

The study on the impact of molecular interactions on the dynamics and kinetics of isomerization reactions occurring in model systems prepared in an amorphous form

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Abstract

The research was carried out for pure low-molecular systems belonging to the group of monosaccharides, i.e. D-fructose, L-sorbose, binary mixtures of D-fructose with alcohol (i.e. maltitol) and a pharmaceutical active ingredient (API), i.e. glibenclamide.

Investigations of kinetic processes in monosaccharides prepared in an amorphous form near the *glass transition temperature* (T_g), and the so-called *crossover temperature* (T_c) involved monitoring inter- and intramolecular interactions and their impact on changing molecular dynamics and kinetics with respect to the isomerization reaction. The progress of the mutarotation taking place in pure supercooled monosaccharide near the *glass transition temperature* (T_g) correlated with the results for high-viscosity binary systems, in a mixture with maltitol. It turned out that the constant rate of reaction characterizing the mutarotation process change around the T_g temperature, and the activation energy (E_a) value increases from 107 kJ / mol above T_g (supercooled state) to about 250 kJ / mol below T_g (glassy state). The results of these studies for the first time referred experimentally to the hypothesis about changes in the nature of the mutarotation, postulated theoretically, to be dependent on the thermodynamic state of examined system. It also turns out that determining a single activation barrier may not be sufficient to describe the progress of chemical reactions near the glass transition temperature, especially in highly viscous systems. I also attempted to describe the behavior of the low-molecular physical system at temperatures where theory predicts the existence of so-called *crossover temperature* (T_c), which was postulated as the temperature of changing molecular dynamics from non-cooperative to completely cooperative. As a result of experiments, it has been shown that below this temperature there is a change in the strength and dynamics of hydrogen bonds of the molecular system. This allowed for the first time to show that there is a close relationship between physics of condensed matter and the progress of chemical reaction in the area of glassy phase. I would like to emphasize that in my research I have mainly attempted to understand the effects occurring in highly viscous systems, and the obtained results make an important contribution to understanding the heterogeneous nature of condensed matter and the role of hydrogen bonds in controlling mutarotation in the supercooled state.

I have also attempted to describe the tautomerization reaction in relation to systems prepared in the form of nanometric layers and correlate the results with bulk systems. I monitored the dynamics and kinetics of tautomerization in this type of molecular systems, showing that glibenclamide in thin layers ($d = 49$ nm, 120 nm, 220 nm) is only partially transformed from the amide form (present in crystalline state) to a mixture of amide and imide forms (so-called amide tautomerization). In turned, the tautomerization process as a result of undercooling of volume systems leads to the

formation of mainly imide forms with a small content of molecules in the amide form. The obtained results showed that various interrelationships between amide and imide forms have a strong influence on the progress of the tautomerization reaction. The disturbed ratio of amide-imide forms also forces a different nature of the process itself, which in bulk systems has the features of an autocatalytic process (sigmoidal shape of the kinetic curve), while in thin-film systems the kinetic process has an exponential shape characteristic of the first order reactions. This allowed to hypothesize that the autocatalytic nature may be associated with the formation of amide forms, which in the next stage stimulates further imide-amide transformation. I have also shown that changes in the speed of the tautomerization process in thin-film systems of different thickness strongly depend on the degree of interaction of the molecular system with the substrate, which means that in different molecular fragments of the glibenclamide molecule, the proton transfer processes may take place differently. I would like to emphasize that the presented results are innovative, showing that a change in the geometry or thickness of the layer can affect the rate of the tautomerization process, the composition of tautomers or the properties of molecular systems. These results seem to be very promising, especially in the context of the development of new drug delivery systems.