The Polymorphic Phase Transformations in the Chlorpropamide under Pressure

SERGEY E. KICHANOV,[1] DENIS P. KOZLENKO,[1] JAN WĄSICKI,[2] WOJCIECH NAWROCIK,[2] LEONID S. DUBROVINSKY,[3] HANNS-PETER LIERMANN,[4] WOLFGANG MORGENROTH,[5] BORIS N. SAVENKO[1]

[1]Frank Laboratory of Neutron Physics, JINR, Dubna 141980, Moscow Region, Russia
[2]Faculty of Physics, A.Mickiewicz University, Poznań 61-614, Poland
[3]Bayerisches Geoinstitute, University Bayreuth, Bayreuth D-95440, Germany
[4]Photon Science, Deutsches Elektronen Synchrotron, Hamburg D-22607, Germany
[5]Institute of Geosciences, University of Frankfurt, Frankfurt D-60438, Germany

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ABSTRACT: The crystal structure and vibrational spectra of the chlorpropamide have been studied by means of the X-ray diffraction and Raman spectroscopy at pressures up to 24.6 and 4.4 GPa, respectively. Two polymorphic phase transitions, between initial orthorhombic form-A and a monoclinic form-AI at $P \sim 1.2$ GPa and, in additional, to another monoclinic form-AII at $P \sim 3.0$ GPa, were observed. At pressures above 9.6 GPa, a transformation to the amorphous phase of chlorpropamide was revealed. The lattice parameters, unit cell volumes, and vibration modes as functions of pressure were obtained for the different polymorphic modifications of chlorpropamide. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

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INTRODUCTION

One of the model compound to study pressure-induced polymorphic transformations in drugs is a chlorpropamide $C_{10}H_{13}ClN_2O_3S$.[1–3] It belongs to a group of sulfonylurea compounds and is used as antidiabetic drug.[4] Several polymorphs of chlorpropamide are known.[5–7]

The commercially manufactured form-A with the orthorhombic crystal structure $P2_12_12_1$[8] is stable at ambient conditions. It is known that after heating of chlorpropamide up to 393 K and keeping it at this temperature for 4 h the polymorphic form-C appears.[9] Recently, the partial transformation from initial form-A to form-C in chlorpropamide has been found under compression to 196 MPa at room temperature.[10] The stability of form-A under compression has been studied extensively[3,11–14] because of the potential for uncontrolled changes into drugs during pharmaceutical manufacturers. In particular, during tablet formation some pressures is required and one could cause irreversible changes to the initial crystal structure by rearranging molecules or disordering of the structure.[15,16] New polymorphic phases of pharmaceutical compounds, which appears during tableting or grinding processes, can differ in physical properties, stability on storage, or bioactivity in comparison with their initial form.[15–17] However, the information about pressure-induced polymorphic transformation in chlorpropamide is contradictory and it is considerable discrepancies between the previously reported data. Previously, two polymorphic transformations in chlorpropamide at pressures 0.9 and 2.0 GPa into unknown phases have been observed by means of Raman spectroscopy experiments.[18] In additional, the X-ray diffraction experimental results indicated polymorphic phase transition into a monoclinic phase with space group $P2_1$ at high pressures above 1.2 GPa.[13] On the other hand, no polymorphic transformations have been observed in dry samples of chlorpropamide by a X-ray powder diffraction at pressures up to 5.5 GPa[3] or by a NMR measurements at pressure up to 0.8 GPa.[11] In same time, the polymorphic phase transition from initial form-A to new high pressure form-A′ of chlorpropamide have been found at $P \sim 2.8$ GPa under hydrostatic compression.[12] Since form-C of chlorpropamide can be prepared from most other chlorpropamide forms, with exception of initial form-A, the observed discrepancy in experimental results have been explained by effects from additional factors like as local heating, partial melting or recrystallization processes. It has been suggested that one of a factors can be the hydrostatic conditions of high-pressure experiments. Further analysis of various applied stress states demonstrates that shear stresses have the key role in mechanism of the pressure-induced transformation in chlorpropamide.[19] In particular, experiments using ethanol solution as pressure transmission medium[12] in comparison with another ones, there compression of chlorpropamide in quasihydrostatic conditions have been studied.[3,13,14]

Nonetheless, the above-mentioned experimental results clearly demonstrate that the pressure-induced polymorphic phase transitions in chlorpropamide are quite complex and require further elucidation. It is very important to study the pressure-induced polymorphic transformations to understand and take advantage of the mechanisms effects on polymorphic phase transition in chlorpropamide.

In order to study in detail the high-pressure effects on the crystal structure and vibrational properties of chlorpropamide, we have performed X-ray diffraction and Raman spectroscopy experiments at pressures up to 24.6 and 4.4 GPa, respectively. In an attempt to account for inner stresses effects,[12,19] we used

Correspondence to: Sergey E. Kichanov (Telephone: +7-49621-62047; Fax: +7-49621-65882; E-mail: ekich@nf.jinr.ru)

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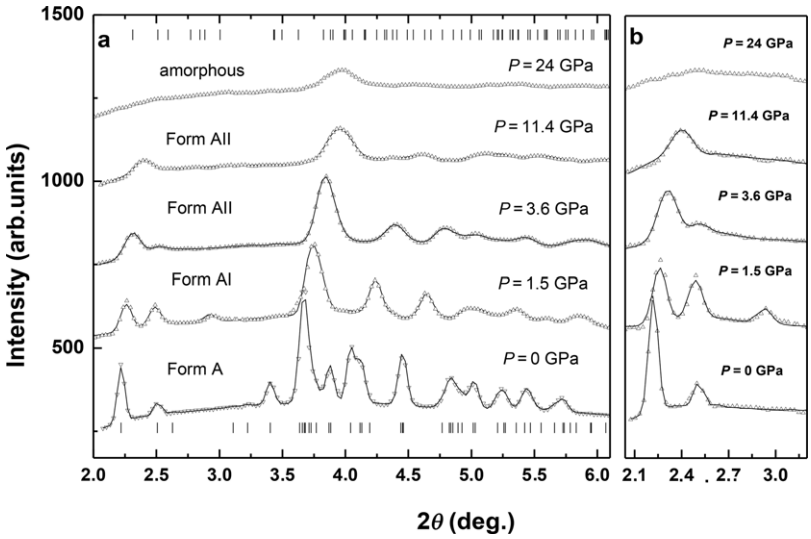

Figure 1. (a) X-ray diffraction patterns of chlorpropamide measured at selected pressures and room temperature, and refined by the profile matching method using FullProf. Experimental points and calculated profiles are shown. The ticks at the bottom and top indicates the calculated positions of a diffraction peaks for the orthorhombic form-A of chlorpropamide at ambient pressure and for the monoclinic form-AI (at $P = 1.4$ GPa), respectively. (b) The enlarged parts of X-ray diffraction patterns of chlorpropamide for low-angles region.

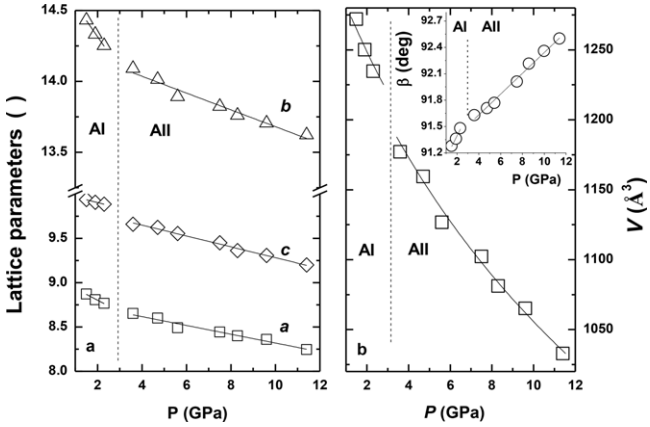

Figure 2. (a) Lattice parameters as a functions of pressure for the AI and AII forms of chlorpropamide. The solid lines represent the linear fit of the experimental data. (b) Baric dependences of unit cell volume and monoclinic angle β (inset) for the AI and AII forms of chlorpropamide. Solid lines represents fit based on the Birch–Murnaghan equation of state [25].

powder sample of chlorpropamide and performed high-pressure experiments without any pressure-transmitting medium.

EXPERIMENTAL

Dry powder sample of chlorpropamide form-A was obtained from Sigma Chemical Company (St. Louis, Missouri) and used as received.

The BX90 type diamond anvil cell[20] was used for the X-ray diffraction and Raman experiments. The sample was loaded into the hole of the 120 μm diameter made in the Re gasket intended to about 30 μm thickness. The diamonds with culets of 250 μm were used. The pressure was determined by the ruby fluorescence technique.[21]

The angle-dispersive X-ray powder diffraction patterns at high pressures up to 24.6 GPa and at room temperature were obtained at the Extreme Conditions Beamline[22] (ECB) P02.2 at the third-generation synchrotron radiation source PETRA-III located at the Deutsches Elektronen Synchrotron (DESY), Hamburg, Germany. The diffraction images were collected with a wavelength of $\lambda = 0.29118$ Å on the amorphous silicon flat panel detector bonded to a ScI scintillator (XRD 1621) from PerkinElmer and located at a distance of 402.33 mm from the sample. The two-dimensional XRD images were converted to one-dimensional diffraction patterns using the FIT2D program.[23] Powder diffraction patterns were refined in the Fullprof[24] program.

Raman spectra at ambient temperature and pressures up to 4.4 GPa were collected using a LabRam spectrometer (NeHe excitation laser) with a wavelength of 632.8 nm, 1800 grating, confocal hole of 1100 μm, and a 50× objective.

The pressurisation rate in both of a Raman spectroscopy and an X-ray diffraction experiments was 10–20 MPa min^{-1}.

RESULTS AND DISCUSSION

X-Ray Diffraction

The X-ray diffraction patterns of chlorpropamide at selected pressures and room temperature are shown in Figure 1. At ambient conditions, the orthorhombic form-A with the space group $P2_12_12_1$[8,13] was identified. The obtained values of lattice parameters at ambient conditions for the form-A were $a = 5.255(3)$ Å, $b = 9.052(3)$ Å, $c = 26.478(8)$ Å, and are consistent with previous studies.[12,13]

At low pressures $P \sim 1.2$ GPa, some changes in the X-ray diffraction patterns were observed as illustrated in Figure 1. The diffraction peaks indexed as (102) and (112) at $2\theta \sim 3.4^\circ$ and 3.9°, correspondingly, was disappeared and new peak at $2\theta = 2.9^\circ$ developed. In additional, a drastic change in relative intensity of the diffraction peaks located at $2\theta = 2.2^\circ$ and 2.5°