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Deformation-Induced Structural Transformations in Molecular Crystals

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The physical mechanisms of the deformation-induced structural transformations in molecular crystals, including morphological changes, amorphization and molecular polymorphous conversions in nano-dispersed bioinorganic compounds are discussed in this work. Integrated study using direct structural and structure-sensitive spectroscopic methods allowed obtaining the data on polymorphous transformations, taking place during mechanical activation in calcium gluconate monohydrate (CG). One of the possible reasons for lattice polymorphous transformations and amorphization, observed in the course of mechanical activation of low-symmetry molecular crystals, might be the spatial molecular isomerization. In this case, the disappearance of the translational invariance of the lattice is conditioned by the simultaneous coexistence of the reactants and reaction products, which have different stereo-organization of the molecular structure.

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1. Introduction

Studying the physical mechanisms of deformation induced transformations in molecular crystals and developing the methods of solid state mechanochemical synthesis resulted in the appearance of a new prospective trend in pharmaceutics. Without changing the chemical composition, one can transform a molecular crystal into a new state with unique physical-chemical properties, increasing the biochemical activity of the substance significantly. Thus, there appears a principal possibility of not only producing highly effective pharmaceutical products but also minimizing the cost and terms of their development.

Among molecular crystals prospective for application in pharmaceutics the coordination compounds of carbohydrates and their derivatives with metals being low toxic substances are increasingly applied as precursors of medicinal compounds and means of their delivery [1, 2].

It is known [3] that the physical-chemical properties of molecular crystals depend essentially both on their morphology, in particular, the habit and dispersity of crystals and on their structural state determined by the lattice and molecular polymorphism as well as by quasi-polymorphism of their solvates. There is some evidence of the interrelationship of the compositional short-range order in the first coordination sphere of the metal ions with the physical properties and reactivity of the coordination compounds [4]. To form the physical-chemical properties of the molecular compounds directly, the compositional short-range order can be varied by a few techniques [5]:

1. Changing the molecular packing in the crystal, i.e. creating polymorphous lattice modifications;
2. Producing high concentration of structural inhomogeneities in the crystal lattice, in particular, non-equilibrium defects and intercalated atoms and molecules (the phenomenon of quasi-polymorphism);
3. Providing spatial reorganization of the molecules themselves, in particular, modifying their conformation (the phenomenon of molecular polymorphism);
4. Transforming the substance into the amorphous state.

The basic physical reasons of structural transformations in the molecular crystals under deformation have remained unclear so far [3, 6]. The structure transformations, the amorphization of highly symmetric ion and metal systems under mechanoactivation included, as a rule, were accounted for by intensive low temperature mass transfer on reaching the nanostructured state of the substance after plastic deformation [7, 8]. At the same time, in low symmetric molecular lattices such a mechanism of amorphization does not seem to work [3, 8], though in some compounds the deformation of the substance after nanodispersion is accompanied by amorphization.

Earlier we carried out investigations of mechanoactivaton of calcium gluconate monohydrate and for the

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first time obtained a mechanochemically modified nano-dispersed amorphous form — the mechanoactivated calcium gluconate (MACG) [9]. Clinical studies revealed its unexpectedly high therapeutic effectiveness in treating the diseases due to the calcium disbolism in the human body (dysplastic and degenerative-dystrophic processes, defects of bone tissue, traumatic and pathological fractures, osteoporosis, periodontology, etc.) [10].

The studies calcium gluconate carried out by the techniques of atomic emission and mass spectrometry, X-ray structure analysis, ss-NMR spectroscopy, infrared spectroscopy, differential scanning calorimetry, atomic force and electron microscopy have shown that [9, 11]:

1. During mechanoactivation a nano-dispersed state forms, with the size of particles not exceeding 100 nm as well as their agglomerates;

2. Under the chosen conditions of mechanoactivation there are no changes in the chemical composition of the initial calcium gluconate. No new chemical compounds are formed;

3. The amorphization of CG takes place.

On the ground of all the experimental date obtained, as a working hypothesis, a supposition was put forward according to which the structural changes occurring in CG under mechanoactivation are accompanied by the changes of stereochemical structure of a CG molecule and by the changes of the chemical composition of the first coordination sphere of calcium [11, 12].

In this paper possible physical mechanisms of structural changes in bioinorganic compounds subjected to the treatment in mechanoactivators are discussed using the example of calcium gluconate monohydrate.

2. Experimental

To carry out the work, we used the calcium gluconate monohydrate produced by Fluka without any additional purification. The mechanochemically modified powders were obtained by the method of mechanoactivation in the planetary ball mill LAIR according to the technique described in [9]. The time of activation (t_a) was from 1 min to 1 h. The content of impurity elements under activation within the error of determination did not change with respect to the initial state. On the whole, there was no contamination of the samples by the material of the vials and balls. The thermal analysis was carried out using the differential scanning calorimeter Diamond DSC (Perkin-Elmer) in the argon atmosphere with the heating and cooling rates of 10 °C/min. To determine the kinetics parameters of the hydrate decomposition, the polytherms of the specific heat flow with the heating rate of 5 °C/min were taken. The reaction order was determined from the Arrenius equation with the software Paris Kinetics Soft. The infrared spectra of adsorption were taken using Fourier-IR spectrometer Excalibur FT-IR 3100 (Varian Inc.) on the pelleted in KBr samples with the resolution of 1 cm^{-1}. The X-ray structural analysis was carried out using APD Miniflex 600 (Rigaku) under Co-radiation. TEM images were taken using high resolution transmission electron microscope TECNAI G30ST with 300 kV acceleration voltage.

3. Results and conclusions

The volume fraction of the CG amorphous phase increases monotonously in activation and with $t_a = 40$ min reaches 100%. Further increase of the mechanical treatment time does not result in any qualitative changes in the X-ray diffraction patterns (Fig. 1). At the same time, no new products were found out in the MACG studied by the methods of mass-spectrometry [11, 12]. However, the temperatures, at which the detection of the sublimated ion output m/z 160 under thermal evaporation characteristic for the beginning of CG destruction along the Ca–O bond starts, differ essentially for CG (210 °C) and MACG (180 °C) [11]. It is brought about by weakening the intermolecular interaction that was found out in [13] to be due to the existence of the intermolecular hydrogen bonds between alcohol anion groups of the gluconic acid and coordination water.

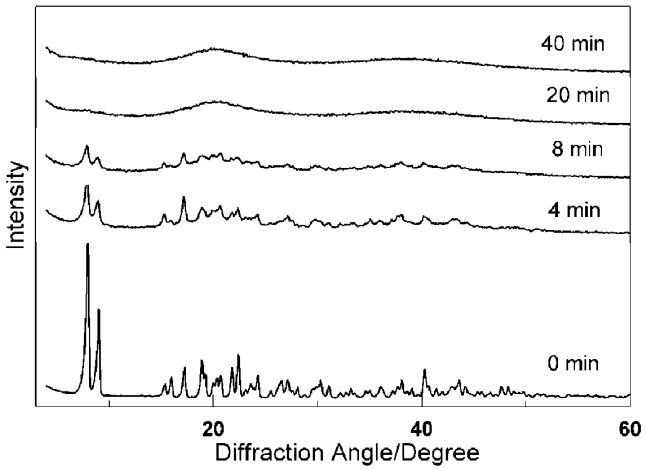

Fig. 1. XRPD of mechanoactivated CG, $t_a = 0$ (initial state); 4; 8; 40 min.

The changes of intermolecular interaction agree with the DSC data: the endothermal peak 130 °C in the curve of heat flow dependences on the heating temperature (Fig. 2), corresponding to the process of breaking the donor-acceptor bond between the molecules of the coordination water and calcium cations [14–16], disappears with simultaneous appearance of a broad band at about 70 °C, corresponding to the output of intercalated water, which tells us about the decomposition of crystalline hydrate under mechanoactivation. The losses of the samples mass after heating equals 4.8% both before and after activation, that corresponds to the molecular mass of water, when after evaluated in molecular mass.

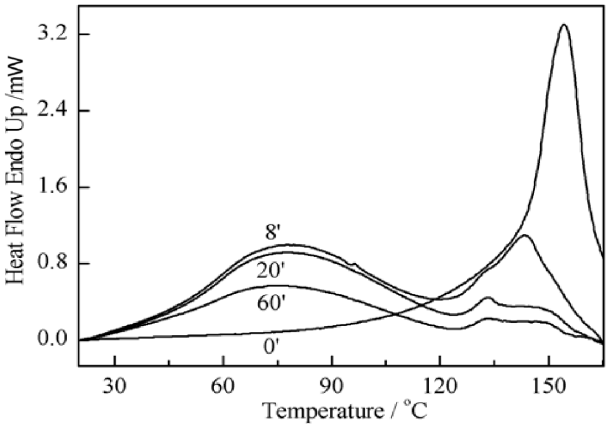

Fig. 2. DSC curves (10 °C min^{-1}), t_a = 0 (initial state); 8; 20; 60 min.

In the study of the reaction kinetics it was found out that the activation energy of the dehydration decreases from 285 to 98 kJ/mol during 1 h of mechanical treatment with the order of the reaction being equal to 2 in both cases. The latter additionally confirms the decomposition of the crystalline hydrate and the conversion of the coordination water into crystal one, weakly bound with acid remnants, surrounding it. The given data of the thermal analysis and thermogravimetry allow us to state that the processes of decomposition of the crystalline hydrate under mechanoactivation are not brought about by thermal heating but are due to the deformation induced changes in the molecular system.

The reasons for crystalline hydrate decomposition become clear while analyzing the changes of the vibrational spectra of CG under mechanical activation and comparing these changes with the spectra transformations taking place in the process of formation of the gluconic acid calcium salt.

Figure 3 presents the IR spectra of CG both in the initial state and after mechanoactivation. The absorption spectra in the initial state agree with those available in literature (see e.g. [14, 16]). The main changes are connected with the decrease of the intensity of the absorption band at 3200 cm^{-1} corresponding to the stretching vibrations of the coordination water. The shift of the center of the broad band of O–H absorption into the region of higher wave numbers points to the breakage of the intermolecular hydrogen bonds in the system [17]

In the crystalline state the gluconic acid is in the form of δ-gluconolactone the hydroxyl groups of which are bound by both intra- and intermolecular bonds [18]. In the process of formation of salt and intramolecular complex compound with calcium δ-gluconolactone undergoes the following changes [19]. The hydrogen bonds weaken, which follows from the shift of the IR-spectra lines of the stretching vibrations the hydroxyl groups 3466 and 3393 cm^{-1} into the region of higher wave numbers 3487 and 3420 cm^{-1}, respectively, as well as the

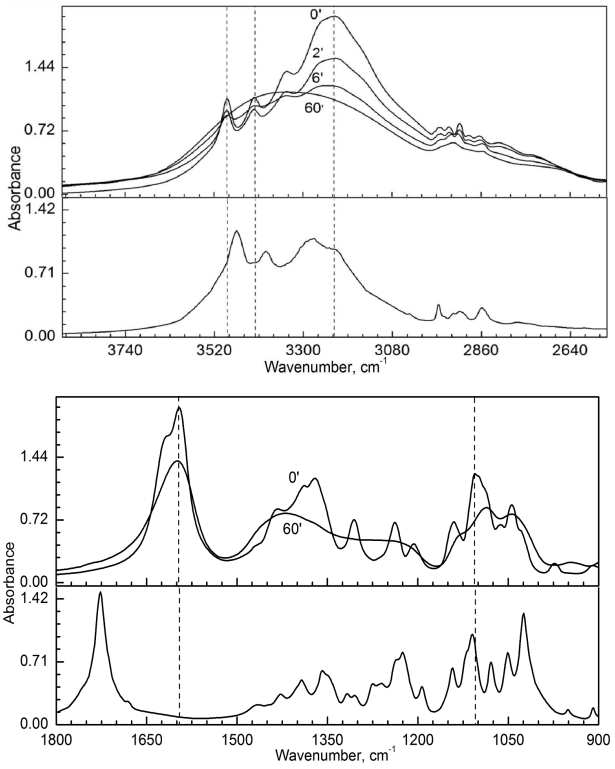

Fig. 3. FTIR absorption spectra of CG before and after mechanical activation (up) and δ-gluconolactone (down).

bending bands of OH-groups 1225–1460 cm^{-1}, stretching C–C and bending vibrations of the OCH-groups 1024–1050 cm^{-1} shift into the region of much higher frequencies, and the stretching vibrations of O–C 1109 cm^{-1} into the region of lower frequencies [19, 20] (Fig. 3). Such changes are attributed to the formation of the donor-acceptor bonds of the oxygen from the hydroxyl groups with calcium ions. In the band of the bound hydroxyl groups there appears a shoulder 2700–3200 cm^{-1} due to the calcium ions coordination of the water molecules. The band at 1727 cm^{-1} corresponding to the stretching vibrations of the carbonyl group is split into two bands attributed to the asymmetric (1620–1597 cm^{-1}) and symmetric (1370–1235 cm^{-1}) stretching vibrations of the carboxylate ion. The split of symmetric and asymmetric vibrations tells us about the nonequivalence of the positions of carbonyl groups of two anions of the gluconic acid, which agrees with NMR data [11].

Thus, the changes of the IR-spectra under mechanical activation and in the process of the CG synthesis are symbate, which points to the increase of number of hydroxyl groups of the gluconic acid anions involved into the coordination bonds with the calcium cations during activation.

At the same time, one can remark two differences. First, during mechanical activation the intensity of the

band 3200 cm^{-1} decreases, which is connected with the decomposition of the crystalline hydrate and, second, a weak band 947 cm^{-1} appears, which seems to be inherent to the libration vibrations of OH–O [18], of the formed intramolecular hydrogen bonds in the coordination. The hydrated calcium gluconate is not characteristic by the intramolecular bonds, since the intramolecular distances between the atoms of hydrogen and oxygen do not exceed 2.20 Å [13]. However, strong intermolecular hydrogen bonds in hydrates are realized between neighboring crystalline planes.

The IR-spectroscopy data giving evidence of the deformation-induced polymorphous molecular transformations in CG agree well with the data on the solid state NMR [11].

The change of the molecules conformation with the breakage of the intermolecular bonds is not something unusual. It is no wonder that in the process of mechanoactivation during milling the stereoorganisation of the molecules undergoes certain changes, which is the result of the intermolecular bonds breaking, but only to some extent. The conformation changes in the process of deforming may seem to be not the result, but one of the sources of destruction of the molecular crystals and formation of 2D structures. In our case, the deformation of the molecules leads to the replacement of the coordination water by the hydroxyl groups of the gluconic acid anions due to the fact that it is impossible for two molecular orbitals to be located in one cell of the phase space owing to the Pauli principle, despite the water oxygen atoms possessing better donor properties in comparison with the hydroxyl groups oxygen atoms. It is solely a deformation-induced process which to our knowledge, is not observed in traditional organic synthesis.

As a result of the forced change of the molecule conformation the crystalline hydrate decomposes, with the water leaving the first coordination sphere of calcium.

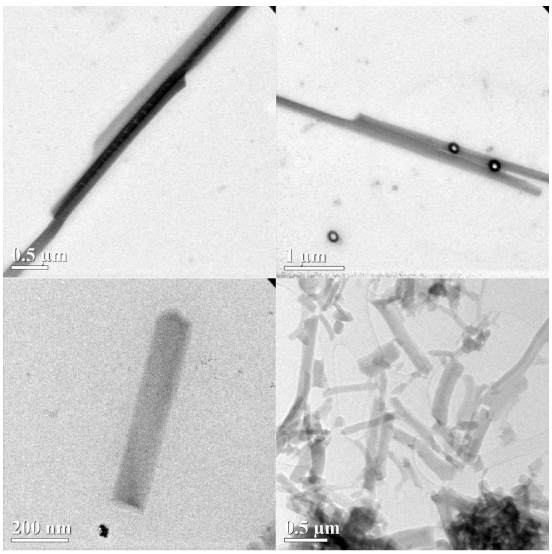

Fig. 4. TEM of mechanoactivated CG.

It is known that the coordination water stabilizes the crystal lattice of the calcium gluconate through the formation of interplanar hydrogen bonds [13]. Its removal results in decrease of the strength of the interplanar bonds and facilitates the possibility of forming 2D structures under the effect of shear stresses, and we see the evidence of crystals splitting along the planes of sliding (Fig. 4).

One of the mechanisms of the amorphization of organic and bioinorganic compounds, in our opinion, can be formulated in the following way. Under mechanoactivation the appearance of steric stresses transforms the system into the excited state at the expense of increase of the kinetic energy of the electrons of binding and non-binding orbitals. If the valence electrons under excitation go to the antibonding orbitals, we observe the destruction of the chemical compound and the following reactions of the solid phase synthesis. In the case of partial delocalization of the electron density on the antibonding orbitals or free orbitals of heteroatoms (e.g. metal atoms) the kinetics energy of the system decreases. At the same time one can observe solid state reactions of the spatial isomerization resulting in the formation of the polymorphous molecular complexes. In this case the initial reagents and reaction products co-exist simultaneously.

If the molecular sizes and spatial organization of the reactants and products of the mechanochemical reaction differ significantly (in the case of CG stereoisomers, e.g. by 1.5–2 times) [11], then the long-range order in the system can be broken, and the appearance of the amorphous phase is observed.

In the case when the isomerization reaction goes on to the end, then the amorphous state can be transformed into crystalline one with the increase of the time of the mechanical treatment of the substance. The latter agrees well with the data given in Ref. [3], where the amorphous phase for a number of mechanoactivated organic compounds is an intermediate one between the crystalline reactant and reaction product.

The data obtained show that carrying out complex systematic investigations aimed at revealing the physical-chemical mechanisms of the mechanically induced structural transformations and the formation of new polymorphous states of nanodispersed coordination compounds of metals as the substances for highly effective medical drugs is prospective and necessary.

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