Pressure-induced phase transitions in organic molecular crystals: a combination of X-ray single-crystal and powder diffraction, Raman and IR-spectroscopy

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Abstract. The contribution summarizes the results of recent studies of phase transitions induced by high pressure in a number of molecular organic crystals, such as polymorphs of paracetamol, chlorpropamide, polymorphs of glycine, L- and DL-serine, β-alanine. The main attention is paid to the following topics: (1) Reversible / irreversible transformations; (2) Different behavior of single crystals / powders; (3) The role of pressure-transmitting liquid; (4) The role of the kinetic factors: phase transitions on decompression, or after a long storage at a selected pressure; (5) Isosymmetric phase transitions; (6) The role of the changes in the hydrogen bond networks / intramolecular conformational changes in the phase transitions; (7) Superstructures / nanostructures formed as a result of pressure-induced phase transitions.

Keywords: phase transition; amino acid; hydrogen bond; molecular crystal; X-ray diffraction; spectroscopy

1. Introduction
Pressure-induced phase transitions in the crystals formed by small organic molecules are interesting in relation to the interplay of the thermodynamic versus kinetic factors affecting polymorphism of solid organic compounds. The studies of these transitions help in achieving a better understanding of the conformational flexibility, rotational dynamics, and intermolecular interactions in organic solids. They can find important applications in pharmaceutical industry and in molecular electronics [1-17]. The present contribution gives a concise overview of a few recent examples from our own experience.
2. Experimental
The phase transitions were studied complementary by single-crystal X-ray diffraction (in laboratory), by X-ray powder diffraction (in laboratory and using a synchrotron source at SNBL, ESRF), by IR- and Raman-spectroscopy, and by optical microscopy. Details of the sample preparation, the types of the diamond anvil cells used, the instrumentation used for data collection and the software used for data processing was described in details in the original publications [18-34].

3. Examples of results.

3.1. Paracetamol
The high-pressure study of paracetamol was, to the best of our knowledge, the first study of a pharmaceutical under hydrostatic pressure by single-crystal X-ray diffraction [19]. The two polymorphs of this compound – the monoclinic (form I) and the orthorhombic (form II) ones – have been known since a very long time (Fig. 1) [35,36].

Polymorph I cannot be tabletted without excipients, polymorph II is easily tabletted, and was supposed to be more compressible [37]. Our X-ray diffraction study has shown, however, that the bulk compressibility of the two forms is the same, but the anisotropy of lattice strain is radically different (Fig. 2) [19,20].

On grinding, polymorph II transforms into polymorph I [20]. Our X-ray diffraction experiments in situ have shown, that on hydrostatic compression, on the contrary, paracetamol I transforms into
paracetamol II [20]. This transformation could be observed only if powder samples were taken, and not on direct compression, but on decompression down to about 1 GPa from a higher (above 4 GPa) pressure [20]. A few years later, paracetamol II was crystallized directly from solution at high hydrostatic pressure [12]. Theoretical calculations and experimental studies of paracetamol polymorphs at variable temperatures and pressures resulted in a conclusion, that form II becomes the stable polymorph at high pressures [38]. Thus, the transformation of paracetamol II to paracetamol I on grinding accounts for local heating at the contacts and / or shear strain, but not from the local pressure generation at the grain contacts. It is possible to avoid this transformation also during the pharmaceutical processing, if the presence of even traces of moisture in the system is excluded [39].

Since the single crystals of paracetamol I could be compressed without any phase transformations up to 4 GPa, the anisotropy of structural strain could be followed in relation to the pressure-induced changes in the molecular conformations and the compression of the intermolecular hydrogen bonds (Fig. 3) [19,40]. An interesting result is that although all the intermolecular hydrogen bonds are compressed with increasing pressure, the crystal structure expands in several crystallographic directions. This expansion is due to the flattening of the molecules and of the pleated molecular layers [19].

![Image](a)

**Figure 3.** Dihedral angle between the phenyl-ring and the plane of the acetamido-group in paracetamol (a) and its change with pressure (b); shortening of the distances between non-hydrogen atoms in the NH...OH and OH...O=C hydrogen bonds (c, full symbols) and corresponding shifts of the vibrational frequencies of the ν(OH) (d) and ν(NH) (e) versus pressure [19,20,40]. Open symbols in Fig. 3c correspond to NH...O bonds between NH3+ and NO2-groups in [Co(NH3)5NO2]Cl2 [18].
The compression of the NH…O and the OH…O hydrogen bonds is comparable, however, it manifests itself differently in the IR-spectra: red shift with increasing pressure was measured for –NH stretching vibrations, whereas the frequency of the –OH stretching vibration shifted to the blue (Fig. 3, d,e). The reason is that the hydroxyl-group is simultaneously a proton donor in the -OH…O=C- hydrogen bond, and a proton acceptor in the –NH…OH hydrogen bond [40].

3.2. Chlorpropamide

The high-pressure study of another solid drug, chlorpropamide (4-chloro-N-((propylamino)-carbonyl)-benzenesulfonamide) (Fig. 5), provides an example of a liquid-mediated phase transition at high pressure.

![Figure 5. A fragment of the crystal structure of chlorpropamide A. Green – Cl, red – O, blue – N, yellow – S, grey – C, white - H](image)

Chlorpropamide can be considered as a model compound to study polymorphic transformations on tabletting [41-43]. On tabletting, form-A has been reported to transform partially into another polymorph, form-C [41-44]. The density of the form-A (measured using an air comparison pycnometer) is larger, than the density of the form-C (measured in the same way), and this let Otsuka et al. conclude, that pressure increase on tabletting cannot account for the A-C transformation, since the molar volume of form-C is larger, than that of form-A [41,42]. Form-C is known to be formed from any other form of chlorpropamide on heating up to about 115 °C [45-47], and one might suppose, that the reported form-A to form-C transformation on tabletting could be a result of local heating, melting and/or recrystallization [41-43].

In a model study of the effect of hydrostatic pressure on form-A of chlorpropamide by Raman spectroscopy in a diamond anvil cell in situ, no “A-to-C” transformation with increasing pressure was observed, but two polymorphic transformations were claimed to occur at approximately 0.9 and 2.0 GPa [48]. Since the saturated solution of chlorpropamide in ethanol was used as a pressure-transmitting liquid in these experiments, one could not exclude the role of ethanol in these transformations.
In order to test, if any pressure-induced transformations can be induced by compressing a dry powder sample of chlorpropamide form-A, we have monitored the sample compressed in a diamond anvil cell in-situ by high resolution powder X-ray diffraction. In the absence of a pressure-transmitting liquid, obviously no A-C polymorphic transformation could be observed [33]. A polymorphic transformation of chlorpropamide form-A to form-C, that was reported during tabletting [41-43], must therefore be due to local heating effects. The pressure-induced phase transitions at 0.9 and 2.0 GPa studied by Raman spectroscopy on a sample of chlorpropamide form-A in its saturated ethanol solution [48] also appear to be solvent-mediated. This was confirmed by comparative X-ray diffraction studies of samples of chlorpropamide compressed in the saturated ethanol solution, or without any liquid at all [33,49].

An important conclusion from this study of chlorpropamide in relation to the tabletting problems, is the importance of taking into account, that liquids present in the system may have effect on the polymorphic transformations. Similar examples were described previously. No polymorphic transition could be induced by pressure in a Co(III)-coordination compound in a fluorinated oil, but it was observed easily at a relatively low pressure in alcohol [50]. Examples are described, when the effects of tabletting on a solid drug substance were also solvent-mediated. Thus, no phase transitions were observed on tabletting dry intact powder of indomethacin, but occurred if an ethanol slurry was compressed [51]. One should be especially careful, if the solid is soluble in the pressure-transmitting liquid at ambient conditions, as is the case of chlorpropamide and ethanol. The crystallization of new polymorphs and solvates of drug substances at high hydrostatic pressures has been described in several recent publications [12,14,15,52-54]. A similar process (a re-crystallization) can occur also when pressure induces polymorphic transformations in solids immersed into liquids.

3.3. Glycine

The polymorphs of glycine provide an example of a radical difference in the stability of several polymorphs of the same compound with respect to hydrostatic pressure, and of the pronounced kinetic effects in the polymorphic transformations (Fig. 6) [22-25,32,55-58]. The α-polymorph is stable at least up to 23 GPa (the highest pressure achieved in Raman spectroscopy experiments) [55], the β-polymorph transforms reversibly and without fragmentation of the single crystal into a high-pressure β'-polymorph at relatively low pressure, 0.76 GPa [24,56], the γ-polymorph transforms irreversibly into another high-pressure form, the δ-polymorph in a wide pressure range [23,25,32,56,58], and with a strong fragmentation of the starting single crystals [23,25,32,56]. On decompression, the δ-form is preserved down to 0.6 GPa, and then it transforms into another high-pressure form, the ζ-form, which is structurally related to other layered polytypes of glycine, such as the α-, the γ, the β', the β', and the δ-forms [32].

The structural changes in the polymorphs of glycine with increasing pressure and on decompression were followed directly by X-ray diffraction [22,23,25,56,57], and manifest themselves also very well in Raman spectra [24,32] and IINS spectra [58]. For example, the frequency of the NH-stretching vibration in the γ-polymorph shifts to the red with increasing pressure as this phase is compressed, then increases jump-wise at about 100 cm⁻¹, when some of the hydrogen bonds formed by these groups in the crystal structure of the γ-glycine break during the phase transition into the δ-form, and the structure, in which the triple helices are linked with each other in a three-dimensional network, transforms into a layered structure (Fig. 7) [32]. The pressure-induced γ-to-δ phase transition can be compared with the irreversible conformational transformations of collagen and other fibrillar proteins [59].
Figure 6. Schematic presentation of transitions between polymorphs of glycine [22-25,55,32]. Notation in brackets was suggested later in [56].

Figure 7. Frequency shifts of the ν(NH)-stretching vibration versus pressure, corresponding to the phase transitions of the γ-glycine into the δ-glycine on compression, and of the δ-glycine to ζ-glycine on decompression [32].
3.4. L- and DL-serine

The effect of pressure on the chiral and the racemic crystalline forms of another amino acid, serine, is very different. The bulk compressibility of the two crystals is the same up to about 5 GPa [27,30], but at higher pressures DL-serine is preserved as the same polymorph, whereas L-serine undergoes a cascade type reversible phase transition, during which an interface propagates rapidly through a crystal, which remains intact [26,60]. The space group symmetry of L-serine does not change on the transformation of L-serine-I into the L-serine-II, but the cell volume and the cell parameters change jumpwise, due to a jumpwise rotation of the side –CH$_2$OH chains. At a higher pressure (8 GPa) one more cascade type phase transition from L-serine-II into the L-serine-III occurs, during which the side –CH$_2$OH chains rotate cooperatively again (Fig. 8) [26,29,31,61]. The reversible polymorphic transitions in the crystals of L-serine at high pressures can be compared with the functioning of serine-serine zippers [62]. Pressure-induced reversible single-crystal to single-crystal isosymmetric phase transition resulting from a cooperative jumpwise rotation of oxalate-ions was observed recently in sodium oxalate [28].

Figure 8. Fragments of the crystal structures of the polymorphs of L-serine: I at ambient pressure (a,d), II at 5.4 GPa (b, e), III at 8.0 GPa (c,f) [29]. Hydrogen bonds to neighboring molecules are shown by dashed lines, numeration of hydrogen bonds refers to table Tables 1.2 in reference 29.

The structure of L-serine-III obtained by compressing a powder sample could be well described, assuming the single-crystal structural model [31] with a superstructural tripling of $a$ and $c$ unit cell parameters [32]. Interestingly enough, a neutron powder diffraction study of the completely deuterated L-serine sample at pressures up to 8 GPa [61] gave the same “basic” structural model for the high-pressure phase III, as the single-crystal study [31], or the X-ray powder diffraction study [32], but did not reveal either the co-existence of several phases in the sample, or the formation of any super- or nanostructures [61]. 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 [61] are rather noisy in the regions, where extra weak peaks were observed in the X-ray synchrotron diffraction spectra collected.
from a sample in a specially designed DAC without Be-background [63,64]. 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 a good agreement for deuterated and non-deuterated samples. One can also expect “simply” an irreproducible formation of the metastable non-equilibrium superstructures / nanostructures, sensitive to subtle changes in the sample characteristics and the compression conditions. This highlights once again the importance of kinetic factors and the role they play in obtaining reproducible results and complete phase transitions.

3.5. β-Alanine
An interesting behavior was observed recently for β-alanine (Fig. 9): the crystals of the ambient-pressure form transformed into a structurally related polymorph sharply at about 5.5 GPa for single crystals, and in an extended pressure range for powder samples. The single crystals were preserved, and the transformation was reversible, but only if the sample was 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 was kept at this pressure for about three days, another phase transition occurred, giving a different high-pressure form, which was preserved on decompression down to 1.6 GPa, and then converted back to the ambient-pressure structure of β-alanine, and the latter transformation resulted in the fragmentation of single crystals giving a fine powder sample [34]. The processes could be followed both by Raman spectroscopy and by X-ray diffraction. As an example, see the changes in the Raman spectra shown in Fig. 10.

Figure 9. A fragment of the crystal structure of β-alanine

Figure 10. Selected fragments of the Raman spectra of β-alanine on compression and decompression. The sample was kept several days at 6.4 GPa [34]
4. Conclusions

The selected examples from our recent experience aim to show, how complex and fascinating the phase transitions induced by very moderate pressures (below 8-10 GPa) in the crystals of organic small molecules can be. Kinetic factors play an enormous role in these transformations, and therefore the polymorph formed at a particular P-T conditions depends strongly not on the equilibrium phase diagram only, but to no less extent from the pre-history of the sample (the choice of a starting polymorph), the hydrostatic liquid, the rate of compression and the details of the compression-decompression procedure [16]. Since the symmetry of the crystal structures is low, the space group is often preserved even when molecules change their conformation, shift, or rotate, and only a detailed study at multiple pressure points makes it possible to distinguish reliably between an isosymmetrical phase transition and an anisotropic compression of the same phase [8].

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