

FORMATION OF NANOSTRUCTURES IN MECHANOACTIVATED MOLECULAR CRYSTALS

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SUMMARY. Deformation-induced polymorphous conversions and transformations take place in calcium gluconate monohydrate. Mechanical treatment of the compound leads to the formation of two-dimensional structures (i.e., plane 2-D structures, nanotubes).

KEYWORDS: nanostructures, amorphous state, polymorphism, bioinorganic compounds, mechanochemistry.

NOMENCLATURE

CaGlu – Calcium gluconate monohydrate
δGluLac – Delta-gluconolactone
MCaG – Mechanoactivated calcium gluconate
TEM – Transmission electron microscopy

INTRODUCTION

Among molecular crystals prospective for application in pharmaceuticals 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].

Recently we have carried out investigations of mechanoactivation of calcium gluconate monohydrate (CaGlu) and for the first time have obtained a mechanochemically modified nano-dispersed amorphous form – the mechanoactivated calcium gluconate (MCaG) [2].

Clinical studies revealed its high therapeutic effectiveness in treating the diseases due to the calcium disbalance in the human body (dysplastic and degenerative-dystrophic processes, defects of bone tissue, traumatic and pathological fractures, osteoporosis, periodontology, etc.).

It is known, that because of the applying of mechanical stress to organic and organometallic molecular crystals the structural transitions take place, including both lattice polymorphic transformations/amorphization and stereo-isomerization molecules and formation of supramolecular nanoscale complexes. Using the deformation-induced transformations the matter can be converted into a new structural condition, having a unique set of physical and chemical properties and high biological activity, which, in some cases, essentially impossible to obtain in the process of liquid assisted chemical synthesis because of the negative effect of the solvent molecules. As a result, a new trend in the pharmaceutical industry appeared: solid-phase mechanochemical synthesis of drugs. However, the physical and chemical mechanisms of solid-state chemical reactions are still poorly understood [5].

Of particular difficulty is the situation when a substance is transferred to the amorphous-like state. The traditional diffraction methods of structural studies become uninformative. However, the kinetics of amorphization is usually studied only by the X-ray or electron scattering, leaving aside the processes occurring at the morphological and molecular scales. The process of amorphization of

molecular crystals is accompanied by structural transformations at the molecular, mesoscopic and macroscopic levels.

In this work for the first time we combined TEM and mass spectrometry for simultaneous exploring deformation-induced molecular conversions and kinetics of amorphization in CaGlu.

EXPERIMENTAL

To carry out the work, we used CaGlu produced by Fluka without any additional purification. The mechanochemically modified powders were obtained by the method of mechanoactivation in the planetary ball mill LAIR. The time of activation (t_a) was from 1 min till 1 h.

The X-ray structural analysis was carried out using XPD Miniflex 600 (Rigaku) at *Mo*-radiation. TEM images were taken using high resolution transmission electron microscope TECHNAI G30ST.

MALDI mass spectra were obtained using a ULTRAFLEX III TOF / TOF mass spectrometer (Bruker GmbH, Germany) equipped with a Nd: YAG laser ($\lambda = 266$ nm) in a linear regime with the registration of positively charged ions. A metal target was used. 2,5-Dihydroxybenzoic acid (2,5-DHB) was used as the template. 0.5 μ l 0.1 % solution in acetone matrix and 0.5 μ l mixture of 0.01 M calcium gluconate sample solution in water were successively applied to the target and evaporated.

The mass spectra of ESI were obtained using an AmazonX mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany). The measurements were carried out in the regime of recording of negative ions in the range m/z from 100 to 2000. The voltage on the capillary was 4500 V. As the gas-drier, nitrogen was used with a temperature of 3000 °C and a flow rate of 8 l/min⁻¹. The compounds were dissolved in water with a concentration of 10⁻⁵ mol/l. Data was processed using DataAnalysis 4.0 (Bruker Daltonik GmbH, Bremen, Germany).

It is essential from a practical point of view that during mechanical activation the contamination of the reaction products by grinding balls and vessels material is not observed.

RESULTS AND DISCUSSION

The volume fraction of the CaGlu amorphous phase increases monotonously in activation and by $t_a = 40$ min reaches 100 %. Further increase of the mechanical treatment time does not result in any qualitative changes in the X-ray and TEM microdiffraction patterns.

We showed that the trace amount of gluconic acid is present in the initial state of CaGlu and proposed its structure [3]. In the study of mechanoactivated form of calcium gluconate by EI and CI, a slight increase in the intensity of ion m/z 160 was observed, as well as the peak of ions m/z 179 in the mass spectra of CI increase. This indicates an increase of the content of δ -gluconolactone molecules in MCaG, that is, partial degradation of CaGlu to the formation of gluconic acid molecules, which, after dehydration, is converted into δ GluLac. Due to the rupture of intermolecular hydrogen bonds, the volatility of the sample increases during mechanoactivation and the gluconic acid molecules are cleaved from the CaGlu to form free molecules of both gluconic acid and δ -GluLac. The increase of the intensity of cluster ions m/z 627 [CaGlu₂+HG1+H]⁺, m/z 665 [CaGlu₂+CaGlu]⁺ in the ESI spectra confirms the previously expressed assumption of partial destruction of calcium gluconate and release of free acid. The formation of cluster ions m/z 627 and an increase in their intensity in MCaG indicate the formation of complexes of calcium gluconate and gluconic acid.

It was found that metal ions play a decisive role as the complexing element when the strain-induced stereo-isomerization takes place [6]. A manifestation of the isomerization is the transition of metal gluconates into the amorphous state. It is assumed that the amorphization is the result of formation of the mixture of the stereoisomers and complexes with substantially different geometric parameters. The resulting intermediate reaction products cannot be packaged in a single lattice, i.e. the translational long-range order disappears.

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 stereo-organization 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 2-D structures [6]. 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 Pauli principle. As a result of the forced changes of the molecule conformation the crystalline hydrate decomposes, with the water leaving the first coordination sphere of calcium.

It is known that the coordination water stabilizes the crystal lattice of the calcium gluconate through the formation of interplanar hydrogen bonds [4]. Its removal results in decreasing the strength of the interplanar bonds and facilitates the possibility of forming 2-D structures under the effect of shear stresses, and we see the evidence of crystals splitting along the planes of sliding (Fig. 1). However, it goes on through primary deformation-induced formation of donor-acceptor bonds [6].

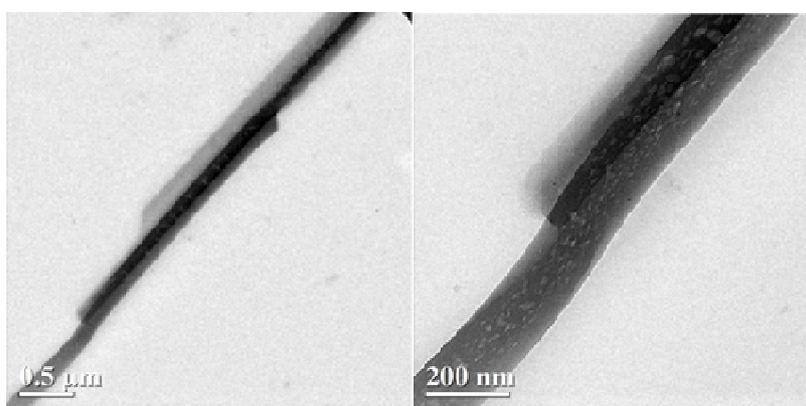


Fig. 1. Splitting of CaGlu crystals under mechanoactivation (TEM, $t_a=40$ min)

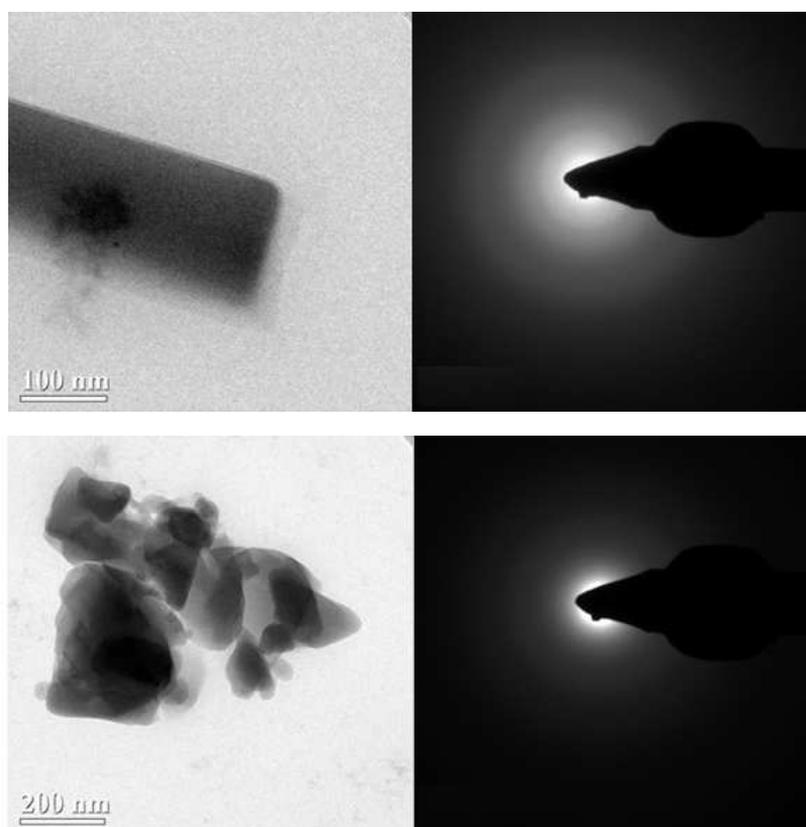


Fig. 2. TEM image (left) and electronic microdiffraction (right) of MCaG $t_a=60$ min

We can see the evidence of crystals splitting along the planes of sliding. One is amazed at the variety of structures being formed: from plane ones of thickness not exceeded 5 nm, with the possibility of their folding into tubes, to globular ones.

In the case when the composition of the opposite surfaces of 2-D objects differs significantly, one can observe the formation of tubes (Fig.3). It is possible, when the formation of slabs occurs, e.g. as a result of the cut along the planes (110). On the one surface there is a maximum reticular density of calcium ions, but on the other – the gluconic acid anions. This mechanism of the appearance of bending stresses reminds that one well-known for the micelle-like structures and can result in the tube formation.

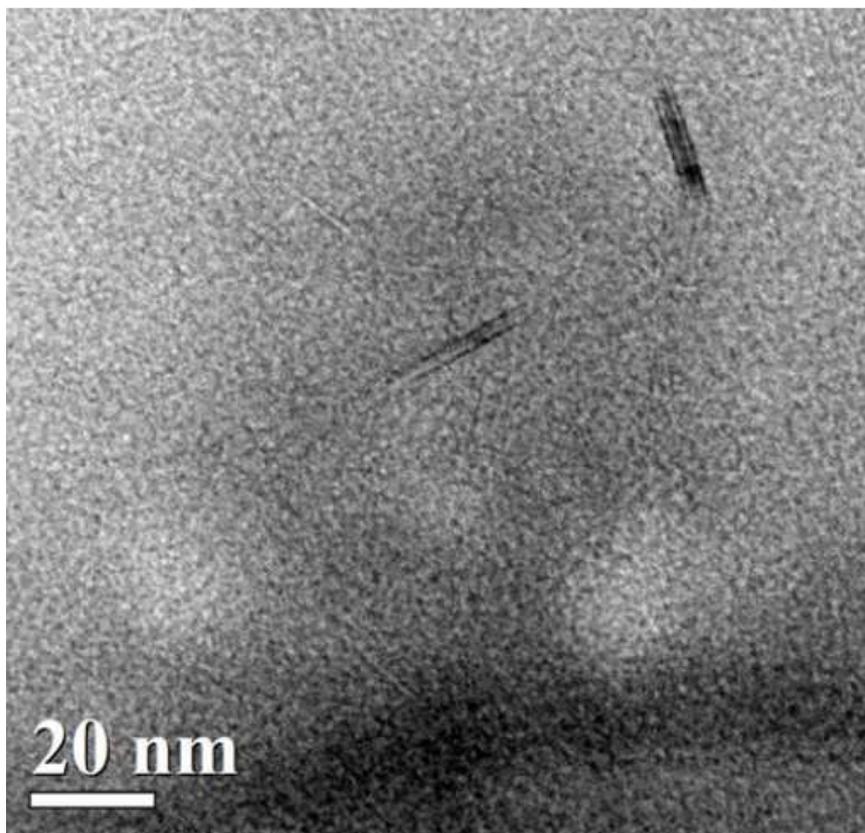


Fig. 3. TEM image of MCaG ($t_a=60$ min)

The formation of plane 2-D structures makes the following crucial question undecided: are they 2-D crystals or is it the amorphous state of the substance? In both cases the Bragg's law does not hold, and we can observe the diffusive scattering of *X*-rays or electrons. A clear differentiation between a truly amorphous state and a two-dimensional crystalline state in organic and bio-organic compounds is not only of fundamental interest, but also of practical importance, since these two states differ in a set of physicochemical parameters. We believe that in our case, we observe the co-existence of 2-D crystalline and globular amorphous structures (Fig. 2). Nevertheless, it is obvious that the morphological studies, although being consistent with this hypothesis, however, require further confirmation using both in-plane scattering of synchrotron radiation and in situ spectroscopic studies.

CONCLUSIONS

In this work, it was shown for the first time that the deformation-induced partial destruction of CaGlu molecules is accompanied by complex formation as a result of the interaction of decomposition products and the subsequent appearance of an amorphous-like state. The deformation-induced formation of two-dimensional structures implies the need for the following clear differentiation between truly amorphous and two-dimensional crystalline states.

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