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The role of proton transfer in multicomponent crystals of pyridine derivative with carboxylic acids

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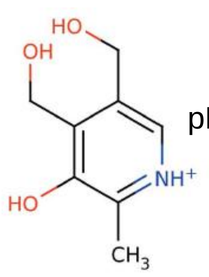
Introduction

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] This is particular important in the field of pharmaceutical cocrystals, due to the presence of aromatic base (e.g. pyridine) and/or carboxylic acid functionalities in many compounds of pharmaceutical relevance[2,3]. In general terms, shared proton between unprotonated pyridine and carboxylic group leads to neutral co-crystal formation, while completely transferred proton, associated with the formation of charge-assisted H bonds between carboxylate anion and pyridinium cation, leads to a molecular salt [4,5]. To predict whether multicomponent systems in solution would co-crystallize as molecular salts or neutral co-crystals, the evaluation of ΔpKa = pKa(protonated base) − pKa(acid) could be of help: according to the so-called "rule of three", a salt is expected if the ΔpK_a ($pK_{a-(base)} - pK_{a(acid)}$) is greater than 2 or 3 units, while the formation of a cocrystals is observed if the ΔpK_a is smaller than 0 [1,6].

The molecular salts of pyridoxine (PN), the alcohol derivative of –hydroxypyridine, part of B-complex vitamins, that is widely used both in therapy and food supplementation, PN-SYR and PN-GAL are form with hydroxyaromatic acids with potent antioxidative activity, syringic acid (SYR) and gallic acid (GAL), respectively.

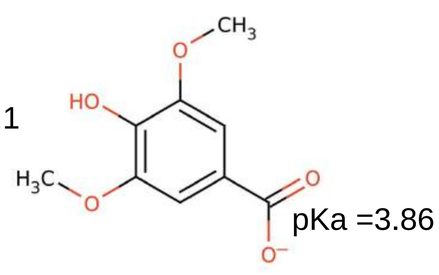
Compounds Studied



pKa =5.1

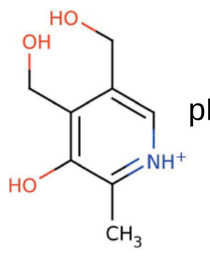
1

Protonated Pyridoxin (PN)



pKa =3.86

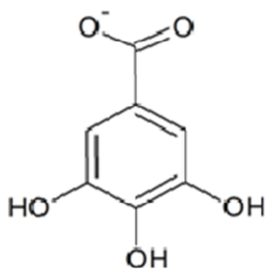
Syrincic acid (SYR)



pKa =5.1

2

pKa = 4.24



Gallic acid (GAL)

ΔpK_a (1) = pK_a(D−H) – pK_a(A−H$^+$) = 1.24

ΔpK_a (2) = pK_a(D−H) – pK_a(A−H$^+$) = 0.86

Sample Preparation

Neutral Pyridoxine free base (PN) was used in cocrystallization with syrigic acid (SYR) and gallic acid (GAL). PN was prepare by neutralization of pyridoxine HCl salt with sodium hydroxide in isopropanol.

Compound 1. PN / SYR 1:1 *M/M* in isopropnol

Compound 2. PN/ GALxH_2O 1:1 *M/M* of isoamyl acetate/ethanol 50/50 *V/V*

Methods

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

Characterization of PCC

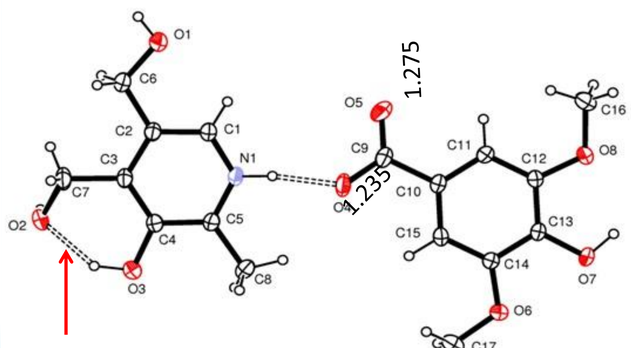
Structure determination was performed by Single Crystal X-Ray Diffraction Analysis confirming the structure 1 and structure 2 to be molecular salt forms of New Chemical Entity (NEC) not so far deposited in the Cambridge Structure Database CCDC.

Crystal Structures

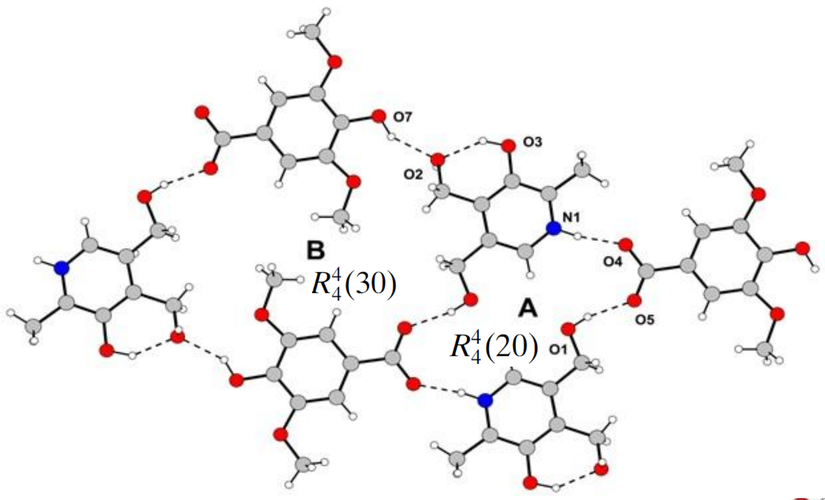
Compound 1: pyridoxinium syringate

C1—N1—C5 123.59°

C—C—O 116.84 °



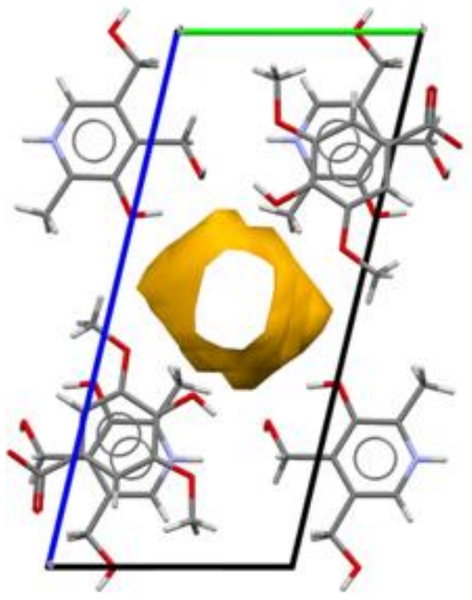
Intramolecular hydrogen bond O3(H3O)···· O2



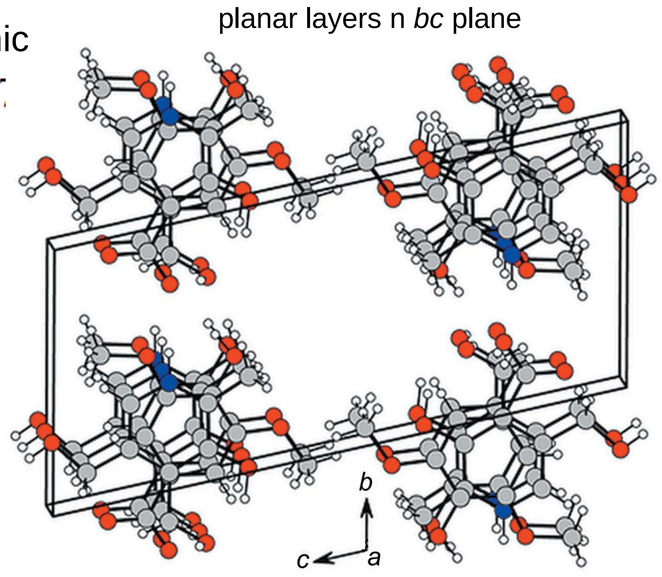
planar layers n *bc* plane

$P\bar{1}$ Triclinic

V = 958.4



The empty space in (1), viewed in projection along the a axis



ππ…ππ

Cg1…Cg2 : *d* = 3.552 Å

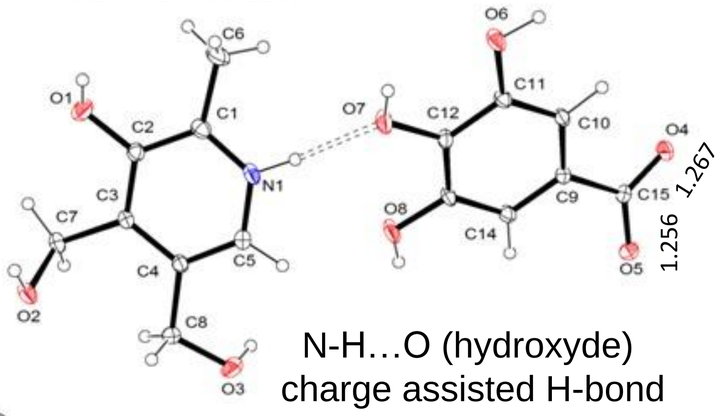
Cg1…Cg2 : *d* = 3.577 Å

The crystal projection showing the molecular stacking

Compound 2: pyridoxinium gallate

C1—N1—C5 123.7°

C—C—O angles: 118.6°,

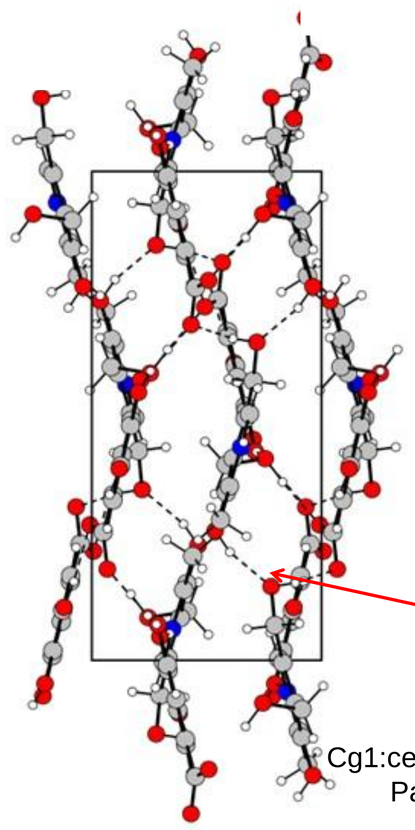


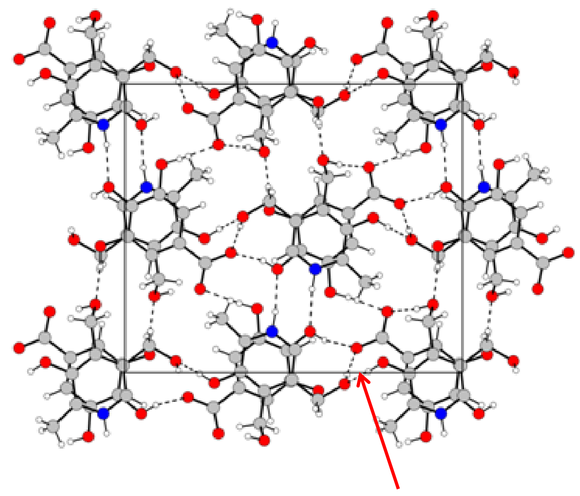
$P2_12_12_1$

Orthorhombic

V = 1406.45 Å^3

N-H…O (hydroxyde) charge assisted H-bond





'mixed stacked'

Bifurcated O4 & O5 (carboxylate)

ππ…ππ

Cg1…Cg2 : *d* = 3.565 Å

Cg1…Cg2 :*d* = 3.508 Å

Cg1:centroid :N1–C5 ring; Cg2:centroid , C9–C14 ring

Parallel stacked rings: he dihedral angle: 2.9°

Cell content of (2) viewed along the *a* and *b* axes

References

[1] S. L. Childs, G. P. Stahly, A., Park, *Mol. Pharmaceutics* **2007**, *4* (3), *323*–338

[2] A., Cvetkovski, V., Ferretti, V., Bertolasi, *Acta Cryst*. **2017**, C73, 1064–1070

[3] A., Cvetkovski, V. Bertolasi, V. Ferretti, Acta Cryst. **2016**. B72, 326–334

[4] A., Lemmerer, S. Govindraju, M. Johnston, X. K.L. Savig, *CrystEngComm*, ***2015***, *17*, *3591*–3595

[5] V. Stilinović, , B. Kaitner, *Cryst.GrowthDes*. ***2012***,,*12*, *5763–5772*

[6] P. Gilli, L. Pretto, V. Bertolasi, G. Gilli, *Acc. Chem. Res*., ***2009,*** *42*, 33–44