

Multicomponent forms of the regioisomers fumaric and maleic acids with Glycine. SALT or CO-CRYSTAL?

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The tremendous growth in number of compounds involving two or more components is due to the fact that the properties of the new compounds can be tuned keeping intact the molecule of interest.¹ Two prevalent types of multicomponent crystals are binary salts and binary co-crystals, which differ by the fact that two counterions or two neutral molecules are present in the crystal lattice, respectively. This strategy has been particularly useful, for example, to improve the solubility of active pharmaceutical ingredients (APIs) or food additives.

There are different methods of synthesis of these multicomponent forms such as solution methods or mechanochemical methods. However different methods of preparation can lead to different compounds even if starting materials from identical batches are used. The assessment of the stability of a specific binary co-crystal or salt relative to its precursors, therefore, becomes of considerable importance. A recent theoretical work predicted that the formation of co-crystals from their precursors is generally enthalpy driven.¹ This is not, however, a necessary condition, as shown by the recent report of an entropically stabilized cocrystal.²

Other relevant issue is that for neutral precursors with ionizable protons the preference for salt or cocrystal formation depends on the tendency for proton transfer between the potential donor and acceptor counterparts.

In this work this preference was analyzed for two systems: maleic acid-glycine (MA-Gly) and fumaric acid-glycine (FA:Gly₂). It was found that a MA-Gly salt and a FA:Gly₂ cocrystal were always obtained regardless of the preparation method used: crystallization from solution or mechanochemistry. The differences in crystal structure between the obtained materials were evaluated based on single crystal X-ray diffraction data. Finally, the relative stability of MA-Gly and FA:Gly₂ relative to their precursors was assessed in terms of lattice energy, based on calorimetric measurements.

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References

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