

Poster Presentation

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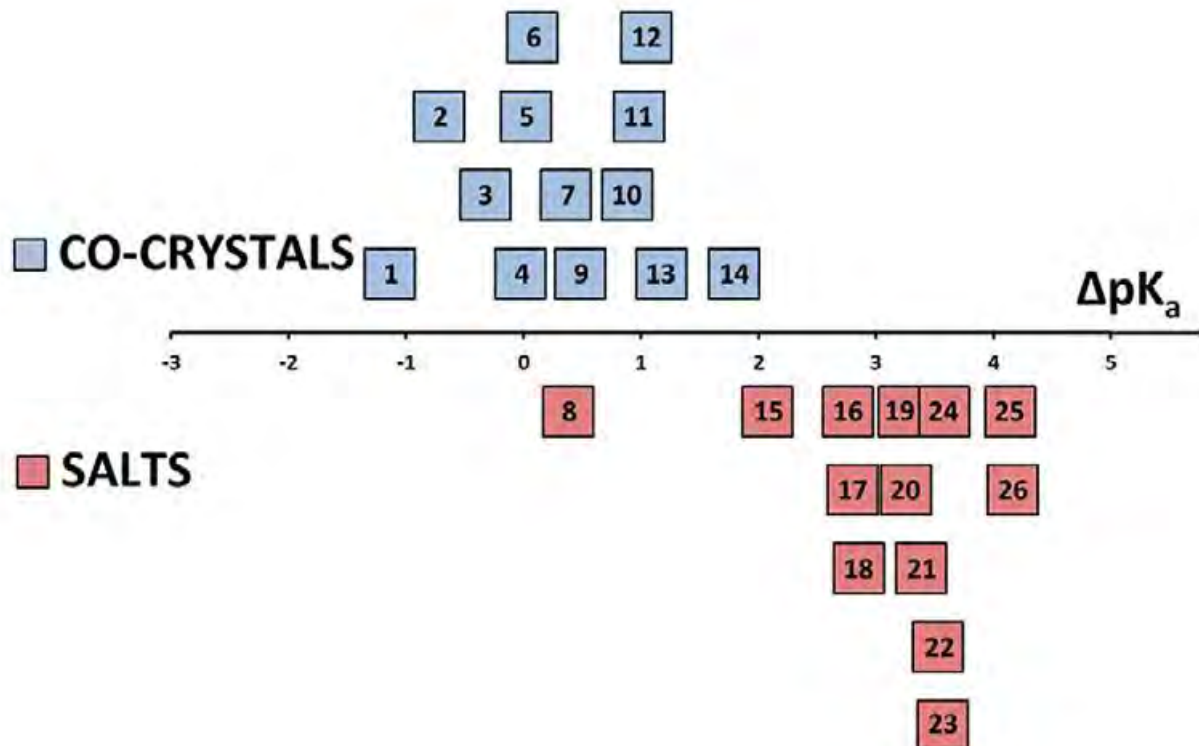
'Uncertainty' region of acid-base ΔpK_a : Salt versus co-crystal formation

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The hydrogen bond is a very important interaction which demonstrates a wide variety in strength and shape and can be held as the central point in the crystal engineering process of a great number of compounds. In the formation of salts versus co-crystals, pH control is necessary in order to obtain one form or the other. In the pharmaceutical industry which is actively developing Active Pharmaceutical Ingredients (APIs) with desirable properties, such consideration is of major concern. In 2012, Cruz-Cabeza[1] carried out a survey of over 6 000 structures and found a linear relationship between ΔpK_a and the probability of proton transfer for the pK_a range of -1 to +4. The cross-over point was determined to be at $\Delta pK_a = 1.3$. Beyond this point the probability to obtain a salt rather than a co-crystal is higher than 50%. Parallel to this work, Gilli & Gilli[2] have built a sliding rule which predicts the strength of a Donor – Acceptor hydrogen bond based on the ΔpK_a of the system. Their device predicts the formation of salts if $\Delta pK_a > 3$, and co-crystals when $\Delta pK_a < -3$. In their paper, Gilli & Gilli point out that the interval of ΔpK_a matching should be shifted by 1.5 units when interpreting crystal structures,[3] which agrees with the findings of Cruz-Cabeza. In this work we discuss the bonding of 22 structures made up of acid-base pairs which either form salts or co-crystals. A series of five substituted benzoic acids with 10 substituted pyridines and quinolines have been crystallized so that their ΔpK_a , defined as $pK_a(\text{base}) - pK_a(\text{acid})$, spans the range -1.14 to +4.16. This covers the 'uncertainty' region for the formation of salt versus co-crystals. Although most of our results confirmed that structure formation of co-crystal versus salt parts at $\Delta pK_a \approx 2$, we report here a structure that does not follow the general rule and serves as a cautionary tale.

[1] Cruz-Cabeza, A. J. (2012). *CrystEngComm*, 14, 6362-6365, [2] a) Gilli, P., Pretto, L., Bertolasi, V. & Gilli, G. (2009). *Acc. Chem. Res.* 42, 33-44. b) Gilli, P. & Gilli, G. (2012). *Supramolecular Chemistry, from Molecules to Nanomaterials*, edited by P.A. Gale & J.W. Steed, Wiley, Chichester, vol. 6, Chapter 2., [3] Huyskens, P., Sobczyk, L. & Majerz, I. (2002). *J. Mol. Struct.*, 615, 61-72.



Keywords: hydrogen bond, proton transfer
Acta Cryst. (2014), A70, C558