

Poster Presentation

MS67.P04

Insights into hydrate formation and stability of morphinanes

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The formation of multi-component crystals with water (hydrates) is a widespread phenomenon among organic molecules. Hydrate formation is of high practical relevance for industrially used materials, as it affects their physicochemical properties. [1,2] To exclude water or moisture in industrial processes is often difficult. Therefore knowledge about the existence and stability of hydrates and the understanding and control of the anhydrate/hydrate balance is mandatory for avoiding manufacturing problems. In order to improve our understanding of hydrate formation we selected representative substances (morphine, codeine, ethylmorphine) from a class of molecules (morphinanes), which are prone to crystallize along with water. Stable hydrates of both, free bases and HCl salts, have been observed in this important class of drug compounds. This allowed us to investigate the influence of different functional groups, the role of water and the Cl⁻ counterion on the structure and properties of these morphinanes. A crystallization screen on the six compounds considerably extended the total number of known solid forms from twelve [3] to 17 and the number of crystal structures from five to twelve. Anhydrous polymorphs were detected for all compounds except ethylmorphine (one anhydrate) and its HCl salt (no anhydrate). The relative stabilities of the hydrated and anhydrous forms differ considerably, which was evaluated by moisture sorption studies and thermal analytical experiments. Two different hydrates, a tri- and dihydrate, were found for morphine HCl. In the free bases, the substituents define the number of hydrogen bond donor groups and lead to differences in the sterical hindrance around polar groups, influencing the intermolecular interactions, packing and stability. Hydrate formation results in higher dimensional hydrogen bond networks, whereas salt formation decreases the packing variability of the structures among the different compounds. Calorimetric measurements and lattice energy calculations were employed to estimate the heat of hydrate/anhydrate phase transformation, showing an enthalpic stabilization of the hydrates over the anhydrates. The combination of a variety of experimental techniques with computational modelling allowed us to generate sufficient kinetic, thermodynamic and structural information to understand the principles of hydrate formation of morphinanes.

[1] C. Sun, D. J. W. Grant, *Pharm. Res.*, 2004, 21, 382-386., [2] R. K. Khankari, D. J. W. Grant, *Thermochim. Acta*, 1995, 248, 61-79., [3] M. Kuhnert-Brandstatter, A. Kofler, W. Heindl, *Pharm. Acta. Helv.*, 1975, 50, 360-372.

Keywords: hydrate, stability