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The correlation of the pKa equalization principle to Charge-assisted Hydrogen bonds in differentiation of the molecular salts from cocrystals

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Introduction

The estimation of the extent of proton transfer between proton donor/electron acceptors and proton acceptor/electron donor moieties, both in intra- and inter-molecular cases, can be considered an emerging approach in crystal engineering, aimed at predicting the strength and the nature of hydrogen bonding interactions.[1]

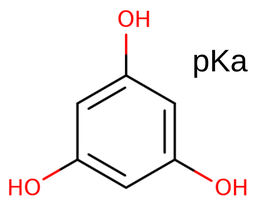
On the basis of the pKa equalization principle, the strongest hydrogen bonds are associated with a very low ΔpKa value, i.e. the difference between donor and acceptor acidic constants. [1,2] The ΔpKa value associated with a general D—H···A interaction is calculated as:

ΔpKa (D—H···A) = pKAH (D—H) – pK⁺BH(A—H⁺)

Thia is applied to correlate the wide range O···N distance distribution to chemical diversity, expressed in terms of acidity constant, displayed by the conformer molecules in Phloroglucinol (PHL) cocrystals and pyridoxime (vitamin B6) molecular salts. [3,4]. The presented crystal structure packing motifs between cocrystallized, both neutral N-heterocycles coformers and O-type of acidic drug model (PHL), as well between protonated and non-protonated N-heterocycle (pyridine type of drug model pyridoxine) and aromatic carboxylic acids confirm that the bond distances correlate to the nature of the hydrogen bond in range from week charge-assisted H-bonds in PHL/N-heterocycles cocrystals (ΔpKa < 0), toward the so-called “salt–cocrystal continuum” in unprotonated pyridine derivative (ΔpKa 0 – 1), till to formation strong charge-assisted H-bonds in molecular salts of the same protonated pyridine (ΔpKa > 3). [5]

Compounds Studied

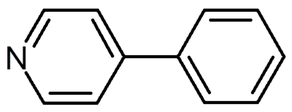
Drug model
Phloroglucinol (PHL)



pKa 8.45

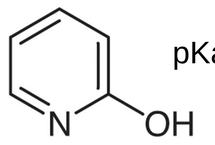
Coformers

4-phenylpyridine



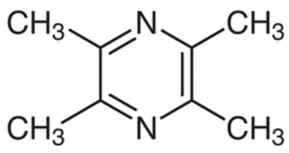
pKa 5.5

2-hydroxy-pyridine



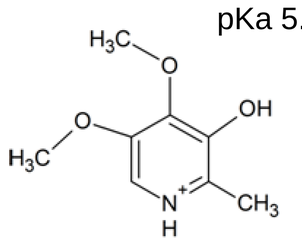
pKa 5.2

2,3,5,6- tetramethylpyrazine
E- cigarette aroma



pKa 3.51

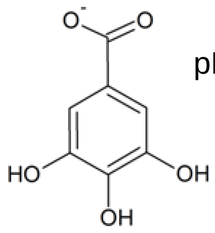
Drug model
Pyridoxine (PN)
Vitamin B6



pKa 5.1

Coformer

Gallic acid
Nutraceutic acid



pKa 4.24

Sample Preparation

An equimolar quantity of PHL and co-crystal partner was dissolved in the minimum quantity of ethanol and left for slow evaporation at room temperature. Colourless crystals were observed after a few days.

Methods

Single crystals of PCC were obtained by slow evaporation of the solvent:

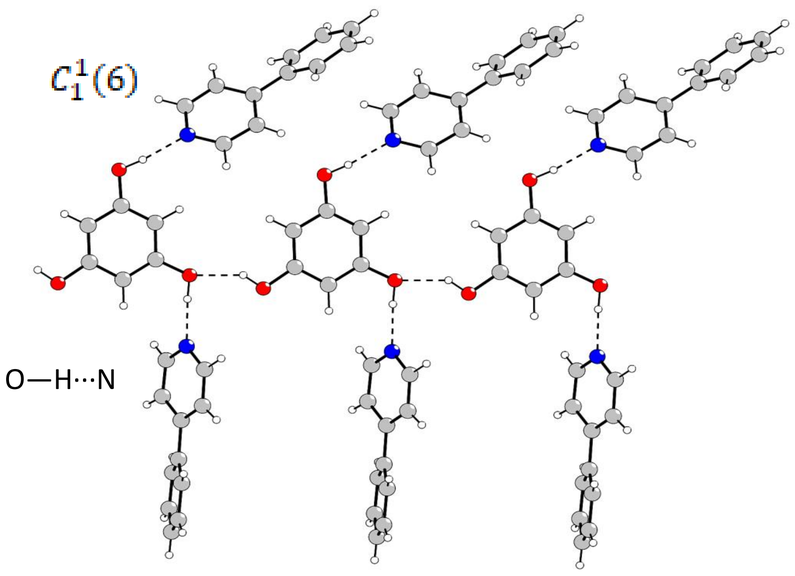
Characterization of PCC

Structure determination was performed by Single Crystal X-Ray Diffraction Analysis confirming the structures and being deposited in the Cambridge Structure Database CCDC.

Crystal Structures of Cocrystals
Packing determined by number od H-bond acceptors, relative size of PHL and coformer molecules

One H-bond acceptor Coformer

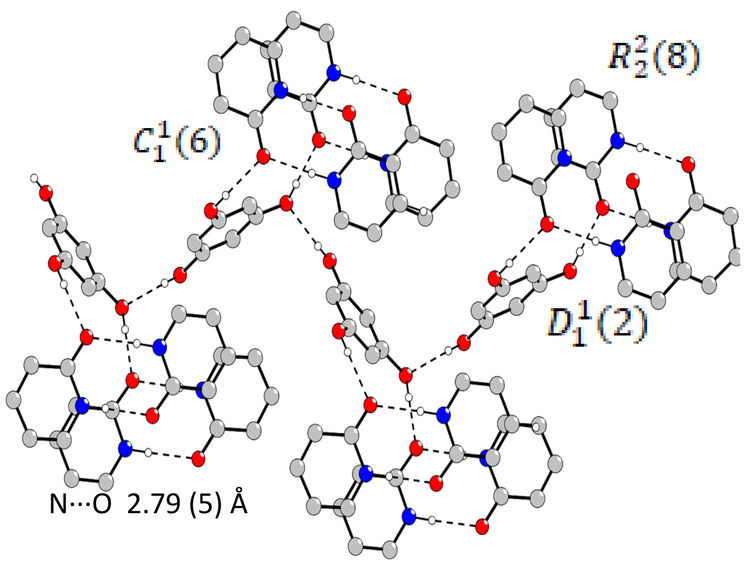
PHL– 4-phenylpyridine 1:2 *M/M*



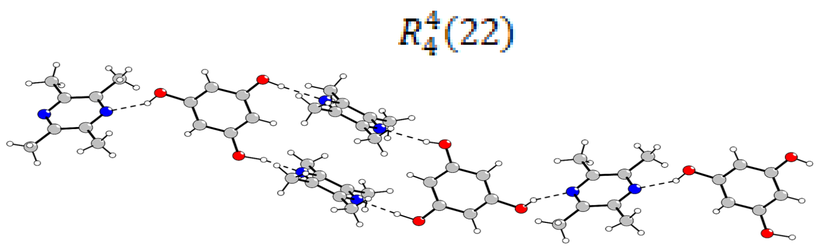
Chains motif

Two H-bond acceptor coformers

PHL — 2-hydroxy-pyridine coformer 1: 2 *M/M*



PHL – 2,3,5,6- tetramethylpyrazine 2:3 *M/M*

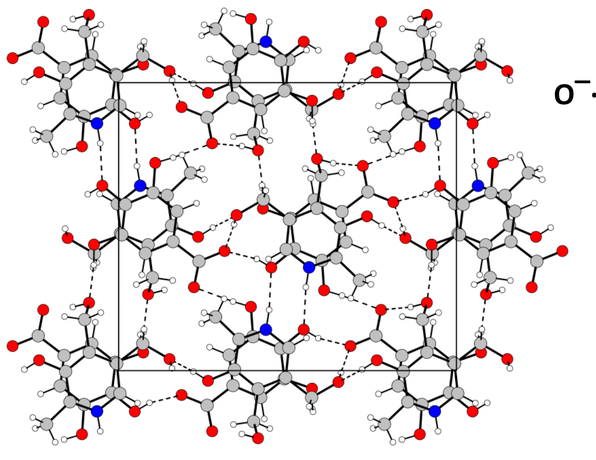


zigzag ribbon motif

zigzag ribbon motif (alternating PHL– coformer molecule layers)

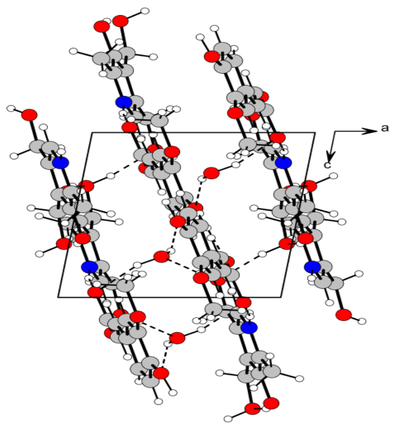
Crystal Structures of “salt–cocrystal continuum”
Strong Charge Assisted H-bonds

PN – Gallic acid 1:1 *M/M*



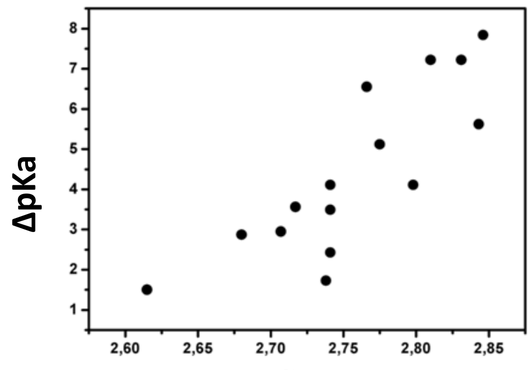
$O^-\cdots H–N^+$

ΔpKa PN-GAL (0.70)



Cg1= centroid of the N1–C5 ring; Cg2= centroid of the C9–C14 ring

ΔpK$_a$ vs N…O distances (Å) in PHL cocrystals



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