

# Oral Contributions

## [MS23] Exploring crystal energy landscapes and crystal structure prediction

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### [MS23-01] Hydrates of Small Organic Molecules -Insights into their Formation and Stability Doris E. Braun,

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Hydrate formation is a phenomenon that is observed for at least a third of pharmaceutically relevant organic molecules [1,2] and is of high practical relevance, as the inclusion of water molecules in the crystal lattice of such substances affects many of their physical properties.[3] The knowledge of the existence and stability of hydrates may be a critical issue for the development of industrial manufacturing processes, where it is mostly difficult to exclude water or moisture. Thus, hydrate formation often cannot be avoided and the understanding and control of the anhydrate/hydrate balance is mandatory for avoiding manufacturing problems. In recent years computational methods have been successfully employed for predicting crystal structures of small molecules, drug compounds and even multi-component systems.[4,5] However, such methods have been rarely applied to predict the formation and stability of hydrates. To improve the understanding of the nature of hydrates we selected different phenols, hydroxybenzoic acids and alkaloids as model compounds for experimental and computational studies. These classes of molecules are prone to form stoichiometric and/or non-stoichiometric hydrates or even multiple hydrates (polymorphic hydrates or hydrates with different stoichiometries).

Calculating the energies of hydrate, anhydrate and

hydrate framework structures (hydrate structure without water) can rationalise the structural role of the water molecule in the hydrate structure, i.e. linking molecules or only filling voids.

The framework structure of the pyrogallol tetrahydrate was found as a higher energy structure on the computationally generated anhydrate crystal energy landscape.[6] This allowed modelling to complement the structure solution of the hydrate from powder X-ray data and provided insights into the dehydration mechanism. Contrasting the computationally generated anhydrate and hydrate crystal energy landscapes also correctly predicted hydrate formation for 2,4-dihydroxybenzoic acid [7] and gallic acid [8], and rationalised why no hydrate was found for 2,5-dihydroxybenzoic acid [7]. The computed gallic acid crystal energy landscapes suggested alternative stable packings that were later identified as experimental hydrate and anhydrate polymorphs.

Thus, the combination of computational techniques and suitable experimental approaches such as moisture sorption analysis and RH-perfusion calorimetry appears to be a very promising strategy for understanding the stability of these common solid forms and the complex phenomenon of hydrate formation.

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