

The phenomenon of polymorphism within the stereoatomic model of crystal structures

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Active research of some organic compounds, which are actual or promising drugs, has led in the last decade to the production of a large number of their new polymorphic modifications [1]. To date, examples of compounds with up to 12 structurally studied modifications are known. From the point of view of crystal chemistry, such highly polymorphic systems are of great interest for studying the relationship between structure and properties since their composition is fixed. At the same time, in the presence of suitable methods of analysis, one can try to establish the influence of the slightest changes in the geometry of molecules (conformation) or their packing on the properties of the final substances. Such changes inevitably affect interatomic interactions in the crystal structures of these compounds.

To study both chemical bonds and van der Waals interactions, classical crystal chemistry uses a comparison of interatomic distances with different tabulated systems of radii. However, practice shows that this approach is insufficient for such complex objects as highly polymorphic compounds. Another method for studying noncovalent interactions, the Hirshfeld surface method, implies a visual one-by-one comparison of compounds and considers only about 95% of the crystal volume, which also leads to many limitations.

In the course of this long-term project, we consider highly polymorphic systems within the framework of the stereoatomic model of crystal structures [2]. The advantage of this model is that it takes into account all possible interactions (chemical bonds and intra- and intermolecular noncovalent contacts) from uniform positions in all 100% of the crystal volume. In addition, this method allows computer programming and, consequently, automatic analysis in large data samples, which is especially important given the volume of already accumulated and progressively increasing information about crystal structures.

Many known highly polymorphic systems have already been successfully analysed using the stereoatomic model of crystal structures. This list includes such champions in terms of the number of structurally studied modifications as flufenamic acid (8 modifications) [3], aripiprazole (9 modifications) [4], galunisertib (10 modifications) [5], etc. For all compounds, various parameters of all types of interatomic interactions in crystal structures were calculated, which can be used for subsequent searches for all kinds of relationships. One of the main results, which was first shown using the example of these compounds, not qualitatively, but quantitatively, is that each polymorphic modification corresponds to a unique set of noncovalent contacts, what, in our opinion, is one of the reasons for the existence of polymorphism.

In the course of this project, additional tools for crystal chemical analysis were developed. For example, one of them is the $k\text{-}\Phi$ criterion, which makes it possible to unambiguously and objectively identify conformational polymorphs [6]. The (RF, d) distributions were introduced in assistance to the $k\text{-}\Phi$ criterion to get an idea of the relationship between the ranks of faces and the corresponding interatomic distances [5]. Also, a method was developed to visualize changes in noncovalent interactions when changing the geometry of molecules [7].

As a result, all the work done brings us closer to understanding how the differences in the energetics of polymorphic modifications can be explained from the standpoint of individual noncovalent interactions - this is the question posed by Professor J. Bernstein in his book in 2002 [1].

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