Polish J. Chem., **76**, 1333–1346 (2002)

The Role of Hydrogen Bonds in the Pressure-Induced Structural Distortion of 4-Hydroxyacetanilide Crystals*

by E.V. Boldyreva[1], T.P. Shakhtshneider[1], H. Ahsbahs[2], H. Uchtmann[2], E.B. Burgina[3] and V.P. Baltakhinov[3]**

[1]*Novosibirsk State University, Institute of Solid State Chemistry and Mechanochemistry, ul. Kutateladze 18, Novosibirsk 128, 630128, Russia*
E-mail:boldyrev@nsu.ru
[2]*Philipps University of Marburg, Hans-Meerwein Strasse, 35032 Marburg/Lahn, Germany*
[3]*Boreskov Institute of Catalysis, pr. Lavrent'eva 5, Novosibirsk 90, 630090, Russia*

(Received November 29th, 2001; revised manuscript April 19th, 2002)

Results of X-ray diffraction and IR-specroscopy studies of the role of hydrogen bonds in the structural distortion of the monoclinic and the orthorhombic polymorphs of paracetamol induced by hydrostatic pressure (up to 4-5 GPa) are analyzed. Two groups of phenomena were studied: (i) the anisotropic structural distortion of the same polymorph, (ii) transitions between the polymorphs induced by pressure. The bulk compressibilities of the two polymorphs are practically equal. The anisotropy of pressure-induced structural distortion is qualitatively different. Lattice expansion in particular crystallographic directions was observed for the monoclinic polymorph. With increasing pressure the intermolecular NH...O and OH...O hydrogen bonds contracted and the intramolecular angles between the planes of the phenyl ring and the acetamide group decreased. Pressure-induced transitions between the polymorphs were poorly reproducible and limited by nucleation of the new polymorph.

Key words: hydrogen bonds, paracetamol, *p*-hydroxyacetanilide, acetaminophen, diamond anvil cell, high pressure crystallography, high pressure IR-spectroscopy, polymorphic transitions, polymorphs

Hydrogen bonds play an important role in various condensed phases, ranging from solutions, molecular crystals to biological systems. The present level of the development of diffraction and spectroscopic techniques makes it possible to study in much details and with high precision both the geometrical parameters of hydrogen bonds and their energies. These data are already available for many systems and are summarized (see [1–4] as examples). The "stiffness" of a hydrogen-bond is no less important for the properties of hydrogen-bonded systems, than the values of energy minima or bond lengths. Already Ubbelohde and his co-workers have correlated in their early papers the directions of weak and strong hydrogen bonds in crystals with the directions of strong and weak thermal expansion and have even suggested to use the data on the anisotropy of thermal expansion for locating hydrogens, if no direct

* Presented at the 1st Russian-Ukrainian-Polish Conference on Molecular Interactions in Gdańsk, June 2001, (Poland).
**Author for correspondence.

structural information is available [5,6]. The typical energies required to extend or to contract a hydrogen bond are very small as compared with those for covalent bonds. According to an estimate made in [7] , the energy required to extend a covalent bond by 0.2 Å is of the order 50 kcal mol^{-1}, while that to extend a hydrogen bond to the same amount is only 1.2 kcal mol^{-1}. Therefore, the changes in the geometries of hydrogen bonds resulting from temperature changes are quite well measurable, and numerous data in this field have been already accumulated. The changes induced by mechanical loading – hydrostatic pressure, elastic stresses, *etc*. – should be (and really are) even larger. The data on the compressibility of hydrogen bonds could be, therefore, very helpful for a better understanding of hydrogen bonds properties and a better adjustment of parameters describing the potentials of interatomic interactions in hydrogen bonds. However, there are only very few data on the effect of high pressure on the structural changes in the systems with hydrogen bonds, as compared with the variable-temperature measurements. The reason is probably in the difficulties related to high-pressure experiments. Still, the first results available for a number of organic and coordination compounds are very promising [8–24].

4-Hydroxyacetanilide is widely used as an analgetic and antipyretic drug under the names paracetamol, acetaminophen and panadol [25]. Physical and chemical properties of paracetamol, as well as its bioavailability, are being extensively studied [26,27]. 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. Paracetamol is no exception in this respect. Up to now, the existence of three polymorphs of paracetamol was reported. Only for two of them (I and II) crystal structures are known [28–31]. The structures of individual molecules in the two polymorphs are similar (Fig. 1). The main difference in the crystal structures of the polymorphs I and II is related to the linkage of molecules. The molecules are connected by intermolecular hydrogen bonds NH...O and OH...O, and form rings (Fig. 2), that are arranged into layers (Fig. 3). The structures of these rings and layers are different in the two polymorphs. Hydrogen bonds, keeping the crystal structure together, are important for controlling

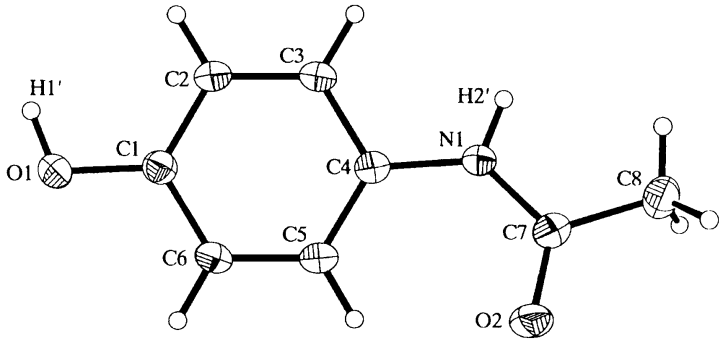

Figure 1. Molecular structure of paracetamol.

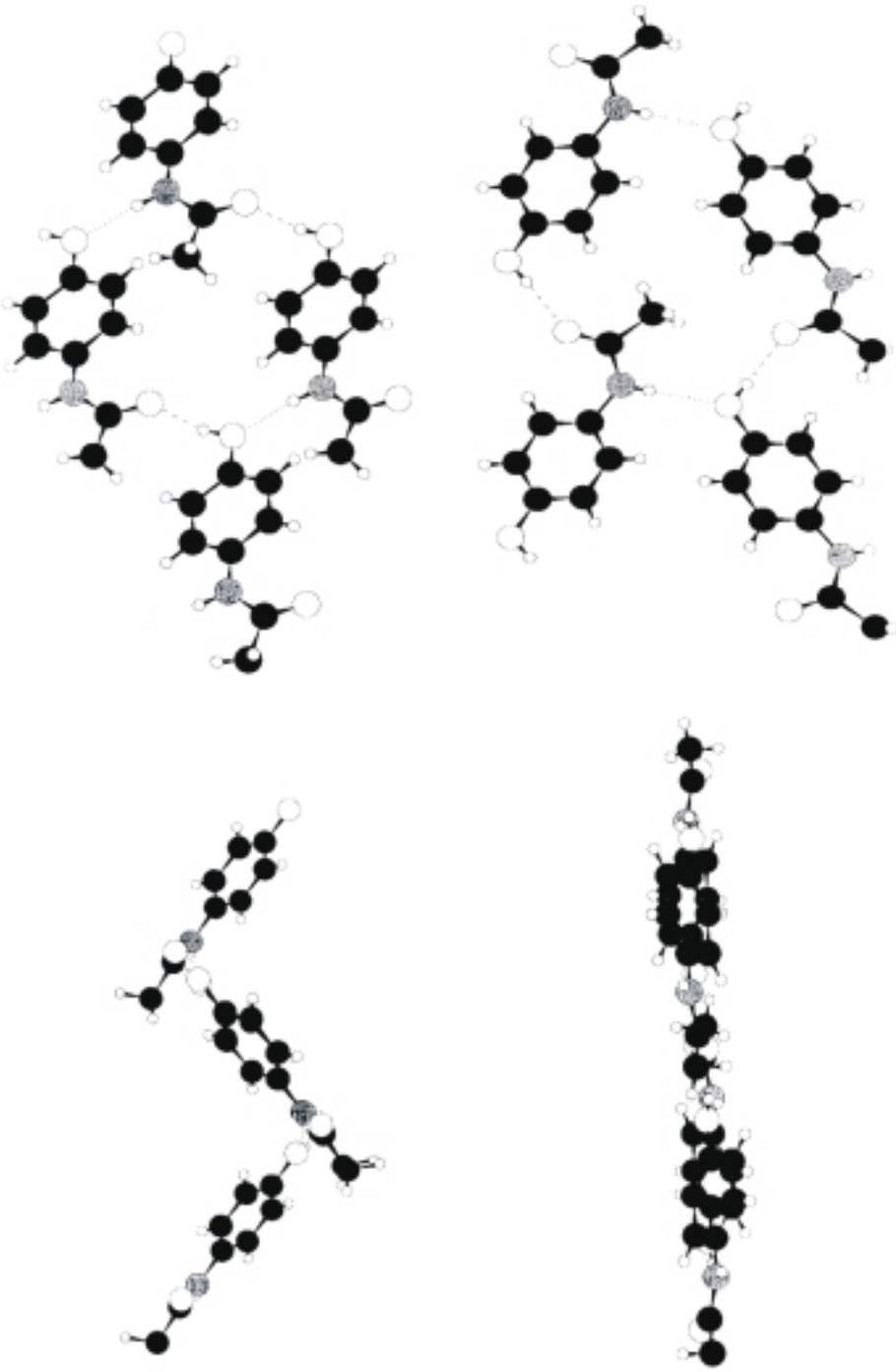

Figure 2. Cycles formed by paracetamol molecules in the crystals of polymorphs I (left) and II (right). Reproduced with permission from [23].

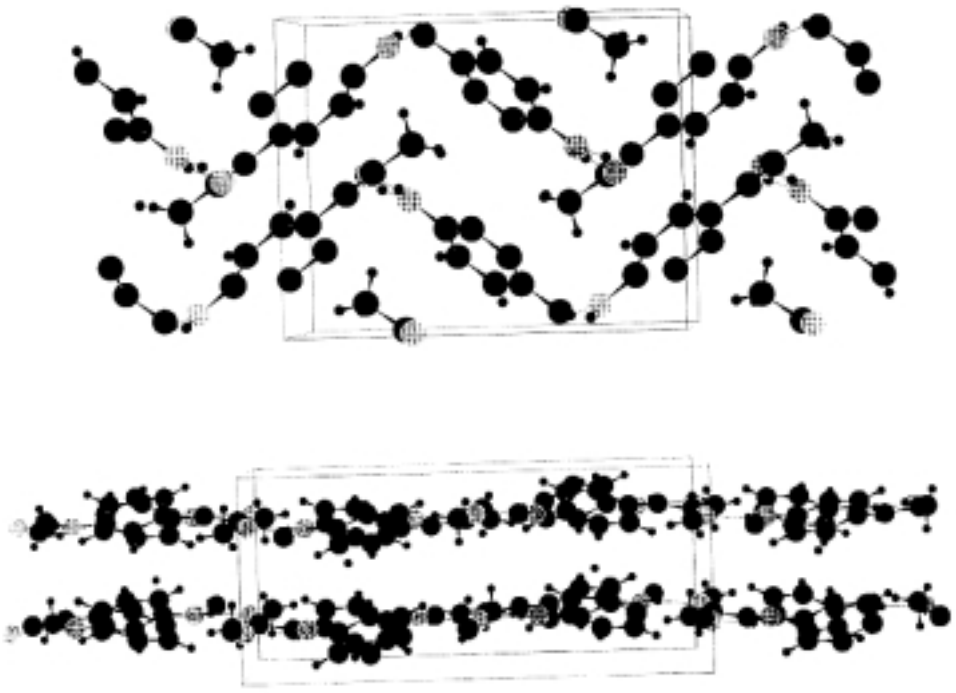

Figure 3. Layers formed by paracetamol molecules in: polymorph I as pleated layers (above), polymorph II as flat layers (below). Reproduced with permission from [23].

the crystallization and dissolution, melting and the polymorphic transitions, and the bioavailability of the polymorphs.

Studies of the effect of pressure on the polymorphs of paracetamol were interesting for us in several respects: (i) we wanted to understand the role of hydrogen bonds in the anisotropy of structural distortion of the two polymorphs, (ii) we were interested to see if variation in pressure could induce any polymorphic transformations or produce any new metastable forms of paracetamol.

This contribution compares the results obtained by pressure changes on the monoclinic [22] and the orthorhombic [23] polymorphs.

EXPERIMENTAL

Commercially available monoclinic polymorph I of paracetamol produced at Kursk Pharmaceutical Plant (Russia) was used. The sample was recrystallized from ethanol solution. X-ray powder diffraction and IR-spectroscopy have not revealed any impurities of other polymorphs. The orthorhombic polymorph II was obtained by slow cooling of the melt of paracetamol in argon atmosphere. For X-ray powder and IR-spectroscopy 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. For single-crystal X-ray diffraction experiments single crystals were grown from ethanol-water (1:1) solution by slow evaporation at ambient temperature under an optical microscope.

Hydrostatic pressure in X-ray diffraction and IR-spectroscopy experiments was created in diamond anvil cells (DAC) of various types. The ruby fluorescence technique [32,33] was used for pressure determination, with the accuracy of ±0.05 GPa. Penthane-isopenthane mixture (1:1) was used as the pressure-transmitting liquid. Single-crystal diffraction experiments were carried out using a STOE four-circle diffractometer with software, specially adapted for high-pressure data collection [34]. Mo-radiation was used. The quality of data refinement during high-pressure single-crystal experiments was comparable with that usually obtained at ambient conditions (Table 1). Details of experiments were described elsewhere [22]. X-ray powder diffraction patterns were obtained by a film technique using Debye-Scherrer method. Mo X-ray radiation was focused by a bent quartz crystal monochromator. The film technique did not enable 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 [28,29]. To avoid ambiguities in the indexing, pressure was increased in small steps. A continuous character of changes in the interplanar spacings d_{hkl} with pressure (in the range, where no phase transitions occurred) and the ratio of relative intensities of the reflections were controlled. More experimental details were given in [15,19–21,23,24]. IR spectra of paracetamol were measured in the solid state and in solutions, in the solid state also up to 4.0 GPa. For a more reliable frequency assignment, IR-spectra of fenacetin were also measured in $CDCl_3$ and in the solid state. Solid samples of paracetamol were diluted with CsBr. The two polymorphs of paracetamol (monoclinic and orthorhombic) were compared. *Ab initio* (DFT) calculations of the structure and spectra of free paracetamol molecules were carried out to interpret the spectra. Spectral regions characteristic for the definite fragments of the molecules were identified on the basis of the normal coordinate analysis.

Table 1. Structure refinement of paracetamol at high pressure.

Number of atoms in the asymmetric unit	20
Number of refined parameters	111
Number of measured reflections	2600
R-factor	3–4%
E.s.d. in the intramolecular bond lengths	0.003–0.005 Å

RESULTS AND DISCUSSION

X-ray diffraction: The anisotropy of structural distortion of polymorphs I and II was well reproducible from powder samples to single crystals. The bulk compressibility of the two forms was practically the same (Fig. 4a). 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 (Fig. 4b). Intermolecular NH...O and OH...O hydrogen bonds shortened with increasing pressure (Fig. 5). In the monoclinic polymorph the molecules rotated with respect to each other within the pleated layers, so that the layers flattened (Fig. 6a). Simultaneously, the molecules themselves also flattened (intramolecular dihedral angle decreased) (Fig. 6b).

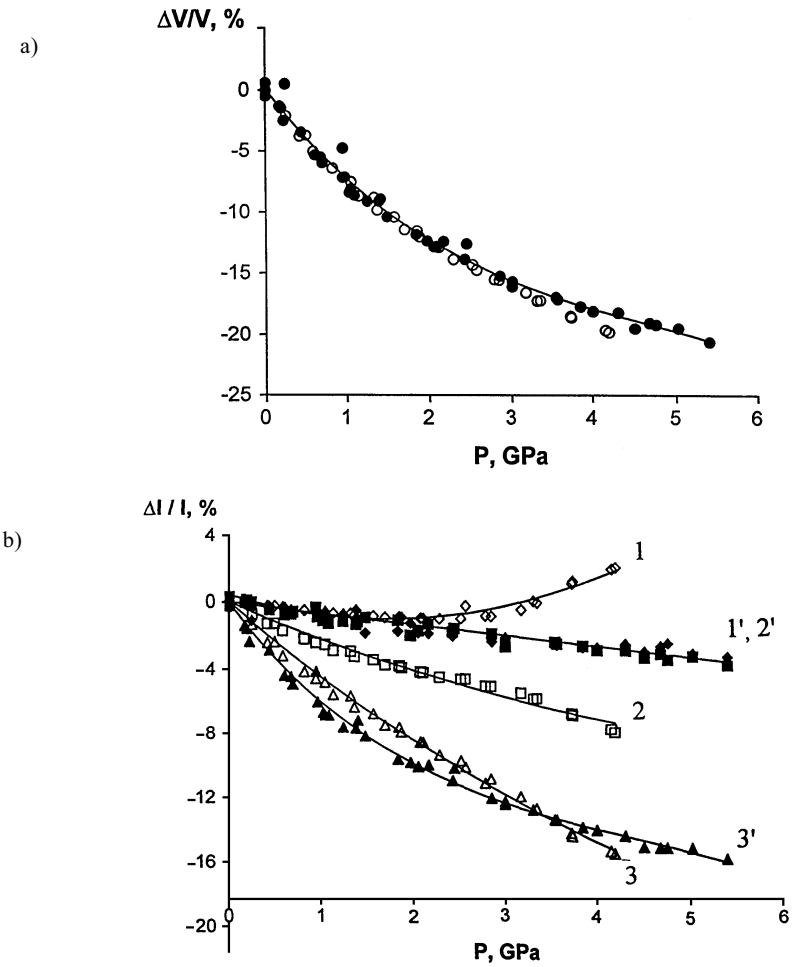

Figure 4. a – Relative volume changes for the two polymorphs; b – Linear strain in the directions of principal axes of strain tensors of polymorphs I (1, 2, 3) and II (1′, 2′, 3′). 1, 2, 3 and 1′, 2′, 3′ denote directions of the principle axes of strain tensors. 1 and 1′ corespond to the directions of 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). Reproduced with permission from [23].

The transitions between the polymorphs, induced by pressure, were poorly reproducible and depended strongly on the sample and on the procedure of pressure changes. No phase transitions were induced in 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. The transition was irreversible and poorly reproducible. It could be observed at approximately 1 GPa, when *decreasing* pressure very slowly from a higher value, only if the pressure first increased rapidly (in one step up to 1.6 GP and then in smaller steps up to 4.2 GPa). Polymorph II transformed partly into the polymorph I during

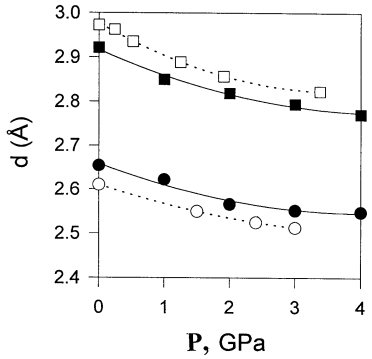

Figure 5. Pressure-induced changes in the distances between non-H atoms in the NH...O (filled squares) and OH...O (filled circles) intermolecular hydrogen bonds in polymorph I [22]. The dashed lines show, for comparison, the data on pressure-dependence of N(H)...O (empty squares) distances in $[Co(NH_3)_5NO_2]Cl_2$ [17] and of the O(H)...O (empty circles) distances in 2-methyl-1,3-cyclopentanedione [12]. Reproduced with permission from [22].

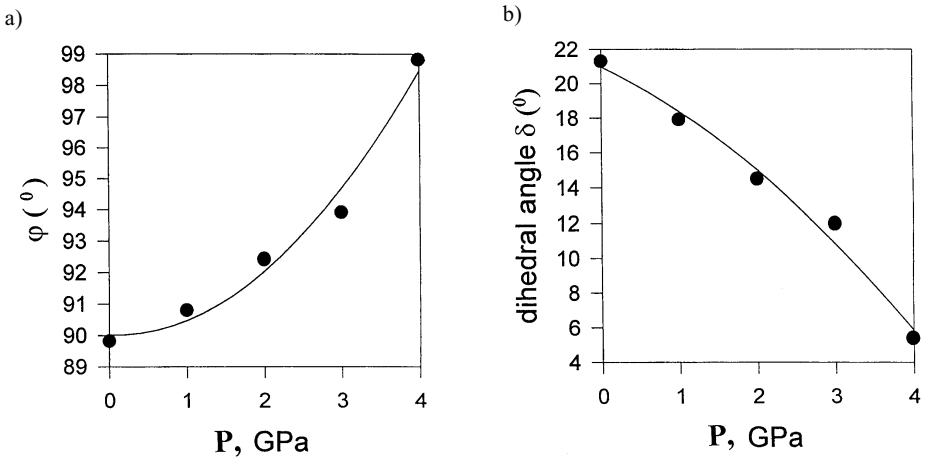

Figure 6. Angles between the planes of the neighbouring benzene rings of the molecules belonging to the same pleated layer, defined as the angle between the normals to the intersection line of the planes (a) and effect of pressure on the dihedral angle between the planes C1–C2–C3–C4–C5–C6 and N1–C7–O2–C8 of a paracetamol molecule in the polymorph I (b). Reproduced with permission from [22].

grinding. The transformation could be hindered, if grinding was carried out in CCl_4. After hydrostatic pressure increase up to 0.6 GPa, the admixture of the monoclinic polymorph produced in the powder sample of polymorph II as a result of grinding, disappeared completely and irreversibly.

IR-spectroscopy: *Ab initio* frequencies of the spectra of free molecules were compared with those in the experimental spectra measured for diluted solutions in $CDCl_3$. The spectra measured in $CDCl_3$ were in a good agreement with those previously reported [35]. IR-spectra of the diluted solutions of paracetamol in $CDCl_3$ dif-

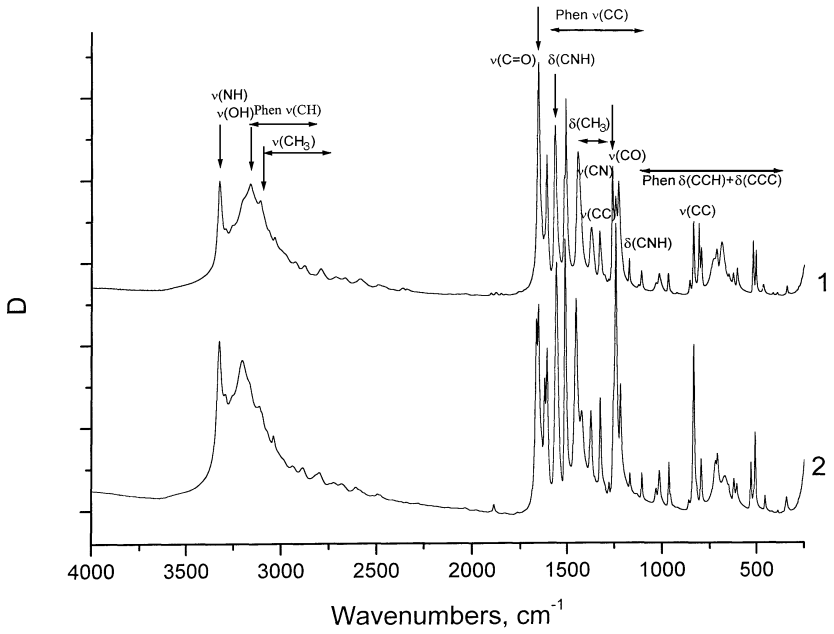

Figure 7. IR-spectra of paracetamol polymorphs I (1) and II (2).

fered from those of solid crystalline phases (Fig. 7). To make attributions of frequences more reliable, we compared the spectra of paracetamol with the spectra of fenacetin, in which no OH-groups are present, in $CDCl_3$ and in the solid state. Still, since the characteristicity of vibrations was not very high, in most cases it was impossible to assign an observed fibrational maximum to a single characteristic vibration. It was more correct to ascribe to individual vibrations the spectral regions (shown by horizontal arrows in Fig. 7), rather than individual bands. Besides, numerous overtones were observed in the spectra. The pressure-induced shifts in the vibrational frequences in the IR-spectra were measured (the bands accessible for the measurement in the DAC). As an example, pressure-induced shifts in the monoclinic polymorph are plotted in Fig. 8.

The effect of pressure on the polymorphs of paracetamol can be interpreted as compression of intermolecular hydrogen bonds, linking all the molecules into two-dimensional layers. The formation of strong hydrogen bonds manifests itself in the IR-spectra of both polymorphs already at ambient pressure: the differences in the spectra of paracetamol in the solid state and in the diluted solutions of $CDCl_3$ can be attributed to strong OH...O and NH...O hydrogen bonds in the molecular crystals. This conclusion is in a good agreement with crystallographic data. The structures of individual molecules in the two forms are similar, but there are also slight intramolecular differences, which can be related to the formation of intermolecular hydrogen bonds. Thus, the length of the C=O bond in the monoclinic polymorph I is 1.232 Å, that is noticeably (about 0.01 Å) longer than 1.223 Å in the orthorhombic

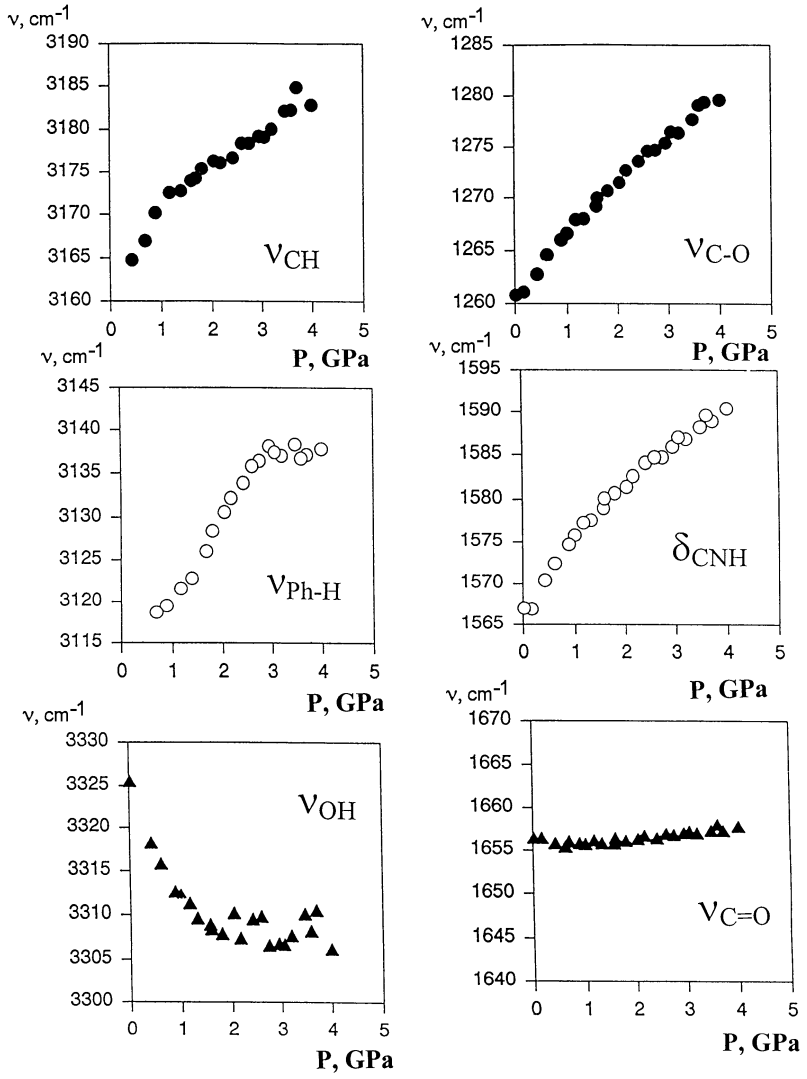

Figure 8. Pressure-induced shifts in the IR spectra of polymorph I of paracetamol.

form II. 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 get shorter. In the orthorhombic polymorph, the intermolecular NH...O and OH...O hydrogen bonds are about 0.04 Å 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 (1.223 Å) is shorter than the same bond in polymorph II (1.232 Å). With increasing pressure a slight elongation of the C=O bond (0.023 Å at 4.0 GPa) was found, which is in good agreement with the data previously reported by Katrusiak [11] for 2-methyl-1,3-cyclopenta-

nedione (0.02 Å at 3.01 GPa) and correlated well with the pressure-induced shortening of the OH...O hydrogen bonds.

Another intramolecular parameter related to the formation of intermolecular hydrogen bonds is the dihedral angle between the planes of the phenyl ring and the acetamide group in the molecule. The dihedral angle in polymorph I is 21.1°. It is 3° larger than that in form II, 17.7°. The intramolecular dihedral angle is strongly sensitive to the degree of the deprotonation of a paracetamol molecule and to the charge distribution in the molecule [35]. Therefore, it should be also sensitive to any changes in the intermolecular hydrogen bonds. This hypothesis can be supported as an *ab initio* optimized individual paracetamol molecule should be flat, with the dihedral angle equal to 0° [35]. As intermolecular bonds become shorter with pressure (Fig. 5), the distribution of charges within paracetamol molecules, their "effective deprotonation" are changed, and this can be one of the reasons of the decrease in the dihedral angle in the molecules with pressure (Fig. 6). The effects of high pressure on the IR-spectra are in good agreement with the direct crystallographic data on the intra- and intermolecular changes in the structure of paracetamol with pressure (Fig. 8).

The anisotropy of structural distortion of solids under pressure is a manifestation of the anisotropy of interatomic interactions, in particular – hydrogen bonds in the crystal. In the two polymorphs maximum compression was observed in the directions normal to the hydrogen-bonded layers. Only weak van der Waals and π-π interactions between the phenyl rings exist between the layers. The compressibility in this direction proved to be almost non-sensitive to the structure of the layer – flat or pleated. On the contrary, the compression of hydrogen-bonded layers in the two polymorphs was qualitatively different, and the difference can be related to their structures. Flat layers in the orthorhombic polymorph II under pressure were compressed isotropically in all the directions, despite a lower symmetry and the different strength in the individual NH...O and OH...O bonds. A possible explanation of this is that the layer responded to an increase in pressure in a cooperative way, since all the molecules within the layer were linked with each other in one net. In the monoclinic polymorph I the pleated hydrogen-bonded layers expanded in particular directions with increasing pressure, although not only the volume decreased, but also every intermolecular bond in the structure shortened. The reason is the pressure-induced flattening of both the individual paracetamol molecules (due to decrease in the intramolecular dihedral angle) and of the layers as a whole (due to rotations of molecules in the layer with respect to each other). Compression of intermolecular hydrogen bonds is involved in both processes. The compression of the hydrogen-bonded molecular layer in the polymorph I of paracetamol is cooperative, and this could be confirmed by a careful analysis of the effect of pressure on various parameters, characterizing the cycles formed by paracetamol molecules in the layer [22].

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, whose 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.

The effect of pressure on the transformations between the polymorphs can also be interpreted only if intermolecular hydrogen bonds in the structure are taken into account. 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 at 168.5°C. Therefore, on the basis of isobaric conditions only solid-state transformation from the orthorhombic modification II into the

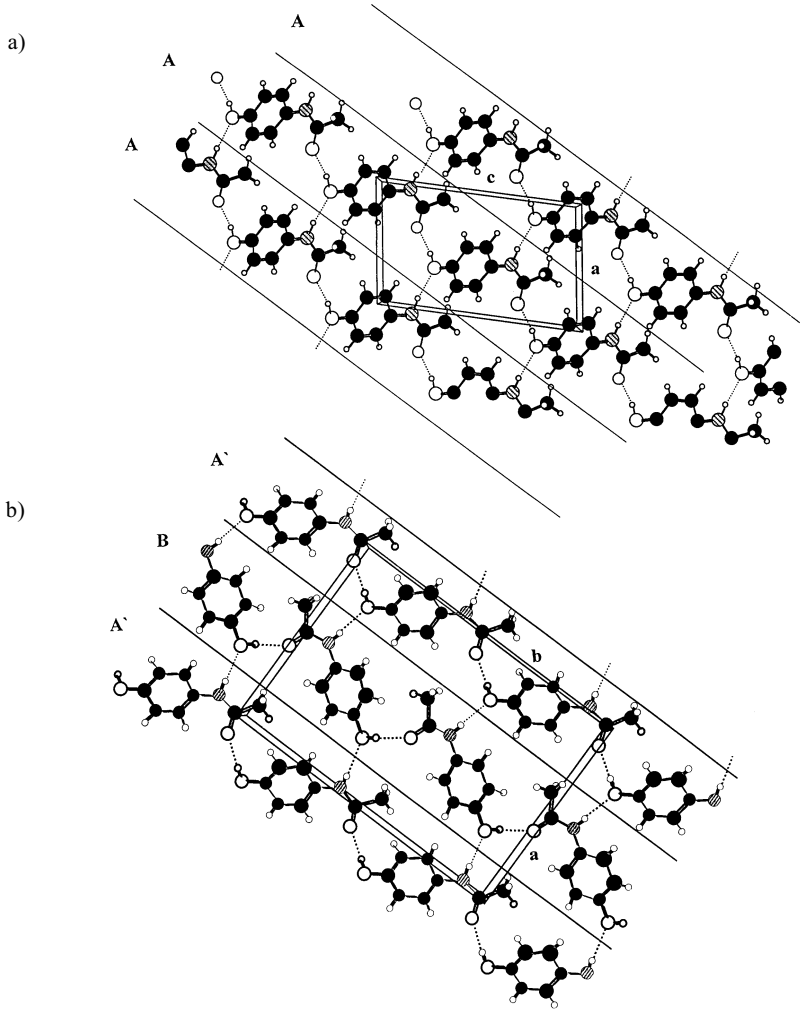

Figure 9. Chains formed by paracetamol molecules in the individual layers in the crystals of polymorphs I (a) and II (b). Reproduced with permission from [23].

monoclinic form I are thermodynamically allowed [36]. This transformation could actually be observed as a result of grinding [23]. 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. 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 orientation. The chains A and A′ have the same orientation of molecules, but the intermolecular bonds and angles in the chains are somewhat different (Fig. 9). A solid-state polymorphic transformation 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. This process must be limited by nucleation, what may explain, why the interconversion of polymorphs I and II often takes place either in contact of the crystals with the saturated solution [30], or in the melt [30,37–46], 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 [47]. 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 [44]. Increased 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 a rapid increasing and a slow decreasing pressure.

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 [20]. 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 both statements.

Further development of the work on this system would require a detailed single-crystal high-pressure X-ray diffraction study of polymorph II, in order to compare the intramolecular distortion and the compression of intermolecular hydrogen bonds with those observed for polymorph I. Another important future study is a comparative study of single-crystal vibrational spectra of polymorphs I and II at ambient and high pressures. Last but not least is the prospect of using the experimental data on the pressure-induced structural distortion of the polymorphs I and II for the elaborating of atom-atom potentials describing the interactions in the systems.

Acknowledgments

The study was supported by a grant from the DLR (RUS-131-97), grants from the RFBR (99-03-32482 and 02-03-33358), several grants of the Russian Federation Ministry of Education (the program "Integration", grant 274; grants 3H-67-00, 3H-120-01, 3H-467-01, E00-5.0-81), and a grant of CRDF (REC-008). The authors are grateful to Prof. V. Boldyrev who has attracted their attention to the studies of paracetamol. The samples of the orthorhombic polymorph were kindly provided by Mr. A. Politov, Ms. Vasilchenko and Mr. Novikov.

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