Elucidation of stability of caffeine-dicarboxylic acid complexes by quantum crystallography

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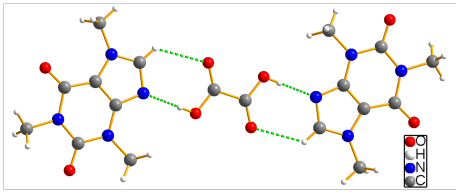
The function of a pharmaceutical product is determined not only by its direct efficacy, but also by its stability during storage and selective action on the necessary sites in the body. Co-crystals, which are constructed by electrostatic interactions between two or more organic molecules, are attracting attention as a new drug discovery technology because one molecule has a pharmaceutical efficacy, the stability and solubility can be controlled by the other constituent molecule. However, the conditions for co-crystallization with the desired functionality have been found through trial and error from an infinite number of combinations, making it extremely difficult. The purpose of this study is to clarify the key points of crystal stability and solubility by analyzing the electrostatic potentials inside the co-crystal, and to construct a design and synthesis method based on this understanding.

Co-crystals are constructed by supramolecular synthons with weak electrostatic interactions such as hydrogen bonding. For these co-crystals, direct visualization of electrostatic potentials experimentally using synchrotron radiation makes it possible to relate the electrostatic field to the crystallization conditions. Furthermore, we visualize molecular functions by clarifying the correlation between the co-crystal and stability and solubility based on differences in the electrostatic field of the co-crystals. This research will enable the design of molecular functions of pharmaceutical functional co-crystals required from the viewpoint of structural science.

In this study, we visualize the stability of the co-crystal of caffeine, a reference material used to evaluate the stability of pharmaceuticals, by means of an electrostatic field calculated based on quantum crystallography. Caffeine co-crystals with different stability constructed by organic compounds with carboxylic acid groups as supramolecular synthons were prepared, and precise structural analysis was performed by X-ray diffraction experiments using synchrotron radiation. The stability of the caffeine co-crystal is visualized by determining the electrostatic potential from the obtained electron density. Furthermore, we will visualize the physical properties of the new caffeine co-crystal by using the electrostatic potential from the precise structure analysis. In this presentation, we report the visualization and discussion of pharmaceutical co-crystals through visualization by electrostatic field analysis.



Hydrogen bond interactions in co-crystal consisted of caffeine and oxalic acid