised compression and shear stress, in addition to localised heating. Milling therefore results not only in an increase in surface area, but can also lead to the formation of various defects in the crystals such as fractures and dislocations. If the number of defects in the crystal becomes large, this can lead ultimately to the disappearance of long range order and crystallinity, *i.e.* the material becomes amorphous. Amorphisation leads to large increases in both the rate of dissolution and the solubility of the substance, and in some cases this can be very desirable for drug delivery, particularly when the solubility of the crystalline form is very low. Cephalexine, cephalotine, and griseofulvine are just a few of the many such examples that have been reported.[4]

Under the conditions of milling or grinding some pharmaceutical substances may undergo a phase transition to a different polymorphic form. Thus the grinding of the α- β- and δ-forms of phenylbutazone at 4 °C has been reported to give the ζ-form, which subsequently transformed to the ε-form.[5] The phase transitions were strongly temperature dependent and different behaviour was observed when the compound was ground at 35 °C.[5] Metastable forms of chloramphenicol palmitate, caffeine, cimetidine, and paracetamol have also been transformed to more stable polymorphs by grinding.[3,6] Grinding of sulfathiazole form III resulted initially in the formation of a non-crystalline phase that subsequently transformed on further grinding to form I.[7]

There is also some interest in the use of mechanochemical methods for the synthesis of pharmaceutical compounds, on the basis that direct reaction between the reactants under mechanical action can remove the requirement for solvent and the associated processing steps such as filtration and vacuum drying.[4] Mechanochemical reactions may also result in purer products compared with corresponding reactions using solvent, thereby obviating the requirement for subsequent purification steps.[4,8] It is clear that at least for some of these solid-state mechanochemical reactions, the high pressures and/or temperatures generated locally play a key role in the outcome of a reaction, but at present the mechanisms remain only poorly understood.

Tabletting involves the direct compression of the pharmaceutical substance with other excipients (*e.g.* starch, lactose, magnesium stearate) that serve a range of purposes that include binding the tablet together, dispersal of the active ingredient, enhancing the thermal and chemical stability of the active ingredient, and imparting colour to the tablet. The pressures produced during tabletting are generally in the range 40–200 MPa and these are applied for relatively short times (typically <1 second). For many pharmaceutical substances routine quality control studies have shown that these conditions are insufficient to induce polymorphic transitions or induce a significant degree of amorphisation. There are, however, several pharmaceutical substances that have been shown to undergo changes in phase composition under compression conditions. Particularly striking is a study of 32 pharmaceutical substances known to be polymorphic, which showed that 11 of these transformed either completely or partially into other polymorphs.[9] In this study, tablets were produced using compression and were subsequently sectioned in order that thermal analysis could be used to investigate polymorphic changes for various zones within the tablets. Thus the metastable form of caffeine was found to transform to the stable form on compression in the range 100–400 MPa, and the extent of transformation was found to depend on the zone of the tablet, the pressure applied, and the particle size of the powder.[9] The results of the study showed that the compression of metastable phases caused transformation to the most stable polymorph. Other drug compounds that have been shown to be susceptible to compression-induced polymorphic transformations when metastable forms are compressed include: fostedil (form II transformed to the more stable form I on grinding); carbamazepine dihydrate (unstable to compression); and chlorpropamide (forms A and C interconverted *via* compression-induced formation of a non-crystalline form).[3,4] A recent study of indomethacin highlights how the relative stability of a polymorph can be modified by pressure.[10] Thus at ambient pressure the α-form in an ethanol slurry transformed to give the more stable γ-form, but compression of an ethanol slurry of the γ-form to 400 MPa resulted in formation of the α-form. This study also illustrates the importance of the solvent in mediating phase transitions–compression of the γ-form in the absence of solvent did not result in a phase transition.

4.2 Pharmaceuticals and supercritical fluids

A supercritical fluid is any substance at a temperature and pressure above its thermodynamic critical point. At the critical point, the densities of the equilibrium liquid phase and the saturated vapour phases become equal, resulting in the formation of a single supercritical phase. Supercritical fluids often have desirable properties such as low viscosity, high diffusion rate, and enhanced solubilities of solutes. Supercritical carbon dioxide is a particularly attractive medium as it is non-toxic and has a relatively low critical temperature and pressure (critical point 304.1 K and 7.38 MPa). It has therefore been used in pharmaceutical applications for particle size reduction and for preparation of micro-spheres and micro-emulsions. A recent study reported the formation of a new polymorph of deoxycholic acid after dissolution of the known form in supercritical carbon dioxide at a pressure of 12 MPa and a temperature of 333 K.[11]

5. *In situ* structural studies of pharmaceuticals and related compounds at high pressure

5.1 The diamond-anvil cell

The studies described so far have focused on the compression and grinding of pharmaceutical solids or treatment under supercritical conditions, with subsequent analysis of the transformed material. Furthermore, the pressures that have been used in these studies have been relatively modest. An ideal method for *in situ* studies of materials at high pressures is the diamond-anvil cell (DAC), and this apparatus has revolutionised high-pressure research in a wide range of areas.[12] The assembly of the gasketed diamond-anvil cell is illustrated in Fig. 2. A force is applied to the large table faces of two parallel, opposing gem-quality diamonds. This force is multiplied at the small culet faces, penetrating and sealing a metal gasket that contains the sample, and pressure is generated in the sample chamber. Designs of diamond-anvil cells are available that allow the attainment of pressures in excess of 100 GPa. Since diamond is transparent to visible light and to large portions of the X-ray spectrum, the DAC is ideally suited for *in situ* spectroscopic and diffraction studies of materials at high pressures.

So far, there have been relatively few high-pressure studies of pharmaceuticals using diamond-anvil cells, but it is an area that is growing in importance and the next sections highlight and summarise some examples of recent studies on pharmaceuticals and related organic compounds.

5.2 Direct compression of paracetamol

Paracetamol (acetaminophen) is a widely used analgesic that has been extensively studied using a range of techniques and its molecular structure is shown in Fig. 3. Under ambient conditions the monoclinic form I is thermodynamically stable (mp 170 °C), and a metastable orthorhombic form II (mp 157 °C) has been prepared. Both forms have been structurally characterised and packing is dominated by the formation of N–H···OH and O–H···O=C hydrogen bonds that give rise to layered 2-D networks. In the monoclinic form,

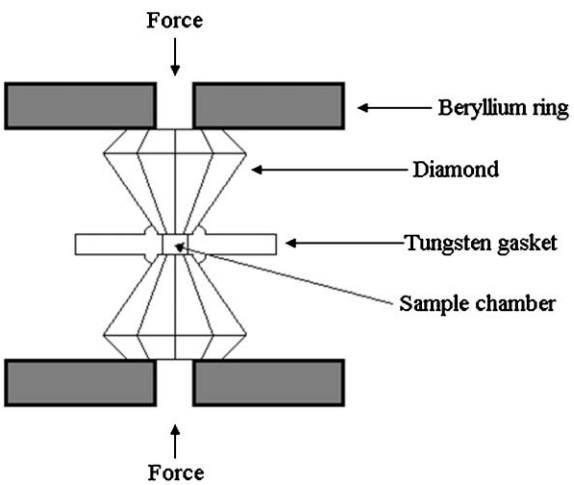

Fig. 2 Schematic assembly of a typical Merrill–Bassett diamond-anvil cell.

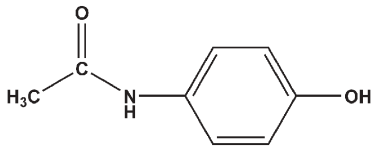

Fig. 3 Molecular structure of paracetamol.

the hydrogen-bonded layers are arranged parallel to the (010) planes: these give rise to polar layers, shown in Fig. 4a, where all the molecules have the methyl group on the left. In the orthorhombic polymorph, glide planes run perpendicular to the layers: methyl groups lie on the left- and right-hand sides of the molecules to form non-polar layers depicted in Fig. 4b. Despite the differences in structure, Boldyreva *et al*. found that both polymorphs have very similar bulk compressibilities (*i.e.* the relative volume decrease as a function of pressure) leading to a *ca.* 20% decrease in volume from ambient pressure to 4.0 GPa.[13] The study also noted that hydrogen bonds that are already quite short are less compressible than longer hydrogen bonds. Whilst bulk compressibilities of materials are useful, more information about the response of a material to pressure at the molecular level can be gleaned by studying the anisotropy of the distortion, *i.e.* how the individual lattice parameters (a, b, c, α, β, and γ) change. The directional character of intermolecular interactions found in organic molecules and their general appreciable asphericity induce significant anisotropy in the response of these crystals to

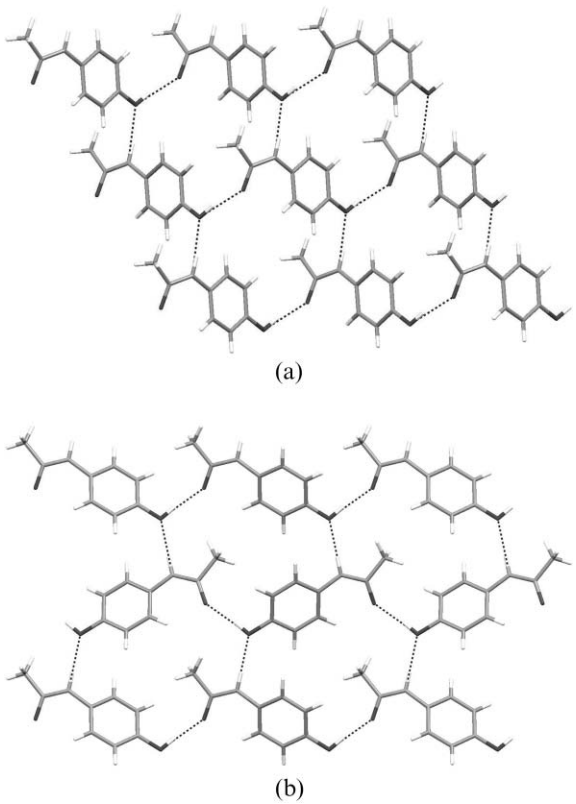

Fig. 4 Hydrogen-bonded layers in (a) monoclinic paracetamol (form I) viewed along the b axis and (b) orthorhombic paracetamol (form II) viewed along the c axis.

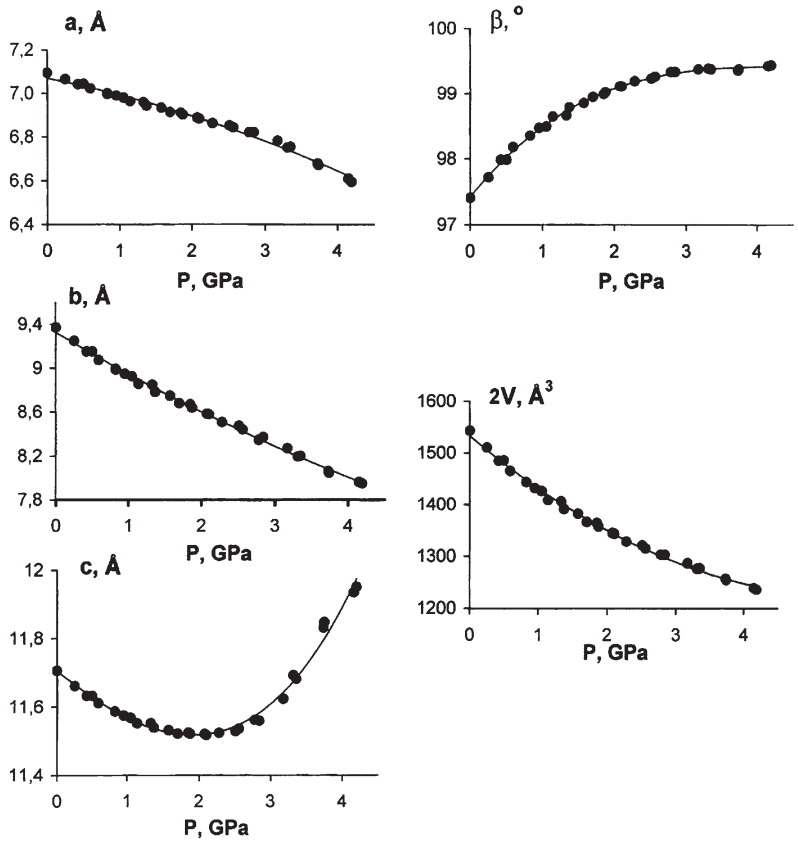

Fig. 5 Changes in cell volume (V) and lattice parameters (a, b, c, β) *versus* pressure for the monoclinic form of paracetamol. (Reprinted with permission from reference 13. Copyright 2003 Elsevier.)

pressure. Such studies can show surprising results, as illustrated by the response of the monoclinic polymorph (form I) of paracetamol for which some of the lattice parameters decrease, but some actually *increase* (see Fig. 5).[13] This is a consequence of the expansion of the molecular layers in some directions due to cooperative rotation of molecules and flattening of the hydrogen-bonded layers within the layer, which accompanies shortening of the intermolecular hydrogen bonds. Strictly speaking, rationalisation of changes at a structural level as a function of pressure should be related to the linear strain in the directions of the principal axes of the strain ellipsoid rather than to the compressibilities of lattice parameters. This is because the unit cell is monoclinic and so two of the strain tensor axes do not necessarily lie along the unit-cell axes. For form II, isotropic compression in the planes of the hydrogen-bonded layers occurred due to the cooperative contraction of the hydrogen-bonded network.[13] For both forms the direction of maximum compressibility correlates with the orientation of molecular layers and is in fact perpendicular to the layers.[13] For other molecular systems anisotropic distortion can be associated with other features of the crystal structure. Thus for both the analgesic drug phenacetin (*p*-ethoxyacetanilide) and for urea, the maximum compressibility was found to be in the direction perpendicular to the chains of molecules linked by hydrogen bonds, whilst for benzoquinone and polymorphs of glycine the maximum and minimum compression correlated well with the directions of the weaker and stronger hydrogen bonds, respectively.[13] Boldyreva *et al.* also demonstrated that the application of pressures in excess of 4 GPa to powder samples of paracetamol resulted in conversion of form I into form II, but for kinetic reasons the conversion was incomplete, poorly reproducible, and no conversion was observed in a single crystal.[6] Such a transition would require reorientation of every other chain in a layer and hence the breaking/reforming of many intermolecular hydrogen bonds, leading to a high activation energy. If the process is also limited by nucleation, it is even less likely to occur within the bulk of the crystal, perhaps explaining why the transition was not observed in a single crystal. This example of paracetamol illustrates the difficulties associated with using direct compression to induce phase transitions in pharmaceutical compounds that contain relatively large molecules which are often extensively hydrogen bonded. The application of pressure alone (even pressures as high as 10 GPa) does not guarantee a phase transition and even in favourable cases interconversion is often incomplete.

5.3 Direct compression of amino acids

One notable class of organic compound for which direct compression of the solid frequently *does* result in polymorphic transformations is represented by the amino acids glycine,[14,15] L-serine and L-cysteine.[16] Amino acids are simple molecules that are the building blocks for polypeptides and proteins, and are often used in the synthesis of larger pharmaceutical molecules. The study of simple compounds containing a

particular functional group is a crucial step towards the understanding of interactions, bonding characteristics and packing motifs of specific classes of compounds. Hence, whilst α-glycine did not transform up to 23 GPa, β-glycine underwent a single-crystal to single-crystal phase transition to yield the δ-form at 0.76 GPa. The γ-form underwent a sluggish transition to a polycrystalline high-pressure ε-form, which started at 1.9 GPa, but was not complete until 4.3 GPa. For L-serine, a transformation to a high-pressure polymorph was observed at 4.8 GPa. The high-pressure behaviour of L-cysteine-I involved an initial single-crystal to single-crystal transition above 1.8 GPa to form III. On decompression of form III to 1.7 GPa a single-crystal to single-crystal transition to form IV was observed, followed by recovery of form I on decompression to ambient pressure. General phenomena that have been observed in these and other compression studies include the tendency for collapse of structural voids and a substantial shortening of hydrogen bonds and other intermolecular interactions. At least in the pressure regime up to *ca.* 10 GPa intermolecular interactions appear to shorten until a minimum distance is attained, this minimum distance being no shorter than the shortest such interactions observed at ambient pressure. Compression beyond this point does not therefore result in the formation of a super-short interaction, but instead is more likely to cause the onset of a phase transition. Conformational changes in flexible molecules are also observed, allowing molecules to adjust to the strain of their surroundings. It is presumably this conformational flexibility that permits phase transitions in single crystals without destruction of the single crystal.

5.4 *In situ* growth of crystals at high pressure

It is clear that even though the application of pressure to compounds containing larger organic molecules may thermodynamically favour the adoption of a new polymorphic form, there is often a substantial kinetic barrier to be overcome before the molecules can rearrange. One potential solution to this problem is to crystallise the material from the melt at high pressure, and this has been used to prepare and characterise new polymorphs of simple low-melting molecular organic and inorganic compounds such as ketones, alcohols, carboxylic acids, amines, chloroalkanes, chlorosilanes, and mineral acids.[17,18] In this method, pressure-induced freezing of a liquid inside a diamond-anvil cell results in the formation of polycrystalline material and the cell is then heated in order to melt the sample until only a single crystallite remains. This acts as a seed from which a larger single crystal grows from the cooling melt under pressure. This process is illustrated in Fig. 6 by the growth of a single crystal of a high-pressure polymorph of acetic acid at 0.2 GPa. This new polymorph packs in a more efficient manner than the low-temperature form *via* puckering of hydrogen-bonded molecular layers.[19] Another structural trend indicative of increased packing efficiency at high-pressure is observed in the structures of simple alcohols, where high pressure overcomes the steric effect of bulky alkyl groups, forcing them to behave like less bulky groups, which arrange themselves in a packing motif characteristic of small alcohols.[17]

Whilst pressure-induced freezing of a liquid is a very powerful method for accessing new polymorphs from compounds with relatively low melting points, it is less applicable to compounds such as pharmaceuticals that typically have melting points significantly higher than ambient temperature. The problem is made more difficult by the substantial increase in melting point induced in most substances by the application of pressure. Generally decomposition or some undesirable chemical reaction takes place before the compound melts, and initial studies on pharmaceutical compounds have been hampered by these problems. These have been overcome by growing single crystals or polycrystalline material *from solution* at high pressure. In this method, a diamond-anvil cell is first loaded with a solution of the compound and then is pressurised. Pressurisation usually causes a decrease in the solubility of the compound and results in precipitation of polycrystalline material, often as a high-pressure form. This powder can then be studied *in situ* by spectroscopic methods and by powder X-ray diffraction. Alternatively, by carefully raising the temperature of the sample it is often possible to dissolve all but one of the crystallites, which on subsequent

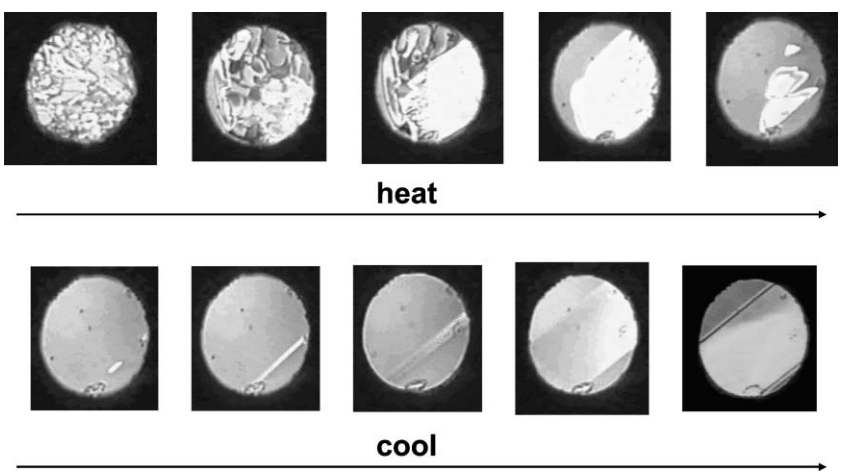

Fig. 6 Sequence of optical images illustrating the growth of a single crystal of the high-pressure phase of acetic acid from polycrystalline material crystallised *in situ* in a DAC at 0.2 GPa. (Figure used with the permission of D. R. Allan.)

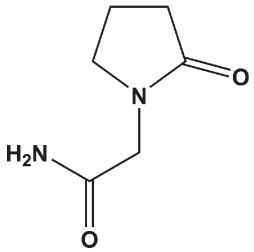

Fig. 7 Molecular structure of piracetam.

cooling then acts as a seed for the growth of a large single crystal suitable for study by single-crystal X-ray diffraction.

In this way, crystallisation of paracetamol from a solution in ethanol at 1.1 GPa resulted in the formation of a single crystal of the orthorhombic form II.[20] Compared with the direct compression study described earlier, much more modest pressures are required and conversion is complete, thereby indicating that the high-pressure recrystallisation technique is able to overcome the kinetic barriers associated with interconversion of polymorphs in the solid state. High-pressure recrystallisation from solution has also allowed access to novel solvates of paracetamol. Thus high-pressure recrystallisation of paracetamol from water or methanol gives a dihydrate[20] and a 1 : 1 methanol solvate,[21] respectively.

Another example of the success of high-pressure recrystallisation is in the discovery of a new polymorph of the drug piracetam. Piracetam (or 2-oxo-pyrrolidineacetamide) is used to treat conditions of age-associated mental decline and disorders of the nervous system (see Fig. 7 for molecular structure). At ambient pressure, three polymorphs (I, II, and III) are known, but recrystallisation from water at 0.4 GPa results in the formation of a new form IV in which the molecular packing arrangement is very different from those of the known forms.[22]

The piracetam molecules also adopt a very different conformation in this new phase (Fig. 8).

Depressurisation to ambient pressure resulted in the formation of form II *via* a single-crystal to single-crystal transition. These studies demonstrate that the use of high pressure as an additional dimension in exploring polymorphism and solvate formation in pharmaceutical compounds is particularly powerful not only for the preparation and identification of new forms, but also in understanding how different forms interconvert.

The discovery and characterisation of the new form IV of piracetam has also provided an excellent opportunity to test recent developments in crystal structure prediction and has highlighted the interplay between theory and experiment.[2] Approaches to crystal structure prediction involve the calculation of the molecular structure by *ab initio* optimisation (*i.e.* estimating the gas phase conformation), followed by modelling of the intermolecular interactions in the crystal to give the lattice energy. Several hundreds of potential crystal structures are generated in this way with a range of different energies. If the effects of temperature and zero-point motion are ignored, the most stable structure is the one with the most negative lattice energy (using the definition of lattice energy as the energy released when molecules/ions are brought from infinity to their positions in the crystal). The case of piracetam was particularly challenging because the gas-phase conformation is different from the conformations observed in the crystalline forms. Nevertheless, through a systematic exploration of conformational space, the authors successfully identified form IV as the most favourable computed crystal structure with a very distinct and different conformation from the previously known polymorphs.[2]

6. Introduction to energetic materials

Energetic materials are defined as those that release heat and/or gaseous products at a high rate upon stimulus by heat, impact, shock, spark, *etc*. They can be broadly classified as explosives, propellants, gas generators, and pyrotechnics. Explosives can be further classified as (a) primary explosives for which a mild impetus leads to a short, strong shock wave, and (b) secondary explosives for which a strong impetus leads to a long-duration shock wave.[23] Primary explosives result in shock waves that have a strong local effect, but which do much less damage over longer distances and so their main function is to act as an initiator for the detonation of a secondary explosive. Examples of primary explosives include lead azide [$Pb(N_3)_2$], lead styphnate (lead 2,4,6-trinitroresorcinate), and mercury fulminate [$Hg(ONC)_2$]. Once initiated, a secondary explosive liberates a large amount of energy and hence a sustained shock wave that causes more damage at a distance. Examples of secondary explosives include trinitrotoluene (TNT), HMX (1,3,5,7-tetranitro-1,3,5,7-tetrazacyclooctane), and RDX (1,3,5-trinitrohexahydro-*s*-1,3,5-triazine). The molecular structures of these compounds are shown in Fig. 9.

The performance of energetic materials can depend on a number of factors that include: sensitivity to detonation by stimulus; the rate of the deflagration-to-detonation transition (*i.e.* a burning reaction that changes to a much faster reaction); the detonation velocity and pressure; the chemical reactivity; the thermal and stability; the crystal density; and crystal morphology. Many of these factors depend on the solid-state structure of the energetic material and hence the performance of the material may be highly dependent on the particular polymorph that is used. The sensitivity of a crystal to shock can depend not only on the orientation of a crystal, but also on which polymorphic form is present. Thus the widely used

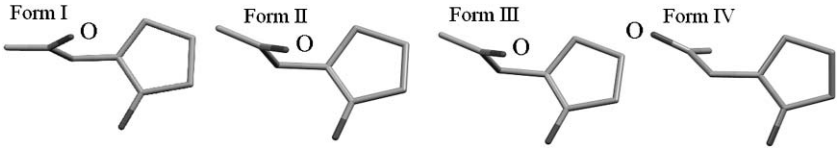

Fig. 8 Molecular conformations adopted by piracetam molecules in each polymorph.

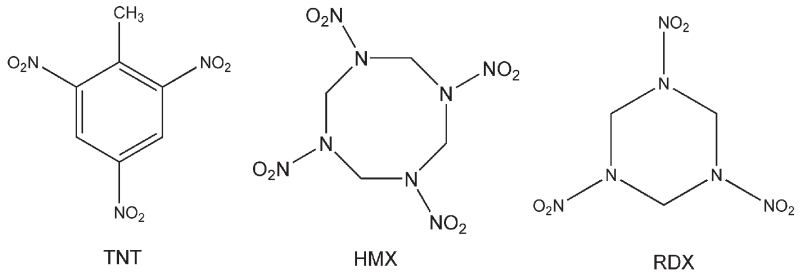

Fig. 9 Molecular structures of TNT, HMX, and RDX.

explosive HMX can exist as 4 crystalline forms (the γ-form is actually a hydrated form rather than a true polymorph) and the sensitivity to impact is in the order $\delta > \gamma > \alpha > \beta$.[24] The high sensitivities of the other polymorphs of HMX and associated risk of accidental detonation mean that only β-HMX is permitted in HMX-containing munitions used by the UK armed forces. Different polymorphs may have substantially different densities; this is important because, to a first approximation, the detonation velocity of an energetic material is proportional to density. Where possible, the densest polymorph of an energetic compound is selected because many applications of energetic materials are volume limited. The crystal morphology of a given polymorph also governs how well material can be processed and packaged, *e.g.* prismatic crystals pack more efficiently than crystals with rod, needle, or platelet morphologies. Solid-solid phase transitions in energetic materials are also important because crystals may develop surface and internal defects, and particle size may be reduced. It is generally true that the more defects in a crystalline explosive, the easier it is to initiate, because these defect sites are where explosive reaction is initiated. Thus the sensitivity of an energetic material to initiation is related to the number of defects in a crystal, and indeed a perfect crystal of a high explosive is a very poor explosive. The question as to how mechanical energy can couple to molecules in order to initiate a chemical reaction is of fundamental importance and continues to be the subject of discussion (see chapter 1 by Brill in ref. 26). One of the early models envisages that during the initiation process and associated compression, energy becomes concentrated at defect sites because of cavitation and/or frictional heating. "Hot-spots" are formed and it is from these that the reaction front propagates outward leading to a violent runaway reaction. Other models consider preferential "up-pumping" (or excitation) of specific vibrational modes at defect sites in the lattice leading to greater local heating at defect sites compared to ordered sites in the crystal lattice. This causes molecules at defect sites to heat more rapidly and to a higher temperature than those in the rest of the lattice. Shear stresses can also play an important role in initiation processes.

A particularly striking example is provided by ammonium nitrate, which undergoes a phase transition between form IV and form III at 32 °C that results in a significant volume increase. Repeated temperature cycling through this transition caused by fluctuations in ambient temperature results in fracturing of crystallites to form a finely divided powder that has a tendency to cake. This powder contains numerous defects making it more sensitive to accidental detonation when attempts are made to break up the caked salt.

Hence polymorphism and phase transitions can alter the sensitivity and performance of an energetic material in a complex manner, and since a key requirement for their use is reproducibility in performance, the polymorphic behaviour of these materials has been extensively studied. Bernstein has summarised much of this information in an excellent review.[1]

7. Energetic materials at high pressure

7.1 Methods for studying energetic materials at high pressures

During the detonation of an explosive material, the shock wave may produce pressures of up to 50 GPa and temperatures up to 5500 K.[25] These extreme conditions result in polymorphic transitions and the initiation of chemical reactions. Hence in order to gain better understanding of the processes occurring during the use of energetic materials, substantial effort has been expended in studying the properties and chemistry of these compounds at high pressures and/or high temperatures. A comprehensive review of experimental and computational methods to characterise decomposition, combustion, and detonation of energetic materials has recently been published.[26]

Three general methods for the study of these materials at high pressures have been employed: (i) direct static compression, (ii) dynamic shock-wave studies, and (iii) computational studies. Direct static compression generally involves compression of the sample in a diamond-anvil cell up to pressures of ~30 GPa and temperatures up to 650 K. The sample can then be studied *in situ* using spectroscopic and diffraction methods. Shock-wave studies typically involve the use of a gas gun or explosive charge that fires a high-velocity projectile (velocities up to 8 km s^{-1} are attainable) at the material under study. When the projectile hits its target a shock wave propagates very rapidly through the material generating pressures in excess of 100 GPa. Shock waves have also been induced by the action of high-power lasers on substrates to produce a high-pressure plasma that either acts directly on the material under study or launches a flyer plate into it.[27] By measuring the propagation speed of the shock-wave front through the material and the jump in particle velocity across the front (*i.e.* the velocity of the material behind the front if the material ahead of the front is at rest), the relationship between the pressure, volume (or density), and temperature can be determined. Together these constitute the equation of state for the material. A plot of pressure against volume (or density) gives the Hugoniot curve for the material, and anomalies in the Hugoniot curves can be used to identify phase transitions.[25]

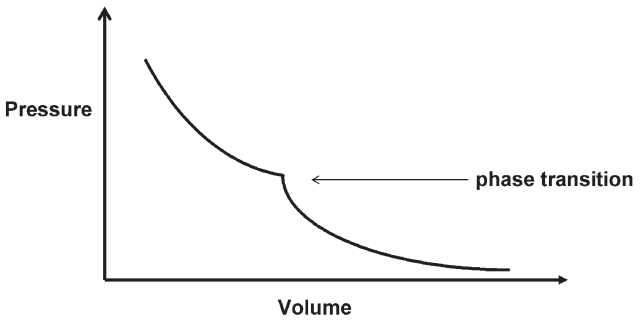

Fig. 10 Hugoniot curves illustrating pressure-induced phase transition.

Other properties of shocked materials may also be measured, *e.g.* electrical and thermal conductivity, velocity of sound, and optical properties.

Computational methods are particularly suited to the study of energetic materials since these allow a wide range of pressures and temperatures to be explored relatively easily, and have the potential to provide detailed information about rates and mechanisms of reactions occurring under extreme conditions. For practical reasons such information is often difficult to obtain from experiment. The ultimate aim of such studies is to be able to construct models that accurately predict the performance and characteristics of existing and new energetic materials (see chapter 9 by Fried *et al.* and chapter 11 by Rice in reference 26).

7.2 High-pressure structural and spectroscopic studies on selected energetic materials

In the following section we summarise and highlight some high-pressure studies on a selection of common energetic materials.

Ammonium perchlorate (AP), $[NH_4]^+[ClO_4]^-$, is a highly energetic oxidiser that is widely used in solid rocket motors. When mixed with a polymeric binder and aluminium powder it forms a powerful, but smoky propellant that is used by launch vehicles such as the NASA Shuttle and the ESA Ariane-5. At ambient temperature and pressure, AP adopts an orthorhombic crystal structure in which the NH_4^+ ions rotate freely. On heating to above 511–513 K, a reversible phase transition to a cubic structure has been observed in which there is almost unrestricted rotational reorientation of the perchlorate ions,[28] and this transition has also been correlated with sudden changes in the reactivity of the compound.[29] Over the years there have been a range of high-pressure studies on AP, the results of which have not always been consistent. These are summarised in an investigation that used energy-dispersive powder X-ray diffraction and IR and Raman spectroscopy up to a pressure of 5.6 GPa.[30] In this study the authors observed one phase transition at about 0.9 GPa, which they attributed to a ''freezing'' of freely rotating NH_4 units, similar to the effects at low temperature, and a second phase transition near 3.0 GPa. A very recent study using powder neutron diffraction and single crystal X-ray diffraction has identified a pressure-induced phase transition at 4.1 GPa to give a structure in which the ammonium ions and perchlorate ions adopt a more close packed arrangement.[31]

Ammonium dinitramide (ADM), $[NH_4]^+[O_2N–N–NO_2]^-$, is another energetic oxidiser that is a possible candidate for the replacement of ammonium perchlorate in rocket propellants in view of the increasing concern about the toxicological effects of the perchlorate ion. Furthermore, combustion products of ammonium perchlorate include hydrogen chloride and other chlorine-containing materials that are damaging both to the upper atmosphere and to wetland areas found near launch sites, *e.g.* Cape Canaveral, and so non-chlorine containing oxidisers are of increasing interest. The crystal structure under ambient conditions has been determined and a pressure-temperature study using X-ray diffraction and Raman spectroscopy has identified a new monoclinic phase above 2.0 GPa.[32] This study also showed that above 140 °C and in the pressure range 1.0–10.0 GPa, ADN undergoes a molecular rearrangement to form ammonium nitrate and N_2O.

Ammonium nitrate (AN), $[NH_4]^+[NO_3]^-$, is widely used in commercial explosives and propellants. Mixed with fuel oil it forms a powerful secondary explosive known as ANFO, or it can be mixed with TNT to form amatol.[23] Ammonium nitrate has been studied by infrared spectroscopy under hydrostatic compression, but no phase change has been observed up to 5.0 GPa. However, when a sample of form IV was compressed in a diamond-anvil cell without a gasket, *i.e.* under conditions in which the pressure distribution is known to depart substantially from hydrostatic conditions, a transition was observed at 3.0 GPa to give a new phase denoted form VIII,[33] and the authors noted that this was in good agreement with the transition pressure measured by Bridgman (2.94 GPa) who used an apparatus designed to apply shear stress in addition to hydrostatic compression. Shock-loading experiments up to *ca.* 20 GPa have suggested the presence of a shock-induced phase transition at a shock pressure of <3.5 GPa with a large associated volume change, indicating the presence of a previously unidentified high-pressure phase.[34]

HMX (1,3,5,7-tetranitro-1,3,5,7-tetrazacyclooctane or cyclotetramethylene tetranitramine or Octogen) is one of the most widely used secondary explosives. Under ambient conditions, three polymorphs (α, β, and δ) and a hemihydrate (usually referred to as γ-HMX) are known and have been structurally characterised. At ambient conditions, the β-form is the most stable and the shock sensitivity of the four forms follows the order $\delta > \gamma > \alpha > \beta$.[24] The high-pressure behaviour of HMX has been summarised in a study that examined the pressure-volume relationship and Raman spectra of β-HMX under quasi-hydrostatic conditions up to 45 GPa using powder X-ray diffraction and micro-Raman spectroscopy.[35] The study suggested a phase transition at 12 GPa with no abrupt volume change, and a discontinuous one at 27 GPa with a 4% volume change. Using an intermolecular potential developed for nitramines, molecular simulations have reproduced the effects of hydrostatic compression on the crystallographic lattice parameters of β-HMX up to 7.5 GPa.[36] The deflagration rate of HMX has been studied in a DAC over the pressure range 0.7–35 GPa and enhanced rates have been observed at pressures above 10 GPa.[37] Theoretical studies using molecular dynamics techniques have been used to

determine rate laws and decomposition mechanisms of HMX under detonation conditions (see Fried *et al.* in chapter 9 of reference 25). These studies show that the rate of H_2O formation is much faster than that of N_2, reflecting the greater ease with which water can be produced compared with the more complex mechanism associated with the formation of N_2

RDX (1,3,5-trinitrohexahydro-1,3,5-*s*-triazine or cyclotrimethylene-trinitramine or Cyclonite) is a widely used explosive that when compounded with mineral jelly and similar materials forms plastic explosives such as C4. Two polymorphic forms are known, originally designated RDX-I and RDX-II, but now more usually referred to as the α- and β-forms, respectively. The structure of the α-form has been determined by single crystal neutron diffraction, but the structure of the β-form has proved elusive because of the difficulty of obtaining and preserving well formed crystals, even for short periods, owing to its extreme instability. The optical and infrared spectra of RDX at pressures up to 65 GPa have been recorded and the observed colour changes with increasing pressure have been ascribed to the decrease in the HOMO–LUMO band gap.[38] The behaviour of RDX towards different types of shock showed that very finely divided material was relatively insensitive to long-duration, low-pressure shocks, but sensitive to short-duration high-pressure shocks.[39] The pressure-temperature phase diagram for RDX has been determined up to 573 K and 7.0 GPa using X-ray diffraction, infrared spectroscopy, and optical polarising microscopy, and the authors successfully identified a new high-pressure γ-form.[40] On raising the temperature the α- and β-forms thermally decompose, but the γ-form transforms into either the α- or β-forms rather than decomposing. The decomposition rate of the α-form increases with increasing pressure and this has been interpreted as a bimolecular mechanism with an activation energy of 51 kcal mol^{-1} and an activation volume of -5.6 cm^3 mol^{-1}.[40] Using an intermolecular potential developed for nitramines, molecular simulations have reproduced the effects of hydrostatic compression on the crystallographic lattice parameters of up to 3.95 GPa.[36]

CL-20 (or hexanitrohexaazaisowurtzitane or HNIW) is currently the densest and most energetic organic compound that has practical use (Fig. 11)

Four well-characterised forms are known under ambient conditions, one of which (the α-form) is a hemihydrate. Under ambient conditions the stability sequence is $\varepsilon > \gamma > \alpha > \beta$, although the β-form is more dense than the γ-form. In a comprehensive study using optical polarising microscopy and infrared spectroscopy the phase diagram and stability fields have been determined up to 623 K and 14.0 GPa.[41] The authors identified a new ζ-form that was obtained by compression of the γ-form above 0.7 GPa. The study demonstrated the different thermal decomposition temperatures associated with the different polymorphs. Thus the γ-form decomposed up to 0.4 GPa at 240–260 °C, whilst the α-form decomposed between 0.4 and 10.0 GPa in the range 250–300 °C and the ζ-form decomposed at >10.0 GPa in the range 300–340 °C.

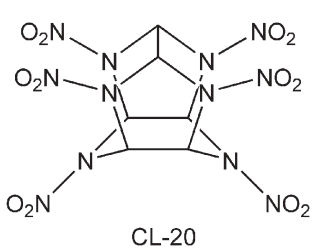

Fig. 11 Molecular structure of CL-20.

Molecular simulations have successfully reproduced the effects of hydrostatic compression on the crystallographic lattice parameters of the ε-form up to 2.5 GPa.[36]

PETN (pentaerythritol tetranitrate), $[C(CH_2O–NO_2)]$ is an example of a nitrate ester that is used in commercial blasting caps and detonation cords.[23] It crystallises in two forms and the structural behaviour of form I has been successfully modelled up to pressures of ~5 GPa, but above this pressure deviations from experimental results became more significant and these were attributed to the assumption in the model that the molecular structure remains rigid.[36]

8. Summary and future directions

In this review, we have aimed to highlight some of the high-pressure studies that have been conducted on these important classes of molecular materials. The response of pharmaceutical compounds and other organic compounds to pressure demonstrates very clearly that the crystal structures of these compounds are very sensitive even to the relatively modest pressures experienced associated with the typical processing methods currently used in the pharmaceutical industry. *In situ* structural studies have revealed that pressure-induced structural distortions are often very anisotropic and can be correlated with the intermolecular interactions within the crystal lattice. Crystal growth from solution under high pressure has demonstrated how the polymorphism of pharmaceutical compounds can be conveniently studied as a function of pressure and how new polymorphs and solvates can be discovered, with implications for the screening of pharmaceutical compounds for polymorph/solvate formation. Future directions in this area should include studies of the solubilities of these materials as a function of pressure and investigations of the relative thermodynamic and kinetic stabilities of polymorphs over a range of pressures. The interplay between theory and experiment has been highlighted by the studies on piracetam, and as methods for crystal structure prediction become more powerful they will predict with greater confidence structures that have as yet been undiscovered—it seems likely that at least some of these will be high-pressure forms.

We have also highlighted the importance of high pressure in the properties and performance of energetic materials, and outlined the methods used for studying these materials at pressure. It is clear that theoretical modelling of their properties and performance under detonation conditions is of great importance and will continue to develop. Such studies frequently require knowledge of the crystal structures of high-pressure phases (at high pressures), but as can be seen from this review, this information is not always available. Hence one of the future experimental challenges is to employ the *in situ*

methods used for the study of pharmaceutical compounds and apply them to the study of energetic materials.

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References

1 J. Bernstein, in *Polymorphism in Molecular Crystals*, IUCr Monographs on Crystallography, Clarendon Press, Oxford, 2002.
2 H. Nowell and S. L. Price, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2005, **61**, 558–568 and references therein.
3 H. G. Brittain, *J. Pharm. Sci.*, 2002, **91**, 1573–1580 and references therein.
4 V. V. Boldyrev, *J. Mater. Sci.*, 2004, **39**, 5117–5120 and references therein.
5 T. Masumoto, J.-I. Ichikawa, N. Kaneniwa and M. Otsuka, *Chem. Pharm. Bull.*, 1988, **36**, 1074–1085.
6 E. V. Boldyreva, T. P. Shakhtshneider, H. Sowa and H. Uchtmann, *J. Therm. Anal. Calorim.*, 2002, **68**, 437–452.
7 T. P. Shakhtshneider and V. V. Boldyrev, *Drug Dev. Ind. Pharm.*, 1993, **19**, 2055–2067.
8 D. Braga and F. Grepioni, *Angew. Chem., Int. Ed.*, 2004, **43**, 4002–4011 and references therein.
9 H. K. Chan and E. Doelker, *Drug Dev. Ind. Pharm.*, 1985, **11**, 315–332.
10 T. Okumura, M. Ishida, K. Takayama and M. Otsuka, *J. Pharm. Sci.*, 2006, **95**, 689–700.
11 Y. Tozuka, D. Kawada, T. Oguchi and K. Yamamoto, *Int. J. Pharm.*, 2003, **263**, 45–50.
12 R. Miletich, D. R. Allan and W. F. Kuhs, *Rev. Mineral. Geochem.*, 2000, **41**, 445–519.
13 E. V. Boldyreva, *J. Mol. Struct.*, 2003, **647**, 159–179 and references therein.
14 A. Dawson, D. R. Allan, S. A. Belmonte, S. J. Clark, W. I. F. David, P. A. McGregor, S. Parsons, C. R. Pulham and L. Sawyer, *Cryst. Growth Des.*, 2005, **5**, 1415–1427.
15 E. V. Boldyreva, S. N. Ivashevskaya, H. Sowa, H. Ahsbahs and H. P. Weber, *Z. Kristallogr.*, 2005, **220**, 50–57 and references therein.
16 S. A. Moggach, D. R. Allan, S. J. Clark, M. J. Gutmann, S. Parsons, C. R. Pulham and L. Sawyer, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2006, **62**, 296–309 and references therein.
17 P. A. McGregor, D. R. Allan, S. Parsons and C. R. Pulham, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2005, **61**, 449–454 and references therein.
18 R. Gajda, K. Dziubek and A. Katrusiak, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2006, **62**, 86–93 and references therein.
19 D. R. Allan and S. J. Clark, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1999, **60**, 6328–6334.
20 F. P. A. Fabbiani, D. R. Allan, W. I. F. David, S. A. Moggach, S. Parsons and C. R. Pulham, *CrystEngComm*, 2004, **6**, 504–511.
21 F. P. A. Fabbiani, D. R. Allan, W. I. F. David, A. D. Dawson, P. A. McGregor, I. D. H. Oswald, S. Parsons and C. R. Pulham, *Chem. Commun.*, 2003, 3004–3005.
22 F. P. A. Fabbiani, D. R. Allan, S. Parsons and C. R. Pulham, *CrystEngComm*, 2005, **7**, 179–186.
23 J. Akhavan, in *The Chemistry of Explosives*, 2nd edn., Royal Society of Chemistry, Cambridge, UK, 2004.
24 S. J. P. Palmer and J. E. Field, *Proc. R. Soc. London, Ser. A*, 1982, **383**, 399–407.
25 Y. B. Zel'dovich and Y. P. Raiser, *Physics of Shockwaves and High Temperature Hydrodynamics Phenomena*, Academic Press, New York, 1966.
26 *Overviews of Recent Research on Energetic Materials*, ed. R. W. Shaw, T. B. Brill, and D. L. Thompson, *Advanced Series in Physical Chemistry*, World Scientific, Singapore, 2005, vol. 16.
27 S. N. Luo, D. C. Swift, T. E. Tierney, D. L. Paisley, G. A. Kyrala, R. P. Johnson, A. A. Hauer, O. Tschauner and P. D. Asimow, *High Pressure Res.*, 2004, **24**, 409–422 and references therein.
28 M. Stammler, R. Bruenner, W. Schmidt and D. Orcutt, *Adv. X-Ray Anal.*, 1966, **9**, 170–189.
29 L. L. Bircumshaw and B. H. Newman, *Proc. R. Soc. London, Ser. A*, 1954, **227**, 115–132.
30 S. M. Peiris, G. I. Pangilinan and T. P. Russell, *J. Phys. Chem. A*, 2000, **104**, 11188–11193 and references therein.
31 A. J. Davidson, D. R. Allan, F. P. A. Fabbiani, D. J. Francis, W. G. Marshall and C. R. Pulham, unpublished results.
32 T. P. Russell, G. J. Piermarini, S. Block and P. J. Miller, *J. Phys. Chem.*, 1996, **100**, 3248–3251.
33 D. M. Adams and S. K. Sharma, *J. Chem. Soc., Faraday Trans. 2*, 1976, **72**, 2069–74.
34 F. W. Sandstrom, P. A. Persson and B. Olinger, *AIP Conference Proceedings*, 1994, **309**, 1409–1412.
35 C. S. Yoo and H. Cynn, *J. Phys. Chem.*, 1999, **111**, 10229–10235.
36 D. C. Sorescu, B. M. Rice and D. L. Thompson, *J. Phys. Chem.*, 1999, **103**, 6783–6790.
37 A. P. Esposito, D. L. Farber, J. E. Reaugh and J. M. Zaug, *Propellants, Explos., Pyrotech.*, 2003, **28**, 83–88.
38 N. Goto, H. Yamawaki, K. Tonokura, K. Wakabayashi, M. Yoshida and M. Koshi, *Mater. Sci. Forum*, 2004, **465–466**, 189–194.
39 A. Chakravarty, M. J. Gifford, M. W. Greenaway, W. G. Proud and J. E. Field, *AIP Conference Proceedings*, 2002, **620**, 1007.
40 P. J. Miller, S. Block and G. J. Piermarini, *Combust. Flame*, 1991, **83**, 174–184.
41 T. P. Russell, P. J. Miller, G. J. Piermarini and S. Block, *J. Phys. Chem.*, 1993, **97**, 1993–1997 and references therein.

