Intramolecular O−H···O Hydrogen Bonding in Crystal Structures of *Ortho*-Hydroxymethyl-hydroxy (Hetero)arenes

Lirim Mustafa,[1] Diba Keyhanfar,[2] Dejan-Krešimir Bučar[2], Aleksandar Cvetkovski[1]

[1]Faculty of Medical Sciences, Goce Delcev University, 2000 PO 201 Stip, R. N. Macedonia

[2]Department of Chemistry, University College London, WC1H 0AJ London, United Kingdom

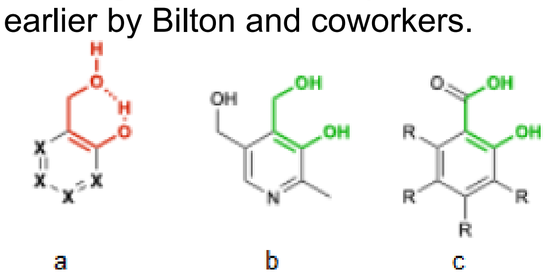
e-mail: aleksandar.cvetkovski@ugd.edu.mk

Purpose

The survey relates to intramolecular hydrogen bonding (**IHB**) in ***ortho*-hydroxymethyl-hydroxyl (hetero)arenes** (**ohha**) in molecular crystals to enhance our understanding of supramolecular interactions in molecular crystals.[1, 2] This study aims to complement the landmark study of Bilton and coworkers [3], who identified *all* existing IHB ring motifs in molecular crystals through a detailed survey of the Cambridge Structural Database (CSD). [4]

The study, published in 2000, was based on a survey of less than 200,000 crystal structures deposited in the CSD, and aimed to determine how reliably various IHB ring motifs occur. Motifs of interest were were based on less than twenty atoms with nitrogen and oxygen atoms as donors and acceptors. It was shown that the most commonly occurring motifs, with a probability of formation (P_m) higher than 85%, are planar conjugated with a predisposition for resonant-assisted hydrogen bonding[5] (RAHB). Saturated six-membered rings, on the other hand, have a P_m lower than 10%, thus emphasizing the importance of conformational flexibility. Other ring motifs involving five or seven atoms occur with a much wider range of P_m values.

IHB in **ohha** has not been considered [3] Bilton and coworkers, as this class of compounds was not well represented in the CSD at the time. Our interest in IHB in **ohha** emerged during a wider study focused the discovery of new crystal forms of nutraceuticals [6-8], whereby at one time particular attention was paid to pyridoxine (**pyd**), one of the forms of vitamin B6. During this study, we have observed that the *ortho*-substituted hydroxymethyl and hydroxyl groups in **pyd** form a variety of hydrogen bond motifs, including IHB. Given that the arrangement of atoms in these functional groups is topologically equivalent to that of the atoms of the ortho-positioned carboxyl and hydroxyl groups in ortho-hydroxybenzoic acids – and that the latter functional groups regularly engage in **IHB** – we aimed to determine how the ability of the wider class of **ohha** to engage in **IHB** compares to that of the carboxyl and hydroxyl groups in ortho-hydroxybenzoic acids; and more generally, to other organic molecules studied earlier by Bilton and coworkers.



a - *ortho*-hydroxymethyl-hydroxyl (hetero)arene (X =C; N)

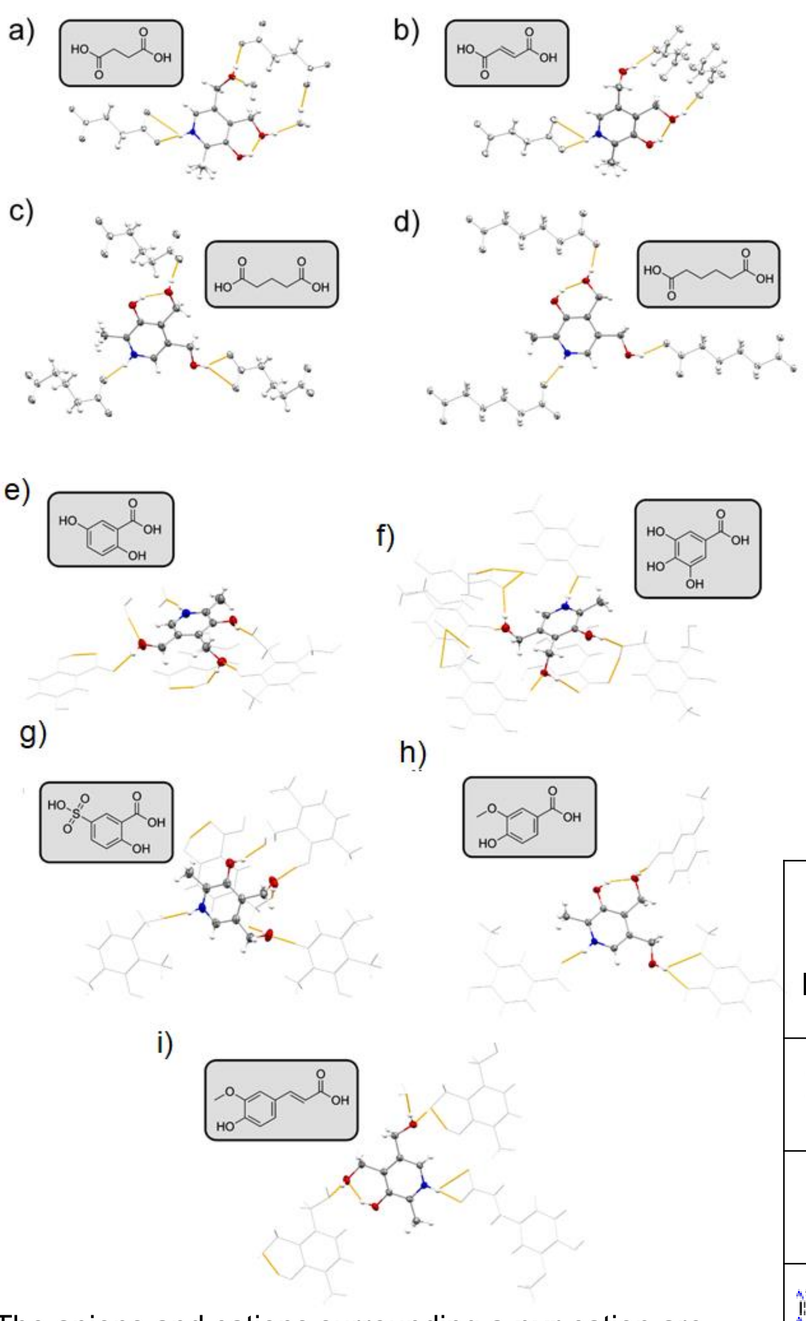
b – Pyridoxine (**pyd**)

c – *ortho*-hydroxy benzoic acid

Experimental design (method of crystal growth & structure determination)

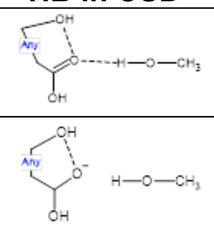
Cocrystallization screening for growing solid phases of single crystals of molecular salts of **pyd** by solvent slow-rate evaporation methods. Single-crystal x-ray diffraction (SCXRD) for structure determination of molecular salts of **pyd** with group of coformers among dicarboxylic acids and ortho-hydroxy benzoic acid derivatives.

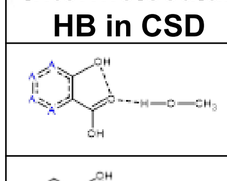
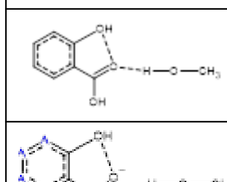
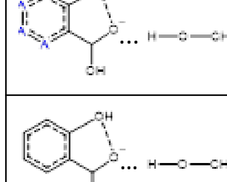
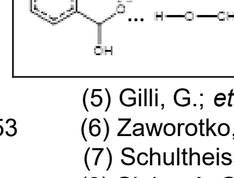
Results



The anions and cations surrounding a **pyr** cation are shown in light grey to enhance clarity. Hydrogen bonds are shown in orange

Nom	Molecular salts	pyd:acid hydrogen bond	pyd IHB	ohha dimer
a	pyd succinate (2:1)	✓	✓	X
b	pyd fumarate (2:1)	✓	✓	X
c	pyd glutarate (2:1)	✓	✓	X
d	pyd adipate (2:1)	✓	✓	X
e	pyd gentisate (1:1)	✓	X	✓
f	pyd gallate (1:1)	X	X	X
g	pyd 5-sulfosalicylicate (1:1)	✓	X	✓
h	pyd vanillate (1:1)	✓	✓	X
i	pyd ferulate (1:1)	✓	✓	X

Fragment Search **Intermolecular HB in CSD**	Nom. of times a motif occurs (Nposs)	Nom.of structures
	491	387
	413	317

Fragment Search **Intermolecular HB in CSD**	Nom. of times a motif occurs (Nposs)	Nom.of structures	$P_{m}=\frac{N_{obs}}{N_{poss}}$ (%)	$P_{s}=\frac{S_{obs}}{S_{poss}}$ (%)
	208	170	42.3	44
	208	169	42.3	43
	50	44	12	13
	42	39	10	12.3

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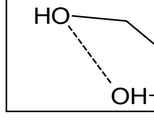
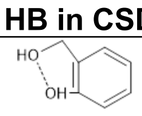
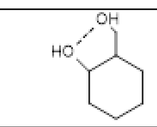
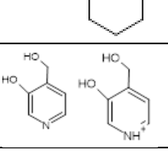
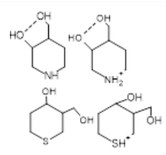
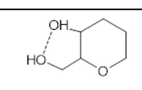
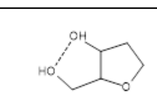
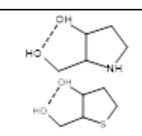
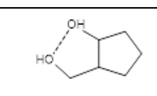
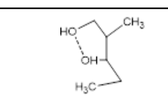
	445	371

Fragment Search **Intramolecular HB in CSD**	Nom. of times a motif occurs (Nposs)	Nom.of structures	$P_{m}=\frac{N_{obs}}{N_{poss}}$ (%)	$P_{s}=\frac{S_{obs}}{S_{poss}}$ (%)
	27	22	6.1	5.9
	67	60	15.0	16.2
	21	18	4.72	4.8
	8	8	1,8	2.1
	103	91	23.1	24.5
	16	15	3.6	4.0
	14	11	3.1	3.00
	19	15	4.3	4.0
	144	112	32.3	30.1

References

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(2) Corpinot, M. K.; Bučar, D.-K. *Cryst. Growth Des.* 2019, *19*, 1426-1453
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(6) Zaworotko, M. J *et al.,* WO2008153945A3, 2008.
(7) Schultheiss, *et al*., *CrystEngComm* 2011, *13*, 611-619.
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