Obtaining and structural studies of ectoine cocrystals with selected anions

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Ectoine is a very interesting compound belonging to the amino acid group. It was first isolated from bacteria of the Ectothiorhodospira species [1]. Due to its strong hygroscopic properties, it is produced by bacteria to protect against adverse conditions such as high salinity. Ectoine is a kosmotrope, stabilizing protein structures through its high water-binding capacity. These properties make ectoine widely used in cosmetics and pharmaceuticals.

The crystal structure of ectoine was only determined in 2020 [2]. It can crystallize in an anhydrous form or as a dihydrate. Interestingly, in these structures different conformations of the carboxyl group in ectoine molecules are observed. In anhydrous crystals the carboxyl group is equatorial, while in dihydrate crystals it adopts a less energetically favorable axial conformation. It is likely that hydrogen bonds between ectoine and water molecules stabilize this arrangement. In dihydrate crystals, ectoine molecules form channels that incorporate water molecules. The structure of ectoine solvate with methanol is also known [3] – it is isomorphic with the dihydrate structure. So far, no co-crystals of ectoine with other substances have been identified.

This research aims to investigate the potential interactions of ectoine in the solid state with inorganic anions and a carboxylate anion. Given the kosmotropic properties of ectoine, emphasis was placed on understanding its influence on the water-binding capacity within the crystal lattice. Furthermore, it is particularly essential to characterize ectoine's interactions with carboxyl groups, due to their presence in protein-building amino acids.

Eight cocrystals of ectoine were obtained and structurally characterized: with oxalic acid, oxamic acid, tartaric acid, malic acid, as well as with inorganic acids such as hydrofluoric acid, hexafluorosilicic acid, and hydrochloric acid (hydrate and anhydrous form).

Analysis of the obtained structures reveals that ectoine readily forms dimers when its carboxyl group adopts an equatorial conformation. This behavior is observed in cocrystals with oxalic acid, malic acid, hydrochloric acid (hydrate), and hydrofluoric acid. Moreover, in each of these structures, proton sharing can be observed: either between the carboxyl group of ectoine and a fluoride anion (in the cocrystal with hydrofluoric acid) or between two carboxyl groups of ectoine (in other mentioned structures). No dimer formation or proton sharing is observed when the carboxyl group of ectoine adopts an axial conformation, probably due to steric constraints imposed by the molecular geometry. Water molecules are incorporated into the crystal lattices of ectoine cocrystals formed with two carboxylic acids (tartaric acid and oxamic acid) and two inorganic acids (hydrochloric acid and hexafluorosilicic acid).

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