Energetics of Maleic acid-L-phenylalanine Bicomponent Crystals with Different Stoichiometry

I.O. Feliciano, C.E.S. Bernardes, M. E. Minas da Piedade

Centro de Química Estrutural, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016, Portugal

The synthesis of multicomponent crystals has emerged as a very convenient strategy to improve important physical properties of active pharmaceutical ingredients (e.g. bioavailability). A key aspect within this scope is the evaluation of the stability of the produced materials relative to their pure components, to ensure that they do not decompose during the storage period. A good indicator of that stability is the standard molar enthalpy, $\Delta_r H_m°$, of the reaction $A_aB_b(cr) \rightarrow aA(cr)+bB(cr)$, which reflects the difference in lattice energy between the aA and bB precursors and the A_aB_b material. Based on this criterion A_aB_b will be stable if $\Delta_r H_m° > 0$. An enthalpic only stability criteria can often be used because available experimental evidence [1,2] suggests, that, in most cases, close to ambient temperature, $|\Delta_r H_m°| > -|T\Delta_r S_m°|$.

The influence of stoichiometry of the stability of the A_aB_b species is a virtually unexplored topic. In this work the energetics of two organic salts consisting of maleic acid (MA) and L-phenylalanine (Phe) with 1:1 and 1:2 stoichiometries was investigated. The compounds were synthesized by mechanochemistry and structurally characterized by single crystal X-ray diffraction (Fig.1).[3] The $\Delta_r H_m°$ determinations relied on enthalpy of solution measurements carried out with a newly developed calorimetric cell for the LKB 2277 Thermal Activity Monitor (TAM) and a previously described methodology.[1] The obtained results indicated that, at least in the present case, despite significant structural differences, $\Delta_r H_m°$ (MA:Phe$_2$) $\approx 2\Delta_r H_m°$ (MA:Phe).

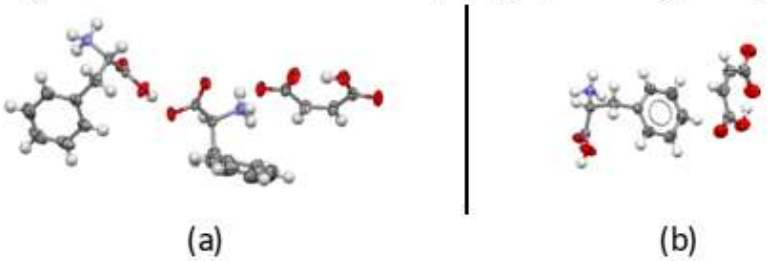

Fig. 1- Molecular structures of (a) zwitterionic salt MA:Phe$_2$ (determined in this work),[3] and (b) MA:Phe salt (CCD reference, EDAXIQ).

Acknowledgements: This work was supported by Fundação para a Ciência e Tecnologia (FCT), Portugal (projects PTDC/QUI-OUT/28401/2017, LISBOA-01-0145-FEDER-028401, UIDB/00100/2020, and UIDP/00100/2020).

(1) A.O.L Évora, et al.; *Cryst. Growth Des*. **2019**, 19, 5054−5064.
(2) G.L. Perlovich; *Cryst. Growth Des*. **2020**, 20, 5526–5537.
(3) D. Silva, M.F.M. Piedade; unpublished results.