Poster

Spironolactone Polymorphism: Do New Methods Yield New Insights?

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The steroidal drug, spironolactone, is a well-established and widely-used diuretic and aldosterone antagonist. It forms numerous polymorphs and solvates, thus frequently featuring in studies within the crystallographic community. The first single-crystal data were available in 1972, with subsequent studies finding other polymorphs or solvates aiming at improving its solubility and, consequently, its bioavailability [1-3]. In earlier research, it often served as a model organic molecule with predominantly weak interactions, aiding the understanding of the phenomena of polymorphism and predicting solvate formation [4-7].

We began our investigation into this topic with the serendipitous discovery of a new spironolactone polymorph, which we have named form III. [8] In an effort to understand how it differs from the previously known forms I and II, we employed modern tools such as Hirschfeld surface (HS) analysis and Non-Covalent Interaction (NCI) plots [9-10]. We also calculated the lattice energies of each form. HS analyses are straightforward to generate, and this study serves as an example of how they can aid in identifying model inaccuracies, particularly those related to disorder. Upon re-investigating the thermodynamically most stable form II, we detected disorder-order transitions at lower temperatures. Consequently, we propose an improved molecular structure model for spironolactone II and showcase potential artefacts that might occur in HS if disorder is overlooked. To understand the energetic relationships between the polymorphs, we turned to integrated NCI properties that revealed form II contains a larger total volume of weak attractive forces than its counterparts.

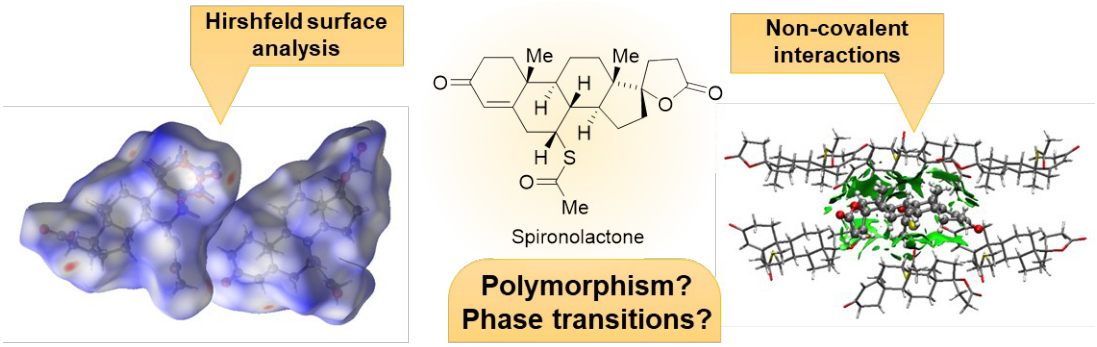

Figure 1. Hirschfeld surface and non-covalent interaction analysis were employed to investigate the polymorphism of the steroidal drug spironolactone.

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