Correlation of H-bonding distances and strengths in Active Pharmaceutical Ingredients (APIs) solvates: case study on nitrofurantoin and pyridoxine

Aleksandar Cvetkovski[a], Elena Drakalska [a]

[a] Faculty of medical science, University Goce Delcev Stip, Krste Misirkov b.b., P. fax. 201, 2000 Stip Republic N. Macedonia ;

e-mail: aleksandar.cvetkovski@ugd.edu.mk

INTRODUCTION

Hydrogen bond solvation affects molecular properties and functions both in solution and solid-state formation of solvates. Many of Active Pharmaceutical Ingredients (APIs) exist as solvates with different solvents that, depend on the nature and polarity, co-crystallize with their appropriate molecular structures in wide range of polarity, either non-ionizable or deprotonated acids and bases and their protonated forms, respectively. Despite H-bonding networking that occurs in a highly competitive solvent in biological systems, synthetic chemists have been facing with difficulties to control and predict the H-bonding motifs from *de novo* in competitive solvents media. The concept of crystal engineering, based on molecular noncovalent recognitions and formation of self-assembled supramolecular clusters opens the opportunities for designing the solvate type of crystals with desirable properties [1].

PURPOSE OF THE STUDY

The correlation of the H-bond distances with the bond strength are depicted on Hirshfeld surface's 2D fingergerprint plots based on the crystallographic parameters of the determined crystal structures of two types of API solvates: the N,N dimetileformamide solvate of the chemotherapeutic class of API for treatment of urinary infection, nitrofurantoin and hydrated form of molecular salt that pyridoxine (vit B6) form with ferulic acid (derivate of hydroxybenzoic acid) [2,3].

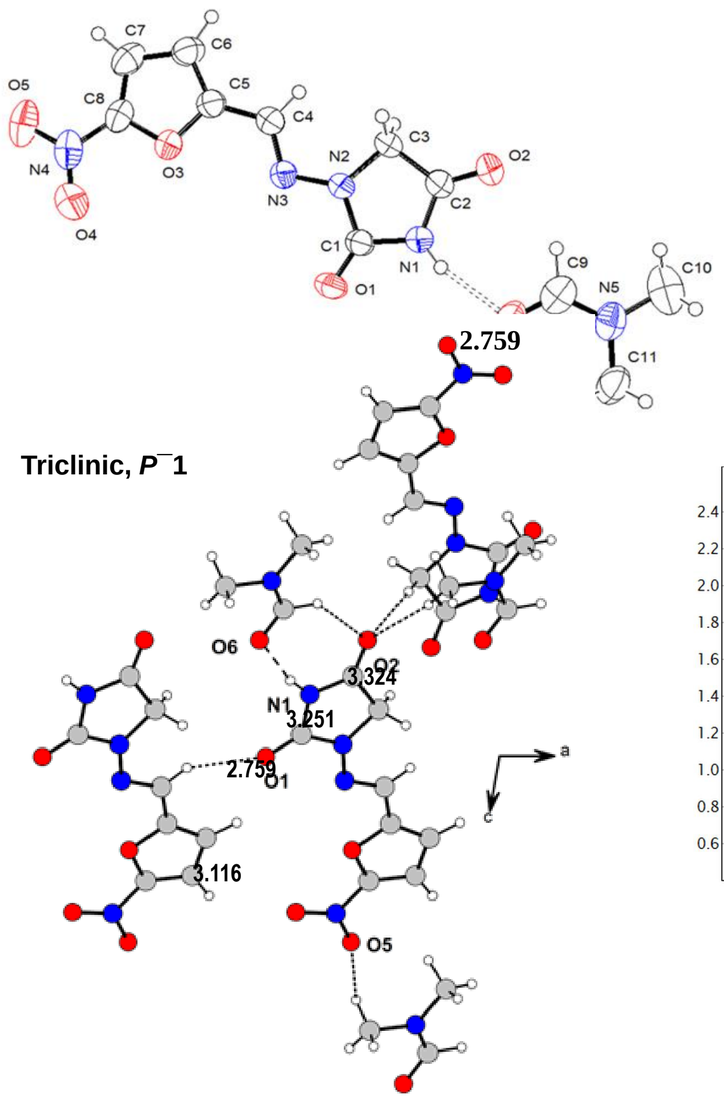
METHODS

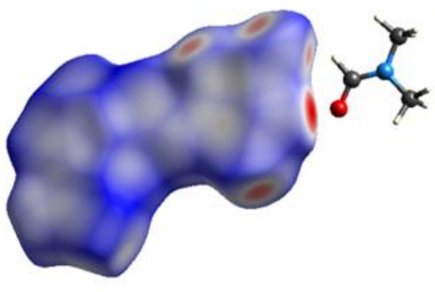
Hirshfeld surface represents the molecule when interacting with the crystal environment and the decomposition of this surface gives a 'molecular fingerprint' , a 2D map indicating not only which intermolecular interactions are present, but also the relative area of the surface corresponding to each kind of interaction. The Hirshfeld surfaces and 2D fingerprint plots were generated using CrystalExplorer 3.0. [4]

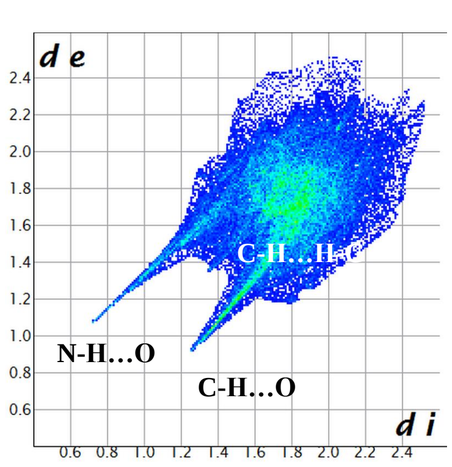
RESULTS

Nitrofurantoin N,N-dimethylformamide Solvate

$C_8H_6N_4O_5 \cdot C_3H_7NO$



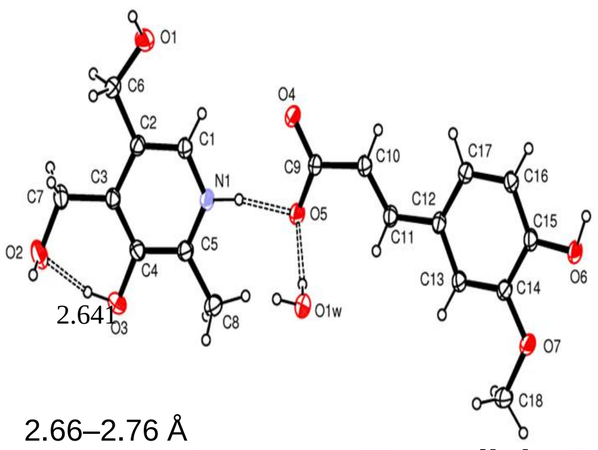




Nitrofurantoin Hirshfeld surface in dimethylformamide co-crystal (colour code: black spots = distances shorter than the sum of vdW radii; white= distances equal to the sum of vdW radii; grey = contacts longer than the sum of vdW radii)

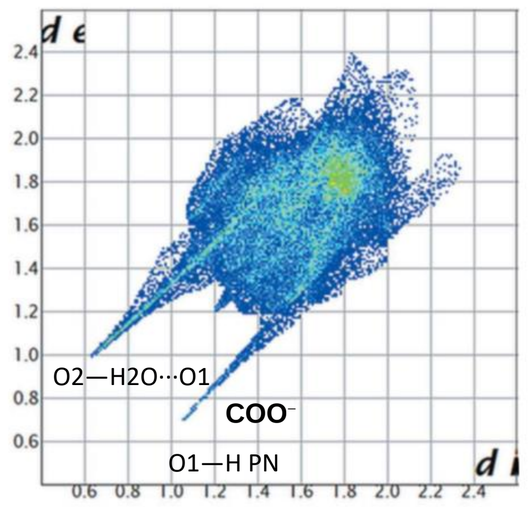
Pyridoxine ferulate hydrate (PN-FER-hydrate

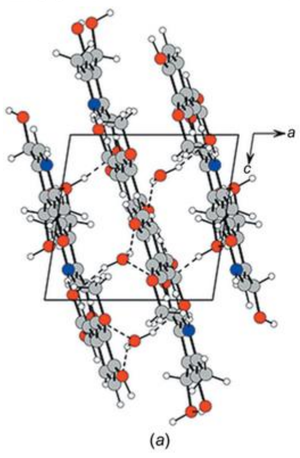
$(C_8H_{12}NO_3)^+ \cdot (C_{10}H_9O_4)^- \cdot H_2O$

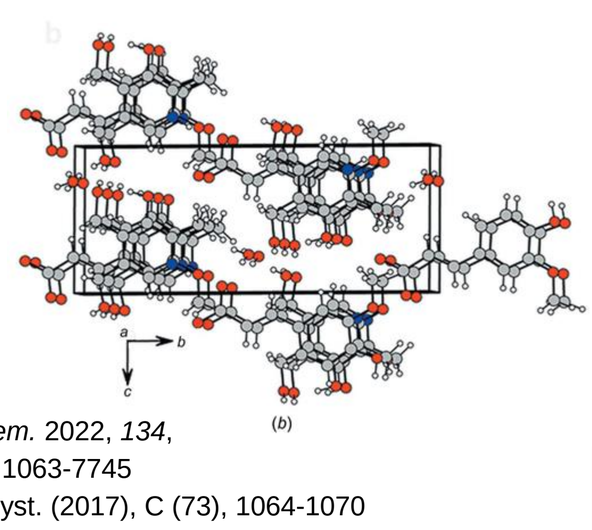


O/N—H···O 2.66–2.76 Å
N ···O & O···O 2.65–2.90 Å

Monoclinic, $P2_1$







Red regions represent distances shorter than the sum of the vdW radii (carboxylate group), white-coloured regions correspond to weak contacts and the blue-coloured regions are considered to be free of significant contacts.

LITERATURE

1. N. Y. Meredith, S. Borsley, I. V. Smolyar, G. S. Nichol, C. M. Baker, K. B. Ling, S. L. Cockroft, *Angew. Chem. Int. Ed.* 2022, *61*, e202206604; *Angew. Chem.* 2022, *134*,
2. Cvetkovski, A., Ferretti, V. *Crystal Structure and Packing Analysis of Nitrofurantoin N,N-dimethylformamide Solvate. C*rystallography Reports, (2016) 4. 1063-7745
3. Cvetkovski, A., Ferretti, V., Bertolasi, V. *New pharmaceutical salts containing pyridoxine.* Acta Crystallographica Section C: Structural Chemistry, Acta Cryst. (2017), C (73), 1064-1070
4. S. K. Wolff, D. J. Grimwood, J. J. McKinnon, M. J. Turner, D. Jayatilaka, and M. A. Spackman, CrystalExplorer (Version 3.0), University of Western Australia (2012).

CONCLUSION & FURTHER WORK

Nitrofurantoin N,N-dimethylformamide Solvate is co-crystallized bimolecular adducts with crystal structure wherein two molecules are linked *via* N−H···O hydrogen bonds, which in turn interact with each others through C−H···O weaker interactions. Hirshfeld analysis applied to the present structure and to other similar solvated nitrofurantoin co-crystal retrieved from CSD have shown that this packing mode is highly reproducible.
Analyses of the crystal structure of the PN-FER hydrate salt revealed the robustness of the pyridine/ carboxylic acid supramolecular synthon, point to its importance in driving the assembly process of different cocrystal units.
The further work intends to put in evidence biopharmaceutical profiles of PN-FER-hydrate that is of pharmaceutical relevance