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High-pressure diffraction studies of molecular organic solids. A personal view

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This paper discusses the trends in the experimental studies of molecular organic solids at high pressures by diffraction techniques. Crystallization of liquids, crystallization from solutions and solid-state transformations are considered. Special attention is paid to the high-pressure studies of pharmaceuticals and of biomimetics.

1. Introduction

The pioneering studies of organic solids at high pressures date back to the beginning of the 20th century (Bridgman, 1931, 1946; Vereschagin & Kabalkina, 1979), but at that time such studies were rather rare. The main interest in the field of high-pressure research was focused either on metals, elements, simple molecules, ices, minerals and inorganic compounds at very high (Mbar) pressures, in relation to the basic and applied problems of physics, geology, mineralogy and materials sciences, or on biopolymers and other soft-matter systems at much lower pressures (usually <1 GPa), in relation to the problems of biology and the food industry [see Tonkov (1988), Hazen & Finger (1982), Hazen & Downs (2000) and Katrusiak & McMillan (2004) as examples of the entry points to the vast literature on the topic]. In the last decades, the number of publications dealing with the effects of hydrostatic pressure on small-molecule organic crystals (usually in the range 0.1–10 GPa) has started to grow rapidly. To a large extent, this was due to the progress achieved in the design of diamond-anvil cells and in the procedures of data collection and reduction. Larger apertures of high-pressure cells provided by new anvil designs, more reliable and less distorted intensities of reflections, two-dimensional detectors, brighter laboratory sources of X-rays and easier access to synchrotron radiation – all this has enabled *in situ* high-pressure studies also of relatively weakly diffracting crystals with low (monoclinic and even triclinic) symmetry. Some of these technical developments are summarized by Katrusiak (2008), who was one of the pioneers of systematic research of the effect of high pressure on organic crystals (see, *e.g.*, his reviews: Katrusiak, 1990*a*, 1991*a*,*b*,*c*, 1996, 2001, 2003, 2004*a*). The aim of my contribution is to complete that by Katrusiak by providing a few examples of the results achieved in recent years using these advanced techniques, and to give my personal vision of the main trends and the prospects in the research of organic molecular crystals.

2. The main research directions

High-pressure studies of small-molecule organic solids are related to one of the following three directions.

(i) High-pressure crystallization of liquids. A comparison of the phases obtained by high pressure and by low-temperature crystallization.

(ii) High-pressure crystallization of solids from solutions. A route to new polymorphs and solvates. Understanding the thermodynamic and kinetic factors in the crystallization of polymorphs from different solvents.

(iii) Studies of the effect of pressure on solids immersed in hydrostatic liquids:

(*a*) compression of the same phase (bulk compressibility, anisotropy of strain, changes in the intramolecular conformations, rotation of molecules, distortion of intermolecular bonds);

(*b*) phase transitions;

(*c*) chemical transformations (induced by pressure; induced by temperature or light and affected by pressure).

These studies are of fundamental importance, giving insight into the nature of intra- and intermolecular interactions in solids, assisting in a better understanding of the polymorphism of molecular organic crystals, as well as of the mechanisms of the phase transitions and solid-state reactions. At the same time, they can find important applications in molecular electronics and in the pharmaceutical industry (Boldyreva & Boldyrev, 1999; Shakhtshneider *et al.*, 1999; Hemley & Dera, 2000; Boldyreva, Shakhtshneider *et al.*, 2000; Katrusiak, 2001; Boldyreva, Shakhtshneider & Ahsbahs, 2002; Boldyreva, Shakhtshneider *et al.*, 2002; Boldyreva, 2003*a*,*b*; Fabbiani *et al.*, 2003, 2004; Boldyreva, Drebushchak, Paukov *et al.*, 2004; Boldyreva, Drebushchak, Shakhtshneider, Ahsbahs, Uchtmann *et al.*, 2004; Boldyreva, Ivashevskaya *et al.*, 2004; Fabbiani, Allan, Marshall *et al.*, 2005, Fabbiani, Allan, Parsons & Pulham, 2005; Fabbiani *et al.*, 2006, 2007; Boldyreva, 2006, 2007*a*,*b*).

3. Crystallization of liquids

Crystallization of liquids at high pressure is known as an alternative to crystallization on cooling since the times of Bridgman (1931, 1946). Later, many examples were published in the papers by several groups (Fourme, 1968; Piermarini *et al.*, 1969; Weir *et al.*, 1969; Fourme *et al.*, 1971; Allan *et al.*, 1998; Allan & Clark, 1999*a*,*b*; Allan *et al.*, 1999, 2001, 2002*a*,*b*; Bujak *et al.*, 2004; Bujak & Katrusiak, 2004; Katrusiak *et al.*, 2004, 2007; Dziubek & Katrusiak, 2005; Podsiadlo & Katrusiak, 2005, 2006; Podsiadło *et al.*, 2005, 2006; Lozano-Casal *et al.*, 2005; Gajda *et al.*, 2005, 2006; Oswald, Allan, Day *et al.*, 2005; Oswald, Allan, Motherwell & Parsons, 2005; Budzianowski *et al.*, 2005; Budzianowski & Katrusiak, 2006*a*,*b*; Budzianowski *et al.*, 2006; McGregor *et al.*, 2006; Bujak *et al.*, 2007; Dziubek *et al.*, 2007; Gajda & Katrusiak, 2007). Sometimes, the same polymorph is formed as a result of crystallization on cooling and with increasing pressure; examples are 1,2-dichloromethane (Podsiadło *et al.*, 2005), and carbon disulfide (Dziubek & Katrusiak, 2004). More often, the high-pressure and the low-temperature polymorphs differ. One of the examples is water – ambient-pressure and high-pressure ices differ significantly in their structures and properties (Petrenko & Whitworth, 1999). Acetone (Allan & Clark, 1999*b*), acetic acid (Allan *et al.*, 1999), alcohols (Allan *et al.*, 1998, 1999, 2001), benzene (Fourme, 1968; Piermarini *et al.*, 1969; Weir *et al.*, 1969; Fourme *et al.*, 1971; Budzianowski & Katrusiak, 2006*a*), chlorotrimethylsilane (Gajda *et al.*, 2006), 1,2-dichloromethane (Podsiadło *et al.*, 2005), sulfuric acid (Allan *et al.*, 2002*b*), phenol (Allan *et al.*, 2002*a*), 2-chlorophenol and 4-fluorophenol (Oswald, Allan, Day *et al.*, 2005; Oswald, Allan, Motherwell & Parsons, 2005) are further examples of compounds, liquid at ambient conditions, which also give different polymorphs on cooling and with increasing pressure.

The low-temperature and the high-pressure forms may differ in the conformations of molecules but, more often, the main structural difference is related to the orientation of the molecules with respect to each other and to the structure of hydrogen-bonded networks, or the type of carbonyl–carbonyl, or halogen–halogen or π–π interactions. As examples, compare the crystal structures of acetic acid formed at low temperatures (Nahringbauer, 1970) and at high pressure (Allan *et al.*, 1999) (Fig. 1). Sometimes, a low-temperature structure is disordered and a high-pressure one completely ordered. This holds, *e.g.*, for 1,3-cyclohexanedione (Katrusiak, 1990*b*).

A comparison of the low-temperature and the high-pressure structures is helpful to estimate the relative energies of different non-covalent interactions, and to study the conformational flexibility and the factors determining the crystallization of a selected polymorph. An example is provided by the crystallization of halogenated compounds. The interest in these phases dates back to the work by Bridgman, who, in particular, compared the high-pressure and the low-temperature polymorphs of CCl_4 and CBr_4 (Bridgman, 1931). The analysis of the high-pressure forms as compared to the low-temperature ones, as well as of the anisotropy of compression of the crystals with increasing pressure, makes it possible to reveal the structures, in which the halogen–halogen interactions can be considered as the main cohesive forces responsible for the molecular arrangements (Podsiadło & Katrusiak, 2006; Bujak *et al.*, 2007), and the structures in which halogen–halogen interactions are not attractive at all (Podsiadlo *et al.*, 2005; Gajda *et al.*, 2006). Very interesting information was obtained for series of substituted dihalomethanes (CH_2XY, where X, Y = Br, Cl, I), 1,2-dihalotetrafluoroethanes $X(CF_2)_2Y$ (X = Br, I; Y = Br, I) and dichloroacetic acid, which show clearly systematic isostructural relations resulting from the specific intermolecular interactions in their pressure-crystallized phases (Podsiadło *et al.*, 2006; Katrusiak *et al.*, 2007). Studies of the effect of pressure on the halogenated organic compounds could be compared with the effect of pressure on the electron lone pairs in inorganic oxides (Grzechnik *et al.*, 2002; Dinnebier *et al.*, 2003; Orosel *et al.*, 2004). A continuous compression of CS_2 up to 8 GPa has allowed the increased energy of the intermolecular S$\cdots$S and C$\cdots$S interactions to be followed (Dziubek & Katrusiak, 2004). A recent study of the pressure-freezing of ethynylbenzene made it possible to resolve $\equiv$CH$\cdots\pi$(arene) and cooperative $\equiv$CH$\cdots\pi$(C$\equiv$C) interactions (Dziubek *et al.*, 2007).

In many cases, the structures formed are thermodynamically stable at the given P–T conditions and phase diagrams can be used to predict reliably the formation of a given polymorph. However, some phases can be crystallized only following a special procedure, combining compression to a high pressure with subsequent decompression to a lower value, at which crystallization eventually occurs. In many cases, the sample is recycled many times, combining compression with slight heating and subsequent cooling, in order to get a single-crystalline sample, for which the structure can be solved more easily. In a recent paper (Boldyreva, 2007*b*), we have supposed that for some highly polymorphic compounds a procedure involving only 'pure' compression without temperature variation at all would give forms other than those given by compression combined with temperature variations (either cooling or heating). The experimental evidence to substantiate this hypothesis was reported recently (Katrusiak *et al.*, 2007). Different polymorphs were crystallized when combining compression of the liquid without heating–cooling cycles and during compression at constant

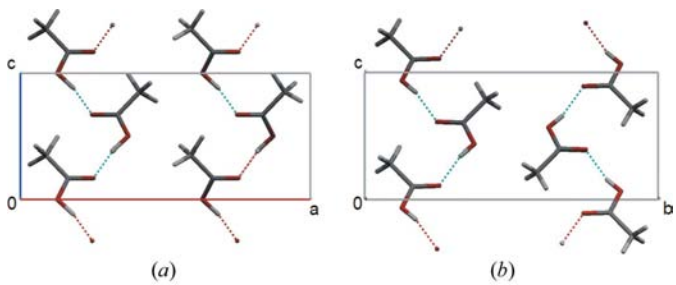

Figure 1
Fragments of the crystal structures of (*a*) the low-temperature and (*b*) the high-pressure polymorphs of acetic acid

ambient temperature, and these two high-pressure phases did not interconvert. Other kinetic factors (such as the rate of compression or the effects of 'over pressurization', the presence of impurities, lack or presence of smooth surfaces in the gasket or even the presence of ruby) might also affect nucleation and crystal growth and in this way could also influence high-pressure polymorphism of liquid compounds. Supersaturation, over-cooling, seeding, impurities and the presence of rough surfaces are well known to be important for nucleation at ambient pressure.

4. Crystallization of solids from solutions

Another trend in the high-pressure research of molecular organic compounds is to crystallize compounds which are *solid* at ambient conditions from their solutions using the decrease in solubility with increasing pressure, similar to how compounds are crystallized on cooling, using evaporation or antisolvent techniques. Crystallization at high pressure has been known for a very long time, but its systematic application for obtaining new polymorphs and solvates started only a few years ago (Fabbiani *et al.*, 2003, 2004; Fabbiani, Allan, Parsons & Pulham, 2005; Fabbiani, Allan, Marshall *et al.*, 2005; Fabbiani *et al.*, 2007). Some of the high-pressure polymorphs and solvates were never before observed at ambient conditions, also those forms that turned out to be quenchable to ambient pressure. This is a vast field of research, not just because of the practical interest in obtaining new forms of pharmaceuticals or new molecular materials. It is very promising for understanding thermodynamic *versus* kinetic factors governing crystal growth and polymorph formation.

Sometimes, high-pressure crystallization from a solution gives a polymorph which is thermodynamically stable in these conditions. Paracetamol provides such an example. At ambient pressure, paracetamol I ($P2_1/n$) is the stable form at ambient temperature, although, once obtained, paracetamol II (*Pbca*) can be preserved for an indefinitely long time and survive until melting if the presence of even traces of water and alcohol is excluded (Boldyreva, Drebushchak, Paukov *et al.*, 2004). Paracetamol II was obtained from paracetamol I at high pressure (see more details in the next section) (Boldyreva, Shakhtshneider & Ahsbahs, 2002) and was later shown to be the thermodynamically preferable phase at high pressures (Espeau *et al.*, 2005; Ledru *et al.*, 2007). Direct crystallization of paracetamol from ethanol solution at 1.1 GPa gave paracetamol II (Fabbiani *et al.*, 2004). In other cases, high-pressure crystallization from a solution gives metastable forms and is strongly affected by 'non-thermodynamic parameters' such as the details of the compression procedure (*e.g.* first compressed, then decompressed to a lower, but still non-ambient, pressure) or the rates of compression and/or decompression. Crystallization may be sensitive to the solvent and to the concentration of the solution. Piracetam provides one such example, giving different forms on crystallization from different solvents and from the solutions of different concentrations in the same solvent (Fabbiani, Allan, Parsons & Pulham, 2005; Fabbiani *et al.*, 2007). High pressure adds a new dimension to the old problems of solvent-mediated polymorphic transformations, solvent effect on crystallization, templating effects in crystallization, crystallization and quenching of metastable polymorphs, varying supersaturation or viscosity of solutions *etc.*

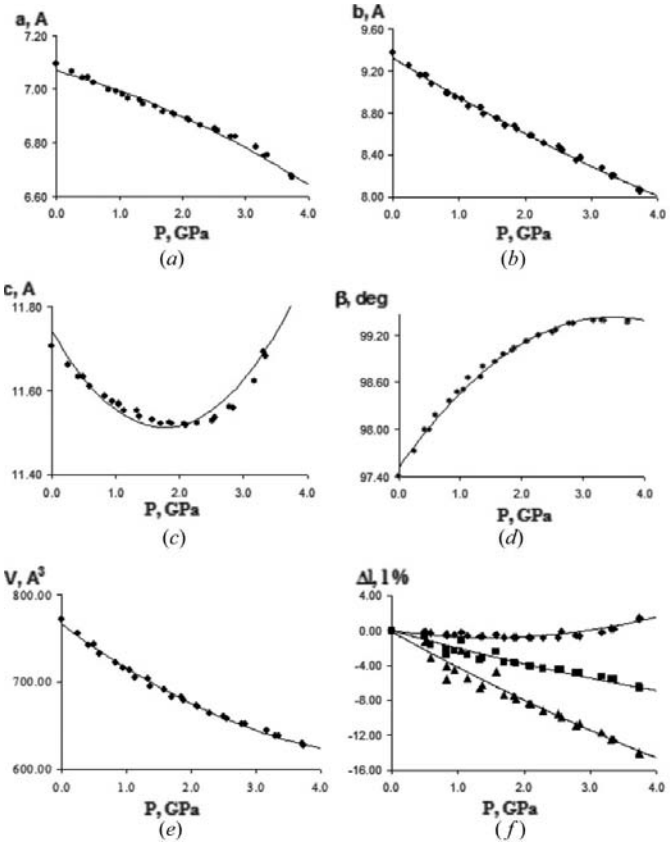

Figure 2
(*a*)–(*e*) Changes in cell parameters and volume and (*f*) linear strain in the directions of principal axes of strain tensor measured for paracetamol I *versus* hydrostatic pressure (based on data from Boldyreva, Shakhtshneider *et al.*, 2000)

5. Pressure effects on solids

5.1. Compression of the same phase

Compressibility is one of the basic quantitative characteristics of the response of a structure to pressure. For crystals, compressibility can be calculated from X-ray diffraction data on the changes in cell parameters *versus* pressure. Bulk compressibility has been systematically studied for inorganic compounds and minerals and discussions on the equation of states, $V(P)$ dependences, always attract much attention (Hazen & Finger, 1982; Hazen & Downs, 2000; Katrusiak & McMillan, 2004). For molecular organic crystals, the values of bulk compressibility are rather high, typical values of relative volume change being about 5% GPa^{-1} (Boldyreva, 2003*a*,*b*, 2004*a*,*b*,*c*, 2006). Although attempts to calculate the equation of states for molecular crystals are also known (Zerilli & Kuklja, 2007; Molodets, 2006), the values of bulk compressi-

bility for low-symmetry crystals are not very informative. Much more information can be obtained if the *anisotropy of structural strain* is followed. Linear strain in the directions of the three principal axes of the strain tensor (the three directions in the crystal structure, which remain mutually orthogonal), as well as in any other selected direction in the structure, can be calculated from the measured changes in cell parameters *versus* pressure, as described in Nye (1957), Hazen & Finger (1982) and Boldyreva (2004*c*). After such a recalculation, peculiar features (minima, maxima) of the pressure dependences of cell parameters may disappear (see the data measured for the monoclinic polymorph of paracetamol as an example, Fig. 2).

Crystals with very similar bulk compressibility can show pronounced difference in the strain anisotropy, reflecting the anisotropy of the crystal structure [see the data for the polymorphs of paracetamol (Figs. 3*a*, *b*), L- and DL-serine (Figs. 3*c*, *d*) as examples].

The analysis of the anisotropy of strain reveals the directions in which the structure is rigid and the directions in which it is softer. For the structures in which molecules form hydrogen-bonded chains or two-dimensional layers, linear strain can be considered in relation to the orientation of these chains and layers (Boldyreva, 2003*a*,*b*, 2004*a*,*b*,*c*, 2006; Boldyreva, Drebushchak, Shakhtshneider *et al.*, 2004).

For example, the structures of amino acids are most rigid in the directions of the head-to-tail chains formed by zwitterions (Boldyreva, 2006). Thus, the structure of γ-glycine is about 2.5 times less compressible along the head-to-tail chains of zwitterions than in the plane normal to these chains (Boldyreva *et al.*, 2003). The compressibility of a helical head-to-tail chain formed by L-serine zwitterions in the structure of DL-serine is about 2.2 times higher, than that of a flat chain formed by the same L-serine zwitterions in the crystals of L-serine (Boldyreva, Kolesnik *et al.*, 2005, 2006). The structure of α-glycine is also most rigid in the direction along the head-to-tail chains (Boldyreva *et al.*, 2003).

Many structures are more compressible in the direction normal to the molecular layers (Boldyreva, 2003*a*,*b*, 2004*a*,*b*,*c*, 2006). This holds for the polymorphs of paracetamol (Shakhtshneider *et al.*, 1999; Boldyreva, Shakhtshneider *et al.*, 2000; Boldyreva, Shakhtshneider & Ahsbahs, 2002; Boldyreva, Shakhtshneider, Ahsbahs, Uchtmann *et al.*, 2002; Boldyreva, Shakhtshneider, Ahsbahs, Sowa & Uchtmann, 2002), pentaerythrytol (Katrusiak, 1995), 1,3-cyclohexanedione (Katrusiak, 1990*b*), 2-methyl-1,3-cyclopentanedione (Katrusiak, 1990*b*, 1991*b*), sodium oxalate (Boldyreva, Shakhtshneider, Ahsbahs, Sowa & Uchtmann, 2002; Boldyreva, Ahsbahs *et al.*,

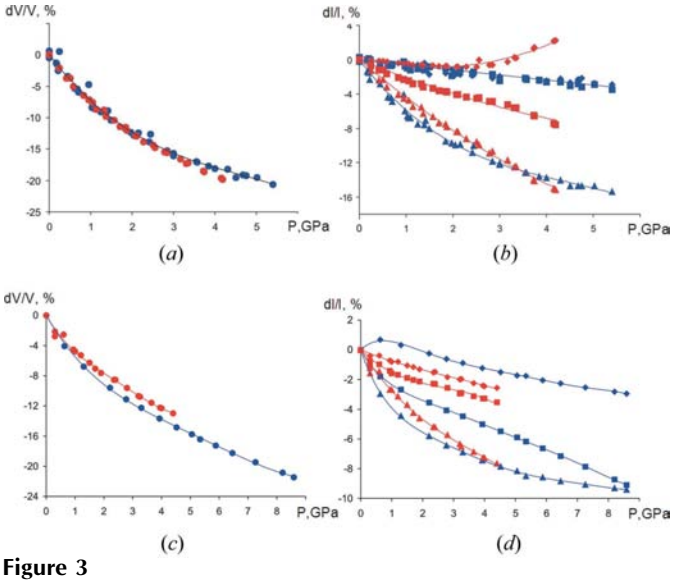

Figure 3
Pressure-induced changes of (*a*, *c*) the volume per molecule and (*b*, *d*) linear strain in the directions of the principal axes of the strain ellipsoids for the polymorphs of (*a*, *b*) paracetamol (red – I, blue – II), (*c*, *d*) L- (red), and DL- (blue) serine (based on data from Boldyreva, Shakhtshneider *et al.*, 2000; Boldyreva, Shakhtshneider & Ahsbahs, 2002; Boldyreva, Kolesnik *et al.*, 2005, 2006)

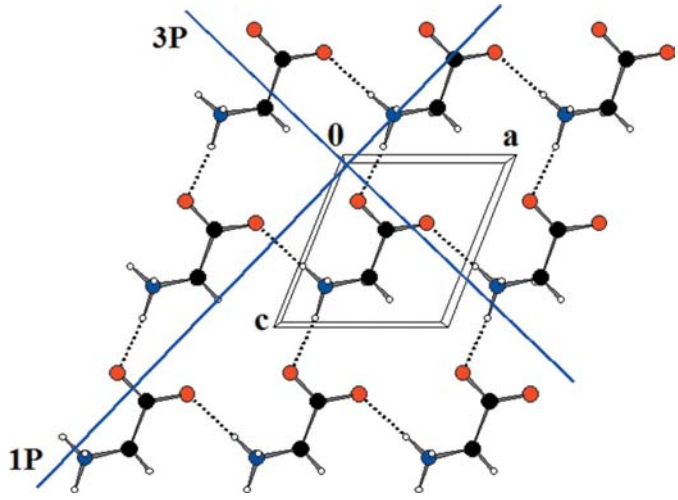

Figure 4
Orientation of the principal axes of the strain ellipsoid under pressure in α-glycine with respect to the chains of the zwitterions in a layer; 1P – minimum, 3P – maximum compression, axis 2P is normal to the projection plane (based on data from Boldyreva *et al.*, 2003).

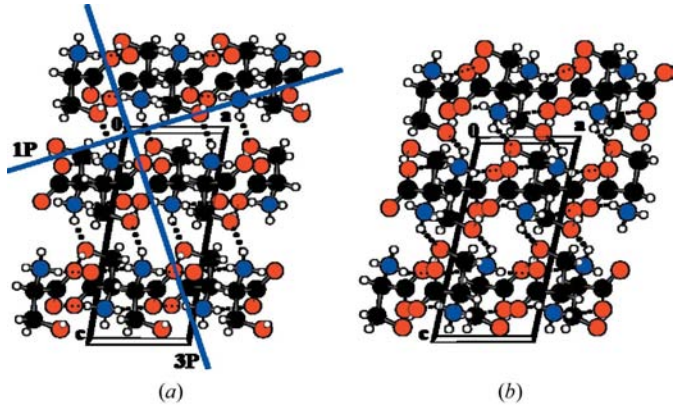

Figure 5
A fragment of the crystal structure of DL-serine as projected on the *ac* plane at (*a*) ambient conditions and (*b*) at 8.1 GPa. The orientation of the principal axes of strain tensor with increasing pressure (1P – slight expansion, 3P – maximum compression) is shown, axis 2P is normal to the projection plane (based on data from Boldyreva, Kolesnik *et al.*, 2006).

2006). The structure of L-cystine is most compressible in the direction normal to the hydrogen-bonded layers of zwitterions, in the direction of S–S bridges: changes in C—S–S—C torsion angles allow cystine molecules to act like springs (Moggach, Allan, Parsons *et al.*, 2005). There are also exceptions. Thus, one could expect the structure of α-glycine to be most compressible in the direction normal to the double layers but it is not. The structure is about 1.2 times more compressible along the direction of the hydrogen bonds linking the head-to-tail chains within a layer (Fig. 4) (Boldyreva *et al.*, 2003). Other examples of structures which are most compressible NOT in the directions normal to the molecular planes are dimedone (5,5-dimethyl-1,3-cyclopentanedione) (Katrusiak, 1991*c*) and benzoquinone (Boldyreva, 2003*a*,*b*). The structure of DL-serine is most compressible in the direction that is about 30° to the normal to the double layers, which approach each other with increasing pressure; this direction coincides with the direction of NH···O hydrogen bonds linking a double layer with another double layer, as well as with the orientation of the type II head-to-tail chains with alternating L- and D-serine zwitterions (Fig. 5). The structure is 5.2 times more compressible along this direction than normal to it (Boldyreva, Kolesnik *et al.*, 2006).

Linear strain in the crystal structure does not always correlate with the changes in the interatomic distances in the hydrogen bonds in the same directions due to the conformational changes and rotation of molecules (Boldyreva, 1994, 2001, 2003*a*,*b*, 2004*a*,*b*,*c*, 2006; Boldyreva *et al.*, 1997*a*,*b*, 1998; Boldyreva, Shakhtshneider *et al.*, 2000; Boldyreva, Shakhtshneider & Ahsbahs, 2002; Boldyreva, Shakhtshneider, Ahsbahs, Uchtmann *et al.*, 2002; Katrusiak, 1996, 2001, 2003, 2004*a*). Hydrogen bonds can be compressed but the structure expands and, *vice versa*, the structure can be compressed despite the expansion of the intermolecular hydrogen bonds.

Systematic studies of the compressibility of various types of hydrogen bonds in organic crystals were initiated by Katrusiak (1990*a*,*b*, 1991*a*,*b*,*c*, 1995, 1996, 2001, 2003, 2004*a*). The compressibility of a bond was shown to depend on the type of intermolecular motif within the crystal structure. For example, the compressibility of the OH···O hydrogen bonds linking molecules into chains or layers in the structures of 1,3-cyclohexanedione, 2-methyl-1,3-cyclopentanedione and squaric acid is similar, whereas that of the OH···O bonds linking the molecules of dimedone into helices is much higher (Katrusiak, 1990*a*,*b*, 1991*a*,*b*,*c*). At the same time, the values of the compression of the NH···O and OH···O hydrogen bonds measured for chemically and structurally different compounds were close (Katrusiak, 1991*a*,*b*,*c*; Boldyreva *et al.*, 1998; Boldyreva, Shakhtshneider *et al.*, 2000; Boldyreva, 2003*a*,*b*, 2004*a*,*b*,*c*; Boldyreva, Drebushchak, Shakhtshneider *et al.*, 2004).

The anisotropy of pressure-induced strain has been studied over the last few years for several crystalline amino acids, and the first generalizations can be made (Boldyreva, 2006, 2007*a*). All the crystalline amino acids have a common structural motif: hydrogen-bonded head-to-tail chains formed by zwitterions. These chains are remarkably robust and can mimic peptide chains (Vinogradov, 1979; Suresh & Vijayan, 1983). The compressibility of shorter NH···O hydrogen bonds linking zwitterions along the head-to-tail chains is usually smaller than that of other hydrogen bonds in the structure (Boldyreva, Drebushchak, Shakhtshneider *et al.*, 2004; Boldyreva, Ivashevsyaya *et al.*, 2005; Dawson *et al.*, 2005; Moggach, Allan, Morrison *et al.*, 2005; Moggach, Allan, Parsons *et al.*, 2005; Boldyreva, Kolesnik *et al.*, 2005, 2006; Boldyreva, Sowa *et al.*, 2006; Moggach, Allan, Parsons & Sawyer, 2006; Moggach, Allan, Clark *et al.*, 2006; Moggach, Marshall & Parsons, 2006; Boldyreva, 2007*b*). It is only slightly affected even by jumpwise structural rearrangements in the course of phase transitions. For example, in L-serine, the N–O distance in this hydrogen bond decreases practically linearly at about 0.01 Å GPa^{-1} in the pressure range from ambient up to 10 GPa (Boldyreva, Sowa *et al.*, 2006), although the crystal structure undergoes two phase transitions, at about 5 and about 8 GPa (Boldyreva, Kolesnik *et al.*, 2005; Kolesnik *et al.*, 2005; Moggach, Allan, Morrison *et al.*, 2005; Boldyreva, Sowa *et al.*, 2006; Moggach, Marshall & Parsons, 2006), which are accompanied by a jump-wise increase in the cell parameter along the same head-to-tail chain (see next section, Figs. 9, 10). The compressibility of the shorter NH···O hydrogen bonds in the head-to-tail chains remains almost unaffected by a structural arrangement of the triple helices formed by these chains in γ-glycine into a layer in δ-glycine in the course of the irreversible extended single-crystal–powder phase transition starting at about 3.5 GPa (see next section, Fig. 7) (Boldyreva, 2003*b*; Boldyreva *et al.*, 2003; Boldyreva, Drebushchak, Shakhtshneider *et al.*, 2004; Boldyreva, Ivashevskaya *et al.*, 2004, 2005). Other hydrogen bonds in the structures of crystalline amino acids are more compressible than the short NH···O bonds within the head-to-tail chains, the changes in the N–O distances usually being about $\pm$0.02–0.05 Å GPa^{-1}. Similar values were measured for the compressibility of NH···O and OH···O hydrogen bonds in other organic crystals (Katrusiak, 1990*a*,*b*, 1991*a*,*b*,*c*, 1995, 1996, 2001, 2003, 2004*a*,*b*; Boldyreva, 2003*a*,*b*, 2004*a*,*b*,*c*, 2006). For a comparison, recently measured typical values for proteins are about $\pm$0.1–0.01 Å GPa^{-1} (Fourme *et al.*, 2001, 2006; Girard *et al.*, 2005, 2007; Colloc'h *et al.*, 2006; Li & Akasaka, 2006).

For crystals with flexible non-spherical molecules, the anisotropy of strain with increasing pressure is the result of an interplay between the changes in the conformations of flexible molecules, the rotation of molecules and the different distortions of intermolecular hydrogen bonds of several types (Boldyreva, 2001, 2003*a*,*b*, 2004*a*,*b*,*c*, 2006). For example, in the monoclinic polymorph of paracetamol, all the intermolecular hydrogen bonds shorten with increasing pressure. Nevertheless, the structure *expands* in several crystallographic directions due to the flattening of the individual molecules and of the pleated hydrogen-bonded layers (Boldyreva, Shakhtshneider *et al.*, 2000). Actually, the flattening of molecules and the shortening of the intermolecular hydrogen bonds are interrelated since the conformation of a paracetamol molecule is very sensitive to the charge distribution at the —OH, —C=O, —NH groups (Binev *et al.*, 1998; Behzadi *et*

al., 2007). The shifts of the vibrational bands in the IR spectra with increasing pressure can be a manifestation of the strengthening or loosening of the intermolecular hydrogen bonds, complementing the geometric data obtained from diffraction experiments. In complex crystal structures, a correlation of the frequency shifts (IR or Raman spectroscopy) and the changes in the interatomic distances (X-ray or neutron diffraction experiments) is not straightforward. For example, although both the N–O and O–O distances in the NH$\cdots$O and OH$\cdots$O hydrogen bonds in paracetamol shorten with pressure, the vibrational frequency ν(NH) of the stretching vibration shifts to the red with increasing pressure (as should be expected), whereas the vibrational frequency ν(OH) increases. A possible interpretation is that the —OH group not only donates a proton to the carbonyl —C=O group but also accepts another proton from the —NH group (Boldyreva, Shakhtshneider *et al.*, 2000; Boldyreva, Shakhtshneider, Ahsbahs, Uchtmann *et al.*, 2002).

The anisotropy of strain, corresponding to the same volume change on cooling and with increasing pressure can be radically different, reflecting the different mechanisms of reducing volume under these two actions (Boldyreva, 2001, 2003*a*,*b*, 2004*a*,*b*,*c*; Boldyreva *et al.*, 1997*a*,*b*, 1998; Boldyreva, Drebushchak, Shakhtshneider *et al.*, 2004). It seems clear that the interpretation of the response of the structures to variations of temperature and pressure should be based on the analysis of the interatomic potentials and their anharmonicity. Still, even for rather simple systems, the predictive power of the models is not perfect, especially when not static but dynamic properties are concerned. Systematic comparative studies of the effects of cooling and increasing pressure on the same hydrogen bonds can be expected to improve our understanding of these interactions. First examples of the attempts to reproduce the experimentally measured pressure-induced strain anisotropy by various level simulations are encouraging (Dzyabchenko & Boldyreva, 2000; Boldyreva, 2003*b*, 2004*c*; Boldyreva, Ahsbahs *et al.*, 2006).

Isotope substitution can serve as a supplementary tool in these studies. Similarity and difference between deuteration and pressure effect in molecular crystals were reviewed by Ichikawa (1998). For example, in the case of strong hydrogen bonds, like in KH_2PO_4 and squaric acid ($H_4C_4O_4$), deuteration corresponds to a negative pressure effect, whereas in the case of $(NH_4)_3H(SO_4)_2$ deuteration corresponds to a positive pressure.

The studies of the anisotropy of structural strain are important for understanding the intra- and intermolecular interactions in organic solids. For particular compounds which serve as biomimetics, such as crystalline amino acids or small peptides, the analysis of the compressibility of selected structural elements (molecular chains, layers, intermolecular hydrogen bonds, 'empty voids') is important in relation to understanding the compressibilities of different structural fragments of peptides and proteins (helices, sheets, turns, non-structured fragments, cavities) (Boldyreva, 2006, 2007*a*). The compressibility of main chains can be compared with the strain in crystalline amino acids. This comparison should be expected to be more informative for fibrillar proteins and for amiloid structures than for globular proteins. While the globular native forms of proteins are side-dominated compact structures evolved by pursuing a unique fold with optimal packing of amino acid residues, amyloid fibrils are a main-chain-dominated structure with an extensive hydrogen-bond network (Chatani *et al.*, 2005; Zanuy *et al.*, 2006).

It is very interesting also to compare the anisotropy of lattice strain in the crystals of amino acids with layered structures with the recently measured elastic properties of two-dimensional layers of oligopeptide films (Isenberg *et al.*, 2006). Compressibility of cavities of biopolymers, the contribution of the rigidity of the cavity to the conformational stability of the biopolymer can also be mimicked by studying structures of smaller molecules (Boldyreva, 2006). Attempts were made to describe the anisotropic compression of some of the crystalline amino acids by 'closing voids' (Dawson *et al.*, 2005; Moggach, Allan, Morrison *et al.*, 2005; Moggach, Allan, Parsons *et al.*, 2005; Moggach, Allan, Parsons & Sawyer, 2006; Moggach, Allan, Clark *et al.*, 2006; Moggach, Marshall & Parsons, 2006). Although any pressure-induced process can be expected to result in a structure with a higher density and smaller voids, crystalline amino acids are still not the best systems to study compression of cavities since their properties are to a large extent determined by dipole–dipole interactions and strong hydrogen bonds (OH$\cdots$O and NH$\cdots$O). For those of the crystals that are piezoelectric, electron-density redistribution must be taken ito account when analyzing the anisotropy of pressure-induced structural strain and the mechanisms of phase transitions. Systematic comparative studies of the series amino acids – salts of amino acids – complexes of amino acids, in addition to the comparative studies of the polymorphs of the same amino acid and of amino acids with different side chains, would be helpful. Much better mimetics for the 'compressibility of cavities studies' can be selected among a family of dipeptides with nanosize cavities and channels, which have been extensively and carefully studied by Görbitz during the last decade (Görbitz, 2001, 2003). One can compare the effect of pressure on layered dipeptides and on the dipeptide crystal structures having large cavities of variable size and hydrophobic or hydrophilic properties. The same systems can be used to mimic the effect of liquids on the compressibility and the conformational stability of the cavity. One can study compression in different liquids: hydrophilic, hydrophobic, containing special organic additives known to stabilize proteins of deap-sea piezophiles, using model crystal structures with the cavities of similar size, but with different – hydrophilic or hydrophobic – properties of the inner and outer walls of the cavities. Comparison of the compressibilities of different polymorphs (different structural arrangements of the same amino acid) and of the crystal structures of different amino acids may be relevant for understanding why the fragments of proteins built by different sequences of amino acids compress differently. The knowledge of the elastic properties of the selected fragments of the amino acid crystals is needed when considering muscles or biopolymers forming silk or spider threads. One can also use

the studies of strain induced by hydrostatic pressure in order to understand better the conformational transitions induced by substrate–receptor interactions by variations in temperature (cooling) or by collisions of the biopolymers. Varying side chains, or the length of the main backbone chains of amino acids and peptides forming the crystal structures, one can obtain control over dipole–dipole interactions, hydrogen-bond patterns, the occurrence or absence of the inversion center, and then study the effect of the molecular arrangement on the mechanical properties in a very systematic way. Hydrates can be compared to anhydrous amino acids, salts to amino acid molecules, mixed crystals with homomolecular phases *etc.* Amino acids can be modified chemically, substituting protons for methyl groups, in order to vary dipole–dipole interactions over a wide range. Selective deuteration can affect kinematic characteristics of zwitterions and hydrogen-bonding ability. Biomolecular assemblies (polyaminoacids, peptides, two-dimensional layered or nanoporous structures) can serve as an important bridge between crystalline amino acids and proteins.

5.2. Phase transitions

For many researchers, this is the most interesting direction of high-pressure research. Obtaining a new high-pressure phase and solving its structure is a real challenge. With recent development of the technique (see Katrusiak, 2004*b*, 2008), even *ab initio* crystal-structure solutions by direct methods are now possible for data collected in a diamond-anvil cell (DAC) using a laboratory diffractometer. Still, one should be very careful in interpreting the results. Many of the pressure-induced polymorphic transitions are isosymmetric and the structures of the ambient-pressure and the high-pressure phases are often related, especially if the structure is solved by single-crystal diffraction, which means that the crystal was brought safely through the phase-transition point. Therefore, it may not be sufficient to have a crystal structure solved and refined at two pressure points only to distinguish between a phase transition and an anisotropic continuous structural distortion. Sodium oxalate provides an example. The crystal structure of sodium oxalate does not change either its space-group symmetry $P2_1/c$ in all the studied pressure range below 8 GPa or the packing of the centroids of the oxalate anions, although the orientation of the oxalate anions at 4 GPa is about 15° different compared to that at ambient pressure, and this rotation is reversible on decompression (Fig. 6) (Boldyreva, 2003*b*; Boldyreva, Ahsbahs *et al.*, 2006). Only multiple-pressure measurements could confirm unambiguously the occurrence of a first-order phase transition, during which both the cell volume, and the cell parameters a, b and β change by a jump, as do the orientation of the oxalate anions and the coordination of the sodium cations by O atoms (Boldyreva, Shakhtshneider, Ahsbahs, Sowa & Uchtmann, 2002; Boldyreva, Ahsbahs *et al.*, 2006).

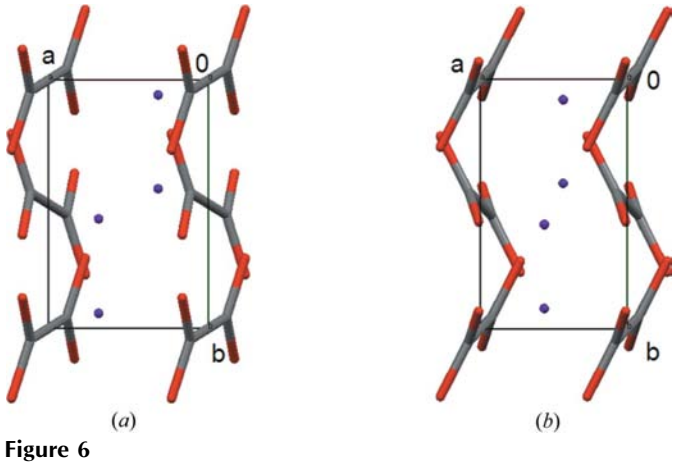

Figure 6
A comparison of the structures of (*a*) the low-pressure and (*b*) the high-pressure polymorphs of sodium oxalate (based on results from Boldyreva, Ahsbahs *et al.*, 2006).

Although discovering a new phase is always exciting, this is just the very beginning of the story. We are still very far from being able not only to predict the occurrence of a phase transition and the structure of the high-pressure phase *a priori* but also from understanding the mechanisms of the transitions that have already been observed and the relative role of thermodynamic *versus* kinetic factors in high-pressure polymorphism. More often than not, the transformations give metastable forms and not the thermodynamically preferable one. The facts which can indicate kinetically and not thermodynamically controlled transformations were discussed in a recent review (Boldyreva, 2007*b*). Different forms can be obtained on compression and on decompression, as well as with the same conditions from different starting polymorphs. Transformations are often not reversible. The effect of pressure is often different for single crystals and for powder samples. The transformation is often characterized by a pronounced induction period or a hysteresis. It can be incomplete or extended in a wide pressure range. Different forms can be observed, depending on how rapid compression and decompression were, and on how long the sample was held at a selected pressure. The transformation can be sensitive to the choice of the pressure-transmitting liquid (in which the sample is emerged in hydrostatic loading experiments).

I shall discuss a few examples. No phase transitions from paracetamol I into paracetamol II at pressures at least up to 4 GPa were observed for single crystals. At the same time, the powder samples of the same polymorph converted partially into form II at lower pressures, but this transformation occurred only on decompression from a higher pressure (Boldyreva, Shakhtshneider *et al.*, 2000; Boldyreva, Shakhtshneider & Ahsbahs, 2002). Other examples of phase transitions occurring on decompression only are described in the literature (Shibaeva & Yagubskii, 2004; Moggach, Allan, Clark *et al.*, 2006). An interesting example of kinetic control is provided by the polymorphs of glycine, which show a very different response to pressure. The structure of α-glycine ($P2_1/n$) is stable with respect to pressure-induced phase transitions at least up to 23 GPa (Murli *et al.*, 2003), β-glycine ($P2_1$) undergoes a reversible single-crystal to single-crystal phase transition at 0.76 GPa (Goryainov *et al.*, 2005; Dawson *et al.*, 2005), whereas γ-glycine ($P3_1$) transforms irreversibly into

δ-glycine (*Pn*) in a wide pressure range starting from about 3.5 GPa (Boldyreva, 2003*b*; Boldyreva *et al.*, 2003; Boldyreva, Ivashevsyaya *et al.*, 2004, 2005), which then converts into the ζ form on decompression down to 0.6 GPa (Goryainov *et al.*, 2006) (Fig. 7); the single crystals of γ-glycine are destroyed during the $\gamma-\delta$ transition. A recent incoherent inelastic neutron scattering experiment has shown that γ-glycine can transform into a layered polymorph (presumably the δ form) at pressures as low as about 0.6–0.8 GPa if the powder sample is kept under pressure in fluorinert in the slow-neutron beam for hours (Bordallo *et al.*, 2007).

It is remarkable that not only do the transformations of the two starting polymorphs (the β and the γ forms) occur at different pressures, but also the structures of the high-pressure phases in these two cases differ radically (β'- and δ-glycine, respectively). The concept of precursor-predetermined transformations, topotaxy, topochemical transformations or the Ostwald stage rule, which are traditionally used to describe solid-state reactions, structural transformations and the crystallization sequence of several polymorphs from solution (Boldyreva, 1999, 2007*a*; Boldyreva & Boldyrev, 1999), are no less applicable to pressure-induced transformations when molecular mobility in a solid is even more limited and one can expect those structural rearrangements to be favored which do not require large atomic displacements and breaking of multiple intermolecular bonds.

Another convincing example of a kinetically controlled pressure-induced phase transition is provided by β-alanine (Boldyreva *et al.*, 2007). The crystals of the ambient-pressure form transform into a structurally related polymorph if the sample is first compressed in small (0.5 GPa) steps up to 8 GPa and then decompressed in similar steps down to ambient conditions within a day; if the sample was compressed up to 5.5 GPa and then kept at this pressure for about three days, another high-pressure phase was formed which was preserved on decompression down to 1.6 GPa, and then converted back to the ambient-pressure form of β-alanine (Fig. 8).

A study of the effect of hydrostatic pressure on a solid implies the necessity of using a hydrostatic medium, usually a liquid. Even if the solid is not soluble in this liquid, one cannot exclude the possibility of an interaction between the solid surface and the liquid, which can affect the occurrence of a phase transition, its kinetics and the structure of the high-pressure phase (Boldyreva, 2007*b*). Examples are known from the literature where pressure-induced transitions could be observed when selected liquids were used and did not occur with other liquids or in dry samples (Boldyreva, Ahsbahs *et al.*,

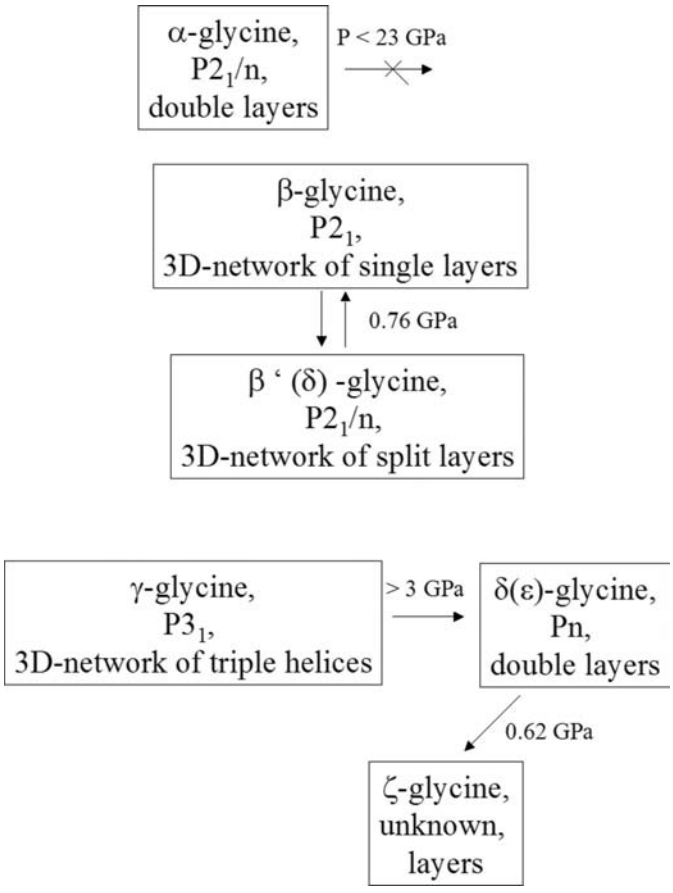

Figure 7
A schematic presentation of the pressure-induced transitions between the polymorphs of glycine; notations for the polymorphs are as in the publications, where the polymorphs were described first (Iitaka, 1960, 1961; Jönsson & Kvick, 1972; Boldyreva *et al.*, 2003; Boldyreva, Drebushchak, Paukov *et al.*, 2004; Boldyreva, Drebushchak, Shakhtshneider *et al.*, 2004; Boldyreva, Ivashevskaya *et al.*, 2004, 2005; Boldyreva, Kolesnik *et al.*, 2005, 2006; Boldyreva, Sowa *et al.*, 2006; Boldyreva, Ahsbahs *et al.*, 2006), notations in brackets were suggested in a later publication (Dawson *et al.*, 2005).

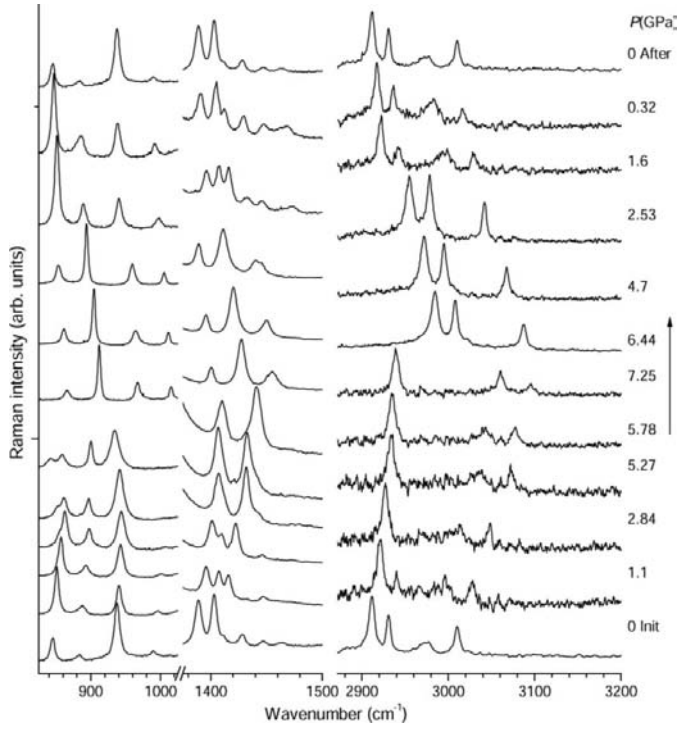

Figure 8
Selected fragments of the Raman spectra of β-alanine on compression and decompression. The sample was kept for several days at 6.4 GPa (based on data from Boldyreva *et al.*, 2007).

2000; Boldyreva, Dmitriev & Hancock, 2006). This phenomenon has relevance to pharmaceutical processing: many phase transitions on tabletting were observed only for slurries or when at least traces of solvent were present (Otsuka *et al.*, 1989, 1995; Okumura *et al.*, 2006).

Single-crystal and powder diffraction experiments can complement each other when studying high-pressure polymorphs. A recent example can be provided by a study of the isosymmetric phase transitions in L-serine. In contrast to glycine, serine zwitterions show significant jump-wise changes in conformation with increasing pressure (some torsion angles change by about 22°); reversible phase transitions are related to jump-wise changes in hydrogen-bond networks; molecular layers expand and get flatter, resulting in a total volume decrease with increasing pressure (Figs. 9 and 10) (Goryainov *et al.*, 2005; Moggach, Allan, Morrison *et al.*, 2005; Boldyreva, Kolesnik *et al.*, 2006; Boldyreva, Sowa *et al.*, 2006; Drebushchak *et al.*, 2006; Moggach, Marshall & Parsons, 2006). Sharp phase transitions I → II and II → III were detected in the single crystals of L-serine by optical microscopy and Raman spectroscopy (Goryainov *et al.*, 2005) and by single-crystal X-ray diffraction at about 5 GPa (Moggach, Allan, Morrison *et al.*, 2005; Drebushchak *et al.*, 2006) and at about 8 GPa (Drebushchak *et al.*, 2006; Boldyreva, Sowa *et al.*, 2006). During the I → II and the reverse II → I phase transitions in L-serine single crystals, an interface propagated rapidly (<0.3 s) from one side of the crystal to the other in the [100] direction, after a pronounced 'induction period' at a fixed pressure value, as if the transformation were of a cooperative 'cascade' type. At every selected time moment, the Raman spectra of only one phase (L-serine I, L-serine II or L-serine III) could be registered, different phases did not co-exist within the same crystal, at least for a time longer than 0.3 s. However, when powder samples of the same compound were studied by high-resolution X-ray powder diffraction, the co-existence of the two phases could be observed clearly in the pressure range between 5.3 and 6.4 GPa. The powder diffraction patterns at pressures higher than 5.3 GPa could not be indexed as belonging to a single-phase system: although most of the main lines corresponded well to those calculated from the model derived from single-crystal diffraction experiments, some weak peaks could not be ascribed to the same phase. The patterns could be interpreted assuming that the system contained some of the non-transformed phase I, decreasing with increasing pressure. The behavior of powder samples of L-serine at pressures higher than 6.4 GPa was even more complicated. The powder diffraction patterns could no longer be described satisfactorily either as belonging to a single phase (II below 7.8 GPa and III above 7.8 GPa) or as corresponding to a two-phase system (I + II, II + III or I + III). Neither could they be described as belonging to a I + II + III system. An alternative to a two-phase description of the observed powder diffraction patterns could be to assume the formation of a superstructure. Physically, a superstructure could result, for example, from a slight reorientation of serine zwitterions linked *via* hydrogen bonds in the head-to-tail chains along axis *a* (or of fragments of these zwitterions, such as $-CH_2OH$ groups or NH_3 tails). Weak extra peaks could also result from a nanostructured state of the sample with alternating very thin layers with slightly different structures (Tsybulya *et al.*, 2004). It is well known that the structures of metastable polymorphs crystallized from solution or of the products of solid-to-solid transformations often cannot be described as a homogeneous framework. Ever more examples are reported when nanosize layers of one structure alternate with the nanosize layers of another structure. Alternatively, some periodically or incommensurately modulated structures can be formed. Kinetic control of the transformations and the

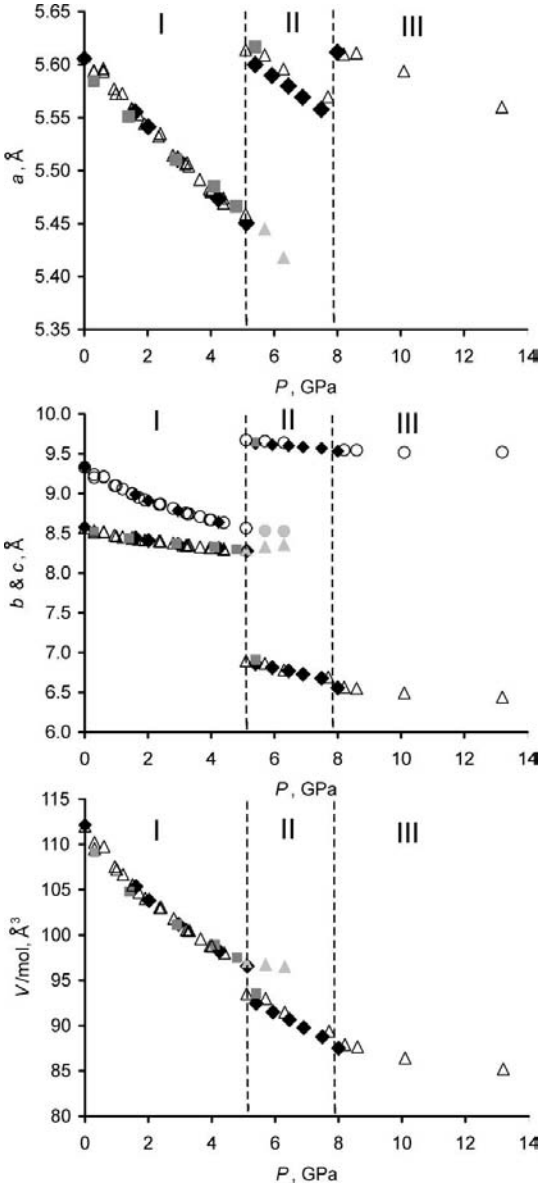

Figure 9
Cell parameters and volume *versus* pressure in the three polymorphs of L-serine; open symbols – powder diffraction data, black symbols – single-crystal diffraction data, gray symbols – phase I partly preserved after the I–II transition in the powder sample (reproduced with permission from Boldyreva, Sowa *et al.*, 2006).

stress field arising in the sample in the course of the transformation can account for this phenomenon.

Evidence that such lamellar intergrown 'polyphase crystals' (nanostructures) can be formed under non-equilibrium crystallization conditions at ambient pressure was provided, *e.g.* for aspirin (Bond *et al.*, 2007). When a structure is formed under high-pressure conditions, the process is also often kinetically controlled, the molecular mobility is restricted, and the sample is stressed and strained. Therefore, the nanostructure and modulated phases at high pressures can be expected to be formed more often than they have been reported up to now. The formation of a superstructure or a nanostructure was supposed in the recently found ζ-form of glycine (Goryainov *et al.*, 2006). For L-cysteine IV formed on decompression of L-cysteine III, the formation of a structure separated into zones which are alternately phase I like and phase III like was supposed (Moggach, Marshall & Parsons, 2006*c*). A similar phenomenon was reported recently for dabcoHBr complexes (Budzianowski & Katrusiak, 2006*a*,*b*). If one starts looking for the nanostructures and superstructures systematically, using appropriate techniques, more examples can be reported. For L-serine, X-ray powder diffraction patterns at pressures above 6.4 GPa could be well described, assuming the single-crystal structural models (for phase II below 7.8 GPa and for phase III above this point) with a superstructural tripling of *a* and *c* unit-cell parameters (Boldyreva, Sowa *et al.*, 2006). Interestingly enough, a neutron powder diffraction study of a completely deuterated L-serine sample at pressures up to 8 GPa (Moggach, Marshall & Parsons, 2006) gave the same 'basic' structural model for the high-pressure phase III as the single-crystal study (Drebushchak *et al.*, 2006) or the X-ray powder diffraction study (Boldyreva, Sowa *et al.*, 2006) but did not reveal either the coexistence of several phases in the sample or the formation of any super- or nanostructures. It is difficult to judge if the origin in this discrepancy is in the different choice of the techniques or of the different samples – the neutron diffraction patterns (Moggachh, Marshall & Parsons, 2006) are rather noisy in the regions where extra peaks were observed in the X-ray synchrotron diffraction spectra collected from a sample in a specially designed DAC without Be background (Sowa & Ahsbahs, 2006). One can also suppose that deuterated and non-deuterated samples may behave slightly differently, although the pressures reported for the two transitions in single crystals and powder samples are in good agreement for deuterated and non-deuterated samples. One can also expect 'simply' an irreproducible formation of the metastable non-equilibrium superstructures (or maybe nanostructures), sensitive to subtle changes in the sample characteristics and the compression conditions.

Predicting the occurrence of phase transitions and the structures of the high-pressure phases is no less difficult than predicting the strain anisotropy (see previous section). The absolute values of bulk compressibilities and the shapes of the $V(p)$ dependencies do not allow one to predict the stability of a structure with respect to pressure-induced phase transitions.

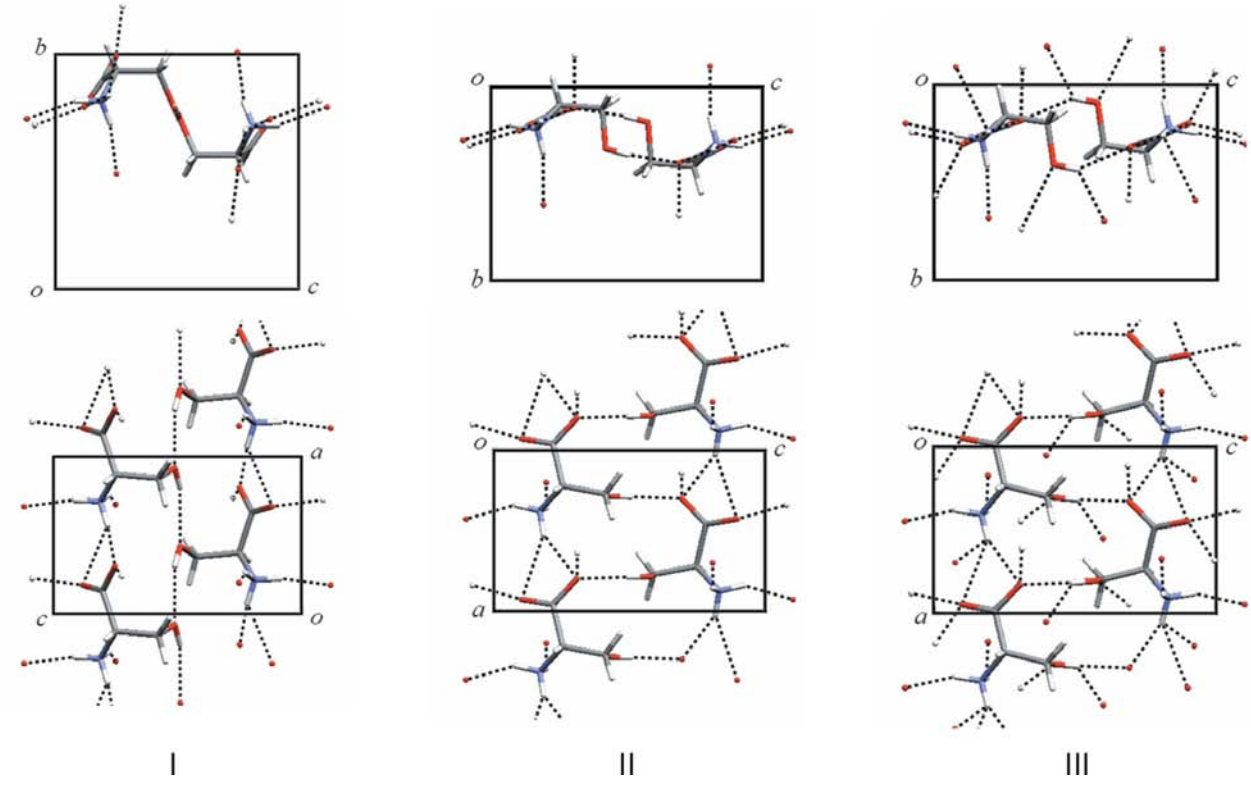

Figure 10
Fragments of the crystal structures of the polymorphs I at 4.2 GPa (left), II at 5.4 GPa (middle) and III at 8.0 GPa (right) of L-serine. Hydrogen bonds to neighboring molecules are shown by dashed lines (based on data from Boldyreva, Sowa *et al.*, 2006).

For example, although L- and DL-serine have very similar bulk compressibilities up to about 5 GPa, the ambient-pressure phase of DL-serine remains stable at least up to 8.6 GPa, whereas L-serine undergoes two isosymmetric phase transitions (at about 5 GPa and at about 8 GPa, see above). Pressure induces phase transitions in low-compressible γ-glycine, middle-compressible L-serine and highly compressible L-cysteine. The analysis of the short contacts, or of some 'limit value' in a hydrogen bond, which is achieved in the structure by a particular pressure, is somewhat more informative. At the same time, even if a particular type of hydrogen bonding is replaced by another one as a result of the phase transition, this conversion in some cases may simply promote efficient packing rather than a stronger hydrogen bond, as was shown recently for salicylaldoxime (Wood *et al.*, 2006).

Pressure-induced phase transitions in crystalline amino acids can mimic conformational changes in proteins and the first generalizations were made in recent reviews (Boldyreva, 2006, 2007*a*,*b*). An important observation is that the head-to-tail chains of zwitterions are preserved, whatever happens to the crystal structure of amino acids, also during the phase transitions. For glycine, a transformation from a triple-helix structure into a layered structure is possible but is irreversible. Transitions between different non-centrosymmetric layered structures are possible, double centrosymmetric layers are extremely stable. These findings may be relevant for the problem of different conformational stability of the regions of the peptides differing in secondary structure, for example of α-helices and β-sheets, as well as for understanding the mechanism of triple-helix-to-layer conformational transitions in collagens and other fibrillar proteins (Pain, 2000). In contrast to glycine, serine changes its conformation in the course of pressure-induced phase transitions. It is worth noting that it is the large conformational flexibility of L-serine that makes this residue so important for the substrate–receptor recognition and for the mechanical functions and cell motility in many biochemical processes (Titus, 1999; Hepler, 2000; Vale & Milligan, 2000; Liang, 2002). Cascade-type cooperative phase transitions in L-serine with a rapidly propagating interface can be compared with conformational changes responsible for the functioning of serine zippers in biochemical systems (Adamian & Liang, 2002; Finger *et al.*, 2006).

5.3. Chemical reactions

Two types of studies can be found in the literature: the reactions which are induced by pressure and the reactions which are induced by temperature or light, but are affected by pressure.

Dimerization, polymerization, more rarely isomerization, and decomposition provide examples of pressure-induced reactions. Traditionally, they were followed by spectroscopic techniques. At best, the structure of the final solid product was characterized by diffraction. With the progress in the experimental techniques (Katrusiak, 2004*b*, 2008), it became possible to apply powder and single-crystal diffraction to follow the fine details of the structural changes at multiple pressures before and after the chemical reaction and to correlate the structural strain preceding the reaction with the chemical transformation. Some of these examples are from inorganic chemistry but it seems to be relevant to mention them also when discussing the high-pressure studies of organic small-molecule crystals as an illustration of what can be done today.

A combined synchrotron X-ray diffraction, Raman scattering and infrared spectroscopy study of the pressure-induced changes in H_3BO_3 to 10 GPa revealed a new high-pressure phase transition between 1 and 2 GPa followed by chemical decomposition into cubic HBO_2, ice-VI, and ice-VII at ~2 GPa. The layered triclinic structure of H_3BO_3 exhibits a highly anisotropic compression with maximum compression along the *c* direction, accompanied by a strong reduction of the interlayer spacing. The large volume variation and structural changes accompanying the decomposition suggest high activation energy. This yields slow reaction kinetics at room temperature and a phase composition that is highly dependent on the specific pressure–time path followed by the sample. The combined results have been used to propose a mechanism for pressure-induced dehydration of H_3BO_3 that implies a proton disorder in the system (Kuznetsov *et al.*, 2006).

For carbon disulfide, the anisotropic structural distortion was followed up to 8 GPa, *i.e.* until the polymerization onset. The crystal structure was determined by direct methods from single-crystal X-ray diffraction at 295 K at two pressure points: 1.8 and 3.7 GPa (e.s.d.'s in the lengths of C=S bond 0.0001 nm!). Molecular rearrangements have been rationalized by the close packing and equidistant S$\cdots$S intermolecular interactions enforced by pressure. Although only slight lengthening of the covalent double C=S bond has been observed up to 3.7 GPa, the increase in the energy of the intermolecular S$\cdots$S and C$\cdots$S interactions revealed the possible reaction pathways of pressure-induced polymerization of CS_2 (Dziubek & Katrusiak, 2004).

A high precision of studying the changes in the intramolecular geometry at high pressure made it possible to follow the mechanism of the solid–solid phase transitions of $Co_2(CO)_6(XPh_3)_2$ (X = P, As) (Casati *et al.*, 2005; Macchi *et al.*, 2007). These metal carbonyl dimers transform the conformation of carbonyls about the Co—Co bond from staggered to eclipsed when the volume is reduced. The phase transition is accompanied by shrinking of metal–metal and metal–ligand bonds.

Polymerization of benzene belongs to one of the most studied pressure-induced reactions. Still, recent detailed diffraction studies of the effect of pressure on the interatomic contacts in the crystal at pressures below the transition point provide new information on the possible mechanism of the polymerization (Budzianowski & Katrusiak, 2006*a*). Interestingly, the polymerization of benzene occurs mainly during the decompression cycle favored by density decrease (Ciabini *et al.*, 2002). The polymerization of furan is similar to that induced in benzene but occurs at much lower pressure. The reaction starts on compression but becomes complete only with releasing pressure (Ceppatelli *et al.*, 2003). Compare

these results with the phase transitions which occur on decompression only (see previous section).

The studies of the effect of pressure on the reactions induced thermally or photochemically is another possible research direction. Such studies are very common in solution chemistry to elucidate the mechanisms of the reactions, *e.g.* to distinguish between the intra- and intermolecular mechanisms of the reactions of the coordination compounds and to study the role of the solvent in the reaction (Sinn, 1974; Stranks, 1974; Swaddle, 1974; Isaacs, 1981; Palmer & Kelm, 1981; van Eldik, 1986, 1999). In relation to the solid-state reactions, high pressure can be used as a tool of a continuous compression of the 'reaction cavity' (Boldyreva, 1996, 1997). A solid-state reaction itself generates strain in the crystal ('internal pressure') and this strain can influence the further reaction course *via* various feed-back mechanisms. High-pressure experiments can be helpful for simulating this strain and for elucidating the role of strain in the solid-state reactivity (Boldyreva & Boldyrev, 1999). This was illustrated for the intramolecular isomerization in a series of Co^{III} complexes (Boldyreva, 1994, 2001, 2003*a*,*b*; Boldyreva & Boldyrev, 1999). Photo- and thermo-isomerization were studied *in situ* at variable pressures up to 4 GPa and the values of the activation volumes were calculated; also, the anisotropy of structural strain induced in these compounds by hydrostatic pressure and by the reaction itself was compared. This allowed us to suggest a detailed mechanism of the feedback during this solid-state reaction and to explain why the reaction with a decrease in molar volume is inhibited by applying hydrostatic pressure. A similar approach could be applied to many solid-state photoisomerization reactions also in organic solids.

6. Prospects

The studies of the various aspects of the effect of pressure on molecular organic solids usually do not require very high pressures and very sophisticated experimental facilities. Much of the work referred to in this article was carried out using laboratory diffractometers. The field has a very promising future. In my opinion, which is of course very personal, the main challenges for the future are related to the following topics.

1. The interrelation between intra- and intermolecular distortions induced by pressure; relative contributions of these two types of distortions to the anisotropy of structural strain within the limits of stability of the same phase, and to the structural rearrangements resulting in phase transitions and chemical reactions; high pressure as a tool for improving the models used to describe the interatomic interactions in molecular crystals.

2. The role of the kinetic factors in pressure-induced phase transitions and chemical reactions; comparative studies of the effect of pressure on the same solid in different hydrostatic media; studies on the effect of hydrostatic or non-hydrostatic loading; the effects of the rate and duration of applying pressure; different behavior of the system on compression and on decompression; comparative studies of single crystals and powders with different particle size of the same compound.

3. Studies of the periodically and incommensurately modulated structures of the high-pressure phases, as well as of the nanostructured states; application of diffuse scattering in addition to 'classical' diffraction studies.

4. High-pressure studies of drugs: the possibility to obtain new polymorphs quenchable down to ambient conditions, acting as seeds for subsequent polymorphic transformations at ambient conditions; model research at hydrostatic conditions in relation to the processes occurring on grinding and on tabletting.

5. High-pressure studies of small-molecule crystals in relation to the dynamic properties of synthetic and natural biopolymers.

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