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EFFECT OF HIGH PRESSURE ON THE POLYMORPHS OF PARACETAMOL

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Abstract

Effect of hydrostatic pressure on the two (I – monoclinic and II – orthorhombic) polymorphs of paracetamol was studied by X-ray diffraction in the diamond anvil cell at pressures up to 4.5 GPa (for the monoclinic form) and up to 5.5 GPa (for the orthorhombic form). The two groups of phenomena were studied: (i) the anisotropic structural distortion of the same polymorph, (ii) transitions between the polymorphs induced by pressure.

The anisotropy of structural distortion of polymorphs I and II was well reproducible from sample to sample, also from powder samples to single crystals. The bulk compressibility of the two forms was shown to be practically the same. However, a noticeable qualitative difference in the anisotropy of structural distortion was observed: with increasing pressure the structure of polymorph II contracted in all the directions showing isotropic compression in the planes of hydrogen-bonded molecular layers, whereas the layers in the structure of the polymorph I expanded in some directions. Maximum compression in both polymorphs I and II was observed in the directions normal to the molecular layers.

The transitions between the polymorphs induced by pressure were poorly reproducible and depended strongly on the sample and on the procedure of increasing/decreasing pressure. No phase transitions were induced in the single crystals of the monoclinic polymorph at pressures at least up to 4 GPa, although a partial transformation of polymorph I into polymorph II was observed at increased pressure in powder samples. Polymorph II transformed partly into the polymorph I during grinding. The transformation could be hindered if grinding was carried out in CCl_4.

Keywords: diamond anvil cell, high pressure, hydrogen bonds, paracetamol, polymorphic transformations, polymorphs, X-ray diffraction

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Introduction

4-Hydroxyacetanilide was first prepared by Morse in 1878 [1]. Its pain and fever relieving properties were discovered in 1893 [2]. Since the late 1950s – early 1960s it is widely used as an analgetic and antipyretic drug under the names paracetamol, acetaminophen and panadol [3]. It is considered to be the most prominent among acetanilide derivatives. Physical and chemical properties of paracetamol, as well as its bioavailability are being extensively studied. The interest in the paracetamol and its importance can be seen e.g. from a detailed (456 references) bibliographic review devoted to this compound [1–4].

Physical and chemical properties of different polymorphs of a drug, as well as their bioavailability may differ to a large extent. The same is true for their behavior during processing and storage. Therefore, comparative studies of different polymorphs of the same drug are of great interest and importance [5–8]. The stability relationship in respect to temperature of the polymorphs I and II is a monotropic one with the polymorph I as the stable modification for all temperatures below the melting point of this form at 168.5°C. Therefore, on the basis of isobaric conditions only solid-state transformations from the orthorhombic modification II into the monoclinic form I are thermodynamically allowed [9].

Up to now, the existence of three polymorphs of paracetamol was reported in the literature. Only for two of them (I and II) crystal structures are known. The monoclinic polymorph I could be obtained by crystallization from aqueous solutions [10], and also from many other solvents [11, 12]. The structure of the polymorph I was first solved and refined by Haisa *et al.* [10]; later more precise data were obtained at 123 K by Nichols and Frampton [13] and at 150 K by Naumov *et al.* [14].

Haisa *et al.* [15] have obtained also a metastable orthorhombic polymorph II (with density about 1.03 times higher than that of polymorph I) by slow evaporation from an ethanol solution and have solved and refined its crystal structure at ambient conditions by single-crystal X-ray diffraction. However, this method of obtaining polymorph II turned out to be not always reproducible, as it often happens when crystallizing metastable polymorphs [16]. In a series of studies [17–19] crystallization of paracetamol from ethanol solutions always gave solely polymorph I. Polymorph II could be reproducibly obtained by crystallization of paracetamol from the melt in a non-oxidizing atmosphere (an anhydrous nitrogen or argon) [13, 20–30]. A reliable laboratory-scale method of crystallizing large crystals of the orthorhombic form II of paracetamol either from a supersaturated benzyl alcohol solution, or from saturated IMS (industrial methylated spiritis solutions, i.e. ethanol with circa 4% methanol by volume), using seeds of polymorph II obtained by cooling the melt, was suggested in [13]. Single crystals suitable for X-ray analysis were obtained by this method, and crystal structure was refined at ambient temperature and at 123 K [13]. The crystallization of polymorph II or, alternatively, of polymorph I from the melt is strongly affected by the rate of cooling. Rapid quenching leads preferably to the crystallization of the monoclinic polymorph I; a low regular cooling rate allows one to obtain mainly polymorph II [27]. Transformation of the crystals of polymorph II into polymorph I

in solution [13], and also as a result of grinding [27] was reported. At the same time, in some papers no transformation of polymorph II into I could be induced by storage, grinding or by compacting [13, 22].

The existence of polymorph III was claimed in several publications [24, 26–30]. This form (obtained by crystallization from the melt) was shown to be very unstable and to convert rapidly into polymorph II. Polymorph III could be considerably stabilized between glass plates or in a glass capillary. Polymorph III was supposed to be an intermediate in the I⇔melt⇔II transitions, important for establishing the recrystallization balance [27]. Transition of polymorph III to polymorph I was never observed. Polymorph III was characterized by infrared and Raman microscopy [27–30]. The transitions of polymorph III into polymorph II and of the polymorph II into polymorph I were characterized by DSC: all the polymorphs were found to be close in energies ($\Delta H_{\text{II-I}} \cong 0.4$ KJ mol^{-1}, $\Delta H_{\text{III-II}} \cong -1.2$ KJ mol^{-1}, $\Delta H_{\text{fus,I}} \cong 28$ KJ mol^{-1}, $\Delta H_{\text{fus,II}} \cong 26.7$ KJ mol^{-1}) [27–30]. Because of the low stability of the polymorph III, the authors of papers [24, 27] were not in the position to get X-ray patterns for it. The authors of the references [20, 26] claimed that they managed to characterize polymorph III by its DSC profile and X-ray pattern, but no data were reported.

The polymorphs of paracetamol differ in their ability to be compressed into tablets. Polymorph II is suitable for direct tabletting, whereas polymorph I requires either various additives (like gelatin, PVP, starch, etc.), or special methods of preparation (e. g. recrystallization from a dioxane solution) [13, 20, 31, 32].

The studies of the effect of pressure on the polymorphs of paracetamol are interesting in several respects:

(i) They can be a helpful for achieving a better understanding of the intermolecular interactions, in particular – hydrogen bonds, in these molecular crystals. This is important for controlling the crystallization and dissolution, the bioavailability of the drugs, as well as for improving potentials used for structure and polymorph predictions [33].

(ii) Variation in pressure could be no less efficient than variation in temperature for inducing polymorphic transformations and for obtaining new metastable forms. It is important also to take into account, that temporal increase in pressure is unavoidable when tabletting the samples.

(iii) In some publications the differences in the compaction properties of different polymorphs and in their mechanical properties were supposed to be directly related to the differences in the compressibilities of their crystal structures [20].

In 1998–2000 we have published some data on the effect of hydrostatic pressure on the crystal structure of the monoclinic polymorph of paracetamol [34–36]. The aims of the present contribution were (i) to compare the bulk compressibilities and the anisotropy of structural distortion induced by high pressure for polymorphs I and II of paracetamol and (ii) to study the possibility to induce polymorphic transformations not by temperature, but by pressure changes.

Experimental

Materials

Commercially available monoclinic polymorph I of paracetamol produced at Kursk Pharmaceutical Plant (Russia) was used. The sample was recrystallized from an ethanol solution. X-ray powder diffraction and IR-spectroscopy have not revealed any impurities of other polymorphs in the sample. The orthorhombic polymorph II was obtained by slow cooling of the melt of paracetamol in argon atmosphere. For X-ray powder experiments the sample suspended in CCl_4 was gently ground to a fine powder using an agate pestle and mortar. Without CCl_4 a noticeable transformation of polymorph II into polymorph I was observed. The purity of the samples was controlled by X-ray powder diffraction and IR-spectroscopy.

High-pressure experiments

Hydrostatic pressure was created in a lever-arm diamond anvil cell (DAC) (opening angle 30°) [37] using a penthane-isopenthane mixture (1:1) as the pressure-transmitting liquid. The ruby fluorescence technique [38, 39] was used for pressure calibration, with the accuracy of ±0.05 GPa. Pressure was measured at least twice for each experiment: prior to measuring diffraction pattern and after this. X-ray diffraction patterns of the samples were investigated first increasing ('way up') and then with decreasing ('way down') pressure.

X-ray powder diffraction patterns were obtained by a film technique using Debye–Scherrer method. MoK_{α_1}-radiation (λ=0.7093 Å) and MoK_{β}-radiation (λ= 0.6323 Å) were used in different series of experiments. Exposure time was 30 and 40 h, correspondingly. X-ray radiation was focused by a bent quartz crystal monochromator. Line positions on the film were measured with a special device, combining measuring microscope with a digital micrometer with 1 μm reading. Relative intensities of the reflections were estimated visually. The film technique would not make it possible to refine atomic coordinates or to solve an unknown crystal structure, but it worked satisfactorily to identify any known phases, to measure the pressure-induced changes in lattice parameters, and to observe the occurrence of polymorphic transitions.

Indexing of diffraction patterns was done based on the structural data for ambient conditions [10, 15]. To avoid ambiguities in the indexing, pressure was increased very steadily, in small steps. A continuous character of changes in the interplanar spacings d_{hkl} with pressure (in the range where no phase transitions occured) and the ratio of relative intensities of the reflections were controlled.

An unpublished computer program of Marburg University was used to calculate d_{hkl}-values from the measured positions of maxima on a photographic film. Lattice parameters were calculated and refined from d_{hkl} using a program ULM [40]. Strain tensors were calculated using the programm TENSOR written by Ohashi [41]. Theoretical powder diffraction patterns were calculated with the program Powder-Cell [42]. The same program was used for the visualization of the fragments of the crystal structures.

Results

Comparison of the anisotropy of structural distortion of the polymorphs of paracetamol

The anisotropy of structural distortion of the monoclinic polymorph I of paracetamol was studied in details at various pressures up to 4 GPa by powder [34, 35] and by single-crystal [36] X-ray diffraction techniques in the diamond anvil cells. In the present study it was compared with the data on the anisotropy of pressure-induced compression of the orthorhombic polymorph II, which were obtained from the powder diffraction experiments.

The changes in the volumes of the unit cells and the lattice parameters of polymorphs I and II of paracetamol *vs.* pressure are plotted in Figs 1 and 2. The anisotropic compression of structures of polymorphs I and II was well reproducible from sample to sample, and also from powder samples to single crystals. No hysteresis was observed when increasing and then decreasing pressure (Fig. 3).

Relative volume changes of the two polymorphs are compared in Fig. 4a. Despite different crystal structures, bulk compressibilities of the two polymorphs were found to be very similar (maybe, the monoclinic polymorph is slightly more com-

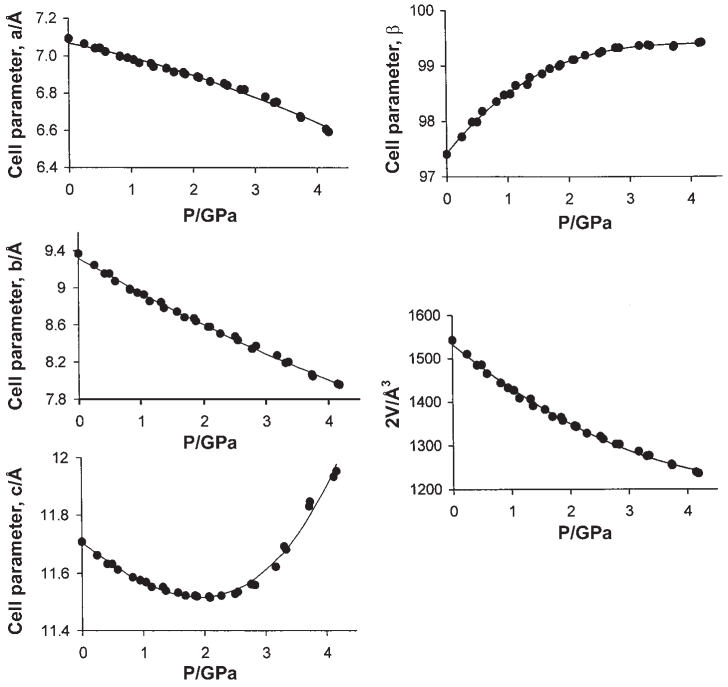

Fig. 1 Cell parameters (a, b, c, β) and volume (*V*) *vs.* pressure in the monoclinic polymorph I of paracetamol. In order to facilitate the comparison with the orthorhombic phase, 2 *V* values are plotted for the monoclinic polymorph

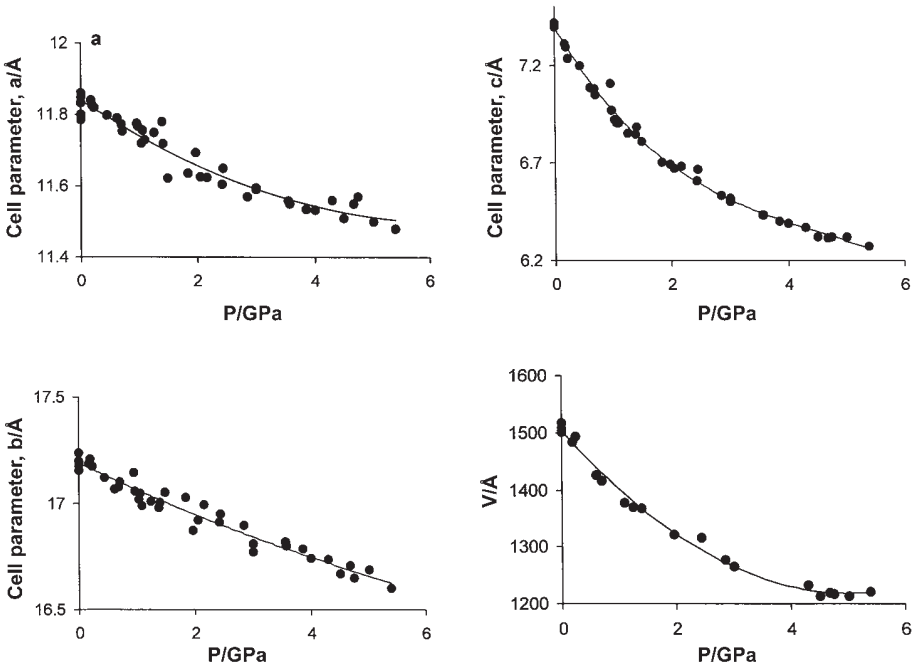

Fig. 2 Cell parameters (a, b, c) and volume (*V*) *vs.* pressure in the orthorhombic polymorph II of paracetamol

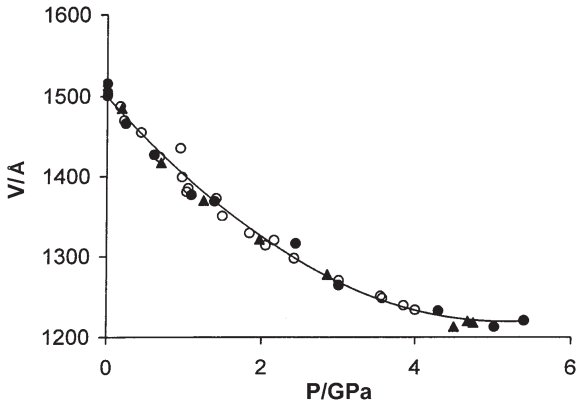

Fig. 3 A comparison of changes in cell volume of the polymorph II of paracetamol: ● – obtained from the melt, pressure increasing; ▲ – obtained from the melt, pressure decreasing; o – obtained from the polymorph I in the DAC, pressure decreasing

pressible). The orthorhombic polymorph was previously supposed to be noticeably more compressible than the monoclinic one [20]. Very recently this result was also

obtained during a model calculations [43]. However, our findings do not support the hypothesis of the higher compressibility of the form II.

At the same time, the anisotropy of pressure-induced structural distortion of the two polymorphs was qualitatively different. With increasing pressure the structure of polymorph II contracted in all the directions, whereas the structure of the polymorph I expanded in some directions. Linear strain in the directions of principal axes of the strain tensors is plotted in Fig. 4b. Maximum linear compressibility was measured to

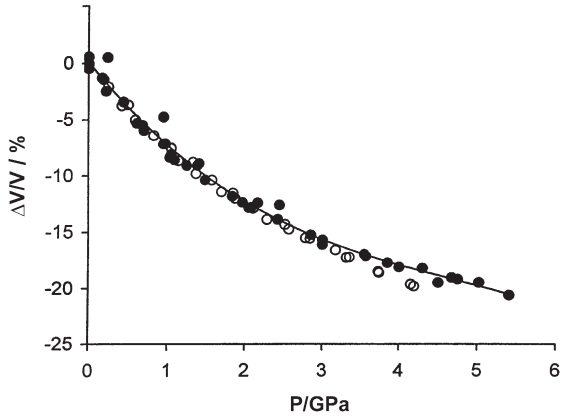

Fig. 4a Relative volume changes for the two polymorphs. White symbols correspond to polymorph I, black symbols – to polymorph II (holds for 4a and 4b)

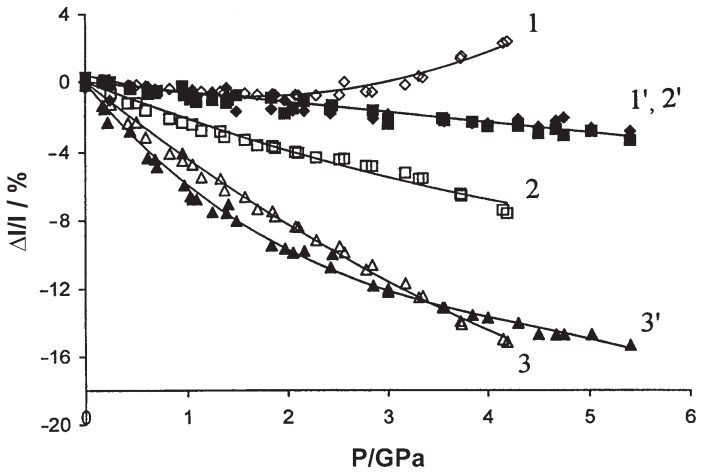

Fig. 4b Relative linear strain in the directions of principal axes of strain tensors of polymorphs I (1, 2, 3) and II (1′, 2′, 3′). 1, 2, 3 and 1′, 2′, 3′ denote directions of the principle axes of strain tensors. 1 & 1′ corespond to the directions of maximum, and 3 & 3′ – of minimum linear dimension of strain ellipsoids. White symbols correspond to polymorph I, black symbols – to polymorph II (holds for 4a and 4b)

be similar (although not identical) for polymorphs I and II. In the orthorhombic polymorph II linear compressibility in the plane normal to the direction of maximum compressibility turned out to be isotropic, at least within the experimental error (compare linear compression along directions of principle axes 1′ and 2′ in Fig. 4b). In the monoclinic polymorph I up to approximately 1.5 GPa linear compression along principle axis 1 was nearly the same as in the polymorph II, whereas at higher pressures the structure of polymorph I started to expand along this axis. Linear compression along axis 2 in the polymorph I was noticeably larger than that in the polymorph II, and as a result, despite the expansion of the structure in particular directions, bulk compressibilities of the polymorphs I and II were similar.

Pressure-induced polymorphic transitions

The transitions between the polymorphs induced by pressure were poorly reproducible and depended strongly on the sample and on the procedure of increasing/decreasing pressure.

Transition I→II.

No phase transitions could be induced in the single crystals of the monoclinic polymorph at pressures at least up to 4 GPa [35]. A partial transformation of polymorph I into polymorph II was observed at increased pressure if a powder sample was used. The transition was irreversible and poorly reproducible. In a first run the pressure in the DAC with the powder sample of the polymorph I of paracetamol was increased in one step from ambient to 1.6 GPa, and then it was further increased slowly (by 0.2–0.3 GPa steps) up to 4.2 GPa. No polymorphic transitions were observed. The powder pattern could be indexed as monoclinic. After this, pressure was decreased slowly, by steps of 0.2–0.3 GPa, and no phase transitions were observed down to 1.3 GPa. At this point the pressure in the cell spontaneously dropped to 0.7 GPa. The powder diffraction pattern obtained from the sample revealed a mixture of polymorphs I and II. With increasing pressure up to 1 GPa and then to 2 GPa the relative content of polymorph II in the mixture increased, but the conversion I→II in this experiment was never complete. After the pressure was released, the sample consisted of a mixture of polymorphs I and II. In investigations of polymorph I no polymorphic transition I→II was observed if the pressure increased slowly up to 1.5 GPa. Also no polymorphic transition could be observed if pressure increased rapidly, during one day, up to 4 GPa, and then decreased slowly.

Transitions II→I and II→?

Polymorph II transformed partly into the polymorph I during grinding. The transformation could be hindered if grinding was carried out in CCl_4. After hydrostatic pressure increased up to 0.6 GPa, the admixture of the monoclinic polymorph (which was produced in the powder sample of polymorph II as a result of grinding) disappeared completely and irreversibly.

In another series of experiments on powder samples of polymorph II, at increasing hydrostatic pressure by 0.3–0.5 GPa up to approximately 2 GPa, some new weak lines were observed in the powder diffraction pattern (with d-values within the range 3.4–3.6). These lines disappeared after pressure was released. In principle, the lines could be indexed as belonging to polymorph II, which were, however, not observed at lower pressures. Alternatively, they could belong to another polymorph, maybe to polymorph III. It is not possible at the present stage to make unambiguous conclusions.

Discussion

In order to interpret the data on the effect of pressure on the polymorphs of paracetamol, it is necessary to compare their crystal structures. Individual molecules in the polymorphs I and II form two-dimensional layers linked by NH···OH···O=C– hydrogen bonds. Only weak van der Waals and π-π interactions between the phenyl rings exist between the layers [10, 15].

The structures of individual molecules in the two forms are similar (Fig. 5). The length of the C=O bond and the value of the dihedral angle between the planes of the phenyl ring and the acetamide group in the molecules somewhat differ. In the monoclinic polymorph I C=O bond is 1.232 Å, that is noticeably (about 0.01 Å) longer than the value 1.223 Å in the orthorhombic form II. The dihedral angle in polymorph I is 21.1°. It is 3° larger than that in form II, 17.7°. These two parameters describing the intramolecular geometry are closely interrelated with the characteristics of the intermolecular hydrogen bonds. Intramolecular C=O bond in paracetamol becomes longer as intermolecular hydrogen bonds are shortened, e. g. with decreasing temperature. In the orthorhombic polymorph, the intermolecular NH···O and OH···O hydrogen bonds are about 0.04 and 0.06 Å longer, than in the monoclinic polymorph, although the crystal structure of the polymorph II is denser than that of polymorph I. Correspondingly, the C=O bond in polymorph II is shorter. The value of the intramolecular dihedral angle is strongly sensitive to the degree of the deprotonation of a paracetamol molecule and to the charge distribution over the atoms in the molecule [44]. Therefore it should be also sensitive to any changes in the intermolecular hydrogen bonds. This hypothesis can be supported by the fact that an

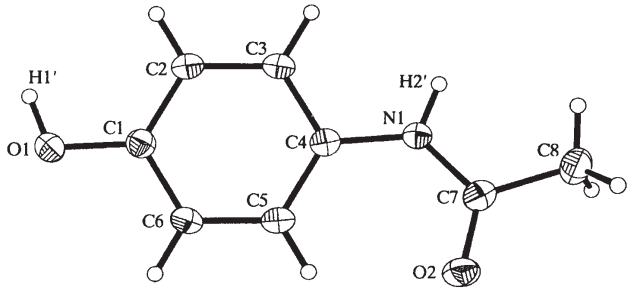

Fig. 5 Molecular structure of paracetamol

ab initio optimized individual paracetamol molecule should be flat, with the value of dihedral angle equal to 0° [44], whereas at ambient conditions the crystals of polymorphs I and II show dihedral angles of 21 and 18°, correspondingly [10, 13–15].

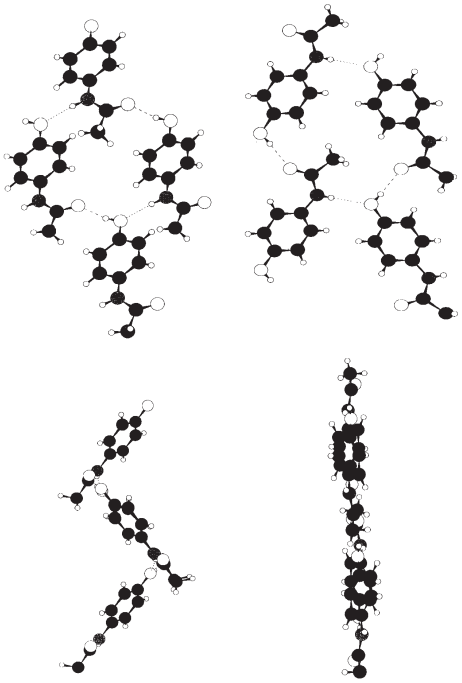

Fig. 6 Two projections of cycles formed by paracetamol molecules in the crystals of polymorphs I (left) and II (right)

The main difference in the crystal structures of the polymorphs I and II is related not to the structure of individual molecules, but to the linkage of them. The molecules are connected by intermolecular hydrogen bonds and form rings (Fig. 6), that are arranged into layers (Fig. 7). The structures of these layers are different in both polymorphs. The orientation of molecules within a ring is different in the polymorphs I and II. In the monoclinic polymorph the rings formed by molecules within the layer are essentially not flat: the mean deviation at ambient pressure is about 0.25 Å. As a result, the layers are pleated. On the contrary, the rings in the orthorhombic polymorph are almost flat (mean deviation 0.08 Å), leading to plane layers.

The two-dimensional hydrogen-bonded networks in both polymorphs can be considered also as built from chains of paracetamol molecules linked with each other. The structure of an individual chain is similar in polymorphs I and II, but the orientation of these chains with respect to each other is different. The sequence of chains within a layer can be defined as A-A-A in the monoclinic polymorph I, and as A′-B-A′ – in the orthorhombic polymorph II. The chains defined as A and B differ in the ori-

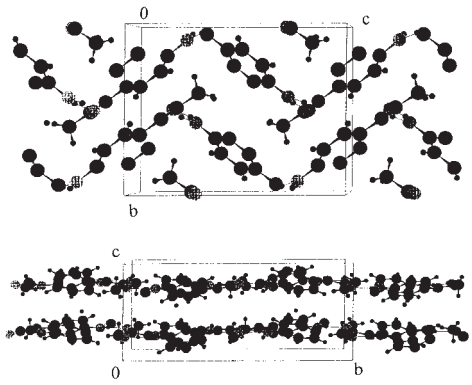

Fig. 7 Layers formed by paracetamol molecules in: polymorph I as pleated layers (above), polymorph II as flat layers (below)

entation. The chains A and A′ have the same orientation of molecules but the intermolecular bonds and angles in the chains are somewhat different (Fig. 8).

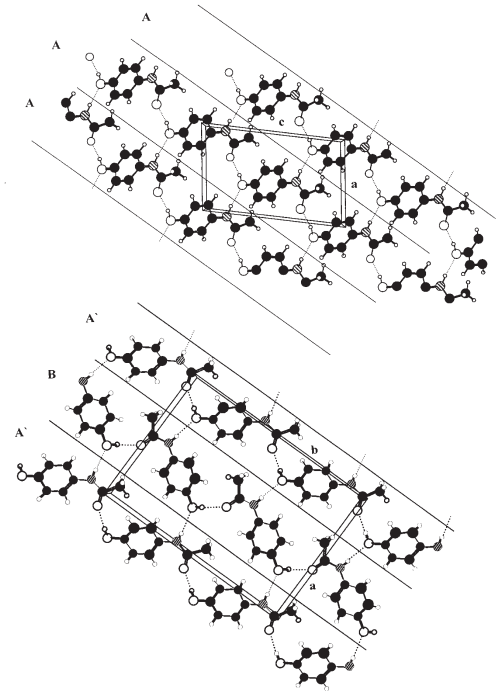

Fig. 8 Chains formed by paracetamol molecules in the individual layers in the crystals of polymorphs I (a) and II (b)

The anisotropy of structural distortion of solids under pressure is a manifestation of the anisotropy of interatomic interactions in the crystal. Maximum compression in

both polymorphs of paracetamol was observed in the directions normal to the layers formed by hydrogen-bonded molecules. Despite different structures of the layers in polymorphs I and II, the linear compressibility normal to the layers was not very different. The qualitatively different anisotropy of structural distortion within the layers in polymorphs I and II must be related to the differences in the structure of these layers, which were discussed above. Not only the compressibility of the intermolecular NH···O and OH···O hydrogen bonds, but also the ability of the molecules in a layer to change the intramolecular dihedral angles and to rotate with respect to each other (reducing both the puckering of the individual molecules, and of the whole layers) determine the observed anisotropy of structural distortion with increasing pressure. For the monoclinic polymorph this was confirmed by single-crystal X-ray diffraction experimental data [36]. Expansion of pleated layers in the monoclinic polymorph is due mainly to the changes in the angles between the neighbouring molecules. No expansion takes place in the orthorhombic polymorph, in which layers are flat already at ambient pressure. Isotropic compression of a layer in the orthorhombic polymorph can be explained by a cooperative behavior of all hydrogen bonds in the network, due to which the differences in the compressibilities of individual NH···O and OH···O bonds do not manifest themselves in the compression of the layer as a whole. In the monoclinic polymorph the hydrogen bond network also acts cooperatively during compression, so that the averaged characteristics of a ring in the network are preserved [36].

Polymorphic transition of I into II with increasing pressure agrees well with the fact that the molar volume of polymorph II is at about 3.5% smaller, than that of polymorph I. Thermodynamically, high pressure should facilitate the I→II transition. At the same time, one can expect an interconversion of forms I and II of paracetamol to be kinetically hindered, since it would require a reorientation of every other chain in a layer. This must be difficult because of steric restrictions, and also because of the necessity of breaking many intermolecular hydrogen bonds in a layer. One can hardly expect such a process to take place within the bulk of a crystal. The process must be limited by nucleation. This may explain, why the interconversion of polymorphs I and II often takes place either in contact of the crystals with the saturated solution [13], or in the melt [13, 20–29], when nucleation can be assisted by the liquid phase. A recent study of Politov and co-workers has shown that amorphous state (in which various orientations of the neighbouring molecules with respect to each other are possible) may act as an important intermediate in the I↔II interconversions [45]. Shear stresses and plastic deformation can facilitate the II→I polymorphic transition, and this may be a reason, why the transformation was often observed as a result of grinding [27]. Increasing hydrostatic pressure must favour the I→II transformation thermodynamically, but, at the same time, the re-orientation of the chains within a layer can become even more difficult at high pressure, than it is at ambient pressure. This may account for the facts, that the transition is poorly reproducible, that it was observed only for polycrystalline samples, and that it requires very special conditions of rapid increasing and slow decreasing pressure.

Poor reproducibility of a polymorphic transition and its sensitivity to the conditions of increasing and decreasing pressure are typical of organic molecular crystals in general. Many examples of polymorphic transitions in organic solids require large overcooling, or are even absolutely hindered [46]. In the same review [46] a phenomenon was described, which is very similar to the one observed in the present paper for the pressure-induced I→II transition in paracetamol. Although the equilibrium pressure of a polymorphic transition in CBr_4 is 13000, no transition could be observed at any pressure up to 50000 kg cm^{-2}, whatever the duration of keeping the sample under pressure was. However, if the pressure was decreased slowly after CBr_4 was kept for some time at 50000 kg cm^{-2}, then the polymorphic transition that is accompanied by a decrease in molar volume could take place (e.g. at a pressure equal to 20000 kg cm^{-2}). Such a phenomenon would be impossible if the transformation were controlled by thermodynamics alone, and the processes of the initiation played no role [46].

The transition in CBr_4 mentioned above provides an example of a kinetically hindered polymorphic transformation, which occurs when decreasing pressure, although the molar volume decreases during the transformation [46]. There are examples of polymorphic transformations, where the transition could be observed for a powder sample at a much lower pressure, than for a single crystal of the same compound. Thus, a powder sample of pentaerythritol underwent a polymorphic transformation at 500 MPa, whereas a single crystal of the same compound transforms only at pressures higher than 1.5 GPa [47]. An explanation should be sought in the different conditions for the nucleation of the new phase in a relatively large single crystal and in small powder particles. It is also known, that the polymorphic transformations, for which nucleation is hindered, can be sensitive to the choice of the pressure-transmitting liquid, presumably because of the interaction of the liquid with solid surface. As one of the recently described examples, one can refer to the pressure-induced polymorphic transition in $[Co(NH_3)_5NO_2]I_2$ [48].

Conclusions and outlook

Studies of pressure-induced structural distortions of the same phase not caused by a polymorphic transition are helpful for achieving a better understanding of intermolecular interactions in molecular crystals . It is of special importance to compare the anisotropy of structural distortion of the polymorphs of the same compound, which differ only in their molecular assemblage. Comparative structural studies at variable pressures can also provide valuable knowledge on the factors affecting the polymorphic transitions between different forms of the same drug. The present study of the effect of pressure on the polymorphs of paracetamol may serve as an illustration of the both statements.

The bulk compressibility of the polymorphs I and II of paracetamol was shown to be nearly identical. However, a noticeable qualitative difference in the anisotropy of structural distortion was observed: with increasing pressure the structure of polymorph II contracted in all the directions showing isotropic compression in the planes of hydrogen-bonded molecular layers, whereas the layers in the structure of

the polymorph I expanded in some directions. Maximum compression in both polymorphs was observed in the directions normal to the molecular layers.

Experimental structural data at variable pressures can be helpful for optimizing the force fields and the atom-atom potentials used in structure simulations and predictions of polymorphs. A recent example of such a study was presented at the ECM-19 in Nancy [50]. For a structure like that of paracetamol, a simulation must take into account several important points, which make a model more complicated than a rigid-body approximation: molecules are flexible, molecules can rotate with respect to each other; any change in the intermolecular hydrogen bonds would result in the redistribution of the electronic density at the atoms and can therefore affect both the intramolecular geometry and the intermolecular interactions. For example, compression of the intermolecular hydrogen bonds in the structure of the monoclinic polymorph of paracetamol is interrelated with the distortion of intramolecular geometry [36], and manifests itself also in the pressure-induced shifts of the intramolecular vibration frequencies in the IR-spectra [51].

A very recent attempt of predicting the anisotropy of the elastic properties of the polymorphs I and II of paracetamol based on a computer simulation of the structures [43] was successful in predicting only the rather obvious fact, that the direction normal to the molecular layers should be the most easily compressible one. However, the simulation failed to reproduce the experimentally observed pressure-induced expansion in a number of crystallographic directions within the puckered layers in the monoclinic polymorph I [36], and has wrongly predicted, that there must be a pronounced anisotropy in the mechanical properties within the molecular layers in the orthorhombic polymorph II, whereas the opposite was observed in experiment. The difference in the values of bulk compressibilities was also predicted wrongly. In our opinion, the reason for this discrepancy between the predictions of the simulations and the experimental results is due to wrong assumptions of an oversimplified model: the molecules in the model remain rigid, they may not change their torsion angles, charge distribution within a molecule is based on the results of ab initio calculations for isolated molecules and is considered to be fixed, not changing as pressure increases and the molecules flatten.

The experimental result, that the bulk compressibilities of the polymorphs I and II of paracetamol are practically the same, contradicts the hypothesis previously published in the literature [20]. The difference in the compacting properties of the powder samples of the two polymorphs should be related rather to the plastic properties (brittle fracture or plastic deformation) of the crystals during tabletting [13, 27], and, largely, to the shape and size of powder particles in the sample of a selected polymorph. It is worth mentioning in this respect, that when the texture of the samples of the monoclinic polymorph I was modified, the crystal structure being preserved, the ability of polymorph I to direct compacting during the tabletting procedure could be greatly improved [32].

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