

Products of the Reactions Between Pyridine and 1,2- or 1,3-phenylenediacetic Acid: Salts or Co-crystals?

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Dedicated to Prof. Dr. Gorazd Vesnaver on the occasion of his 70th birthday

Abstract

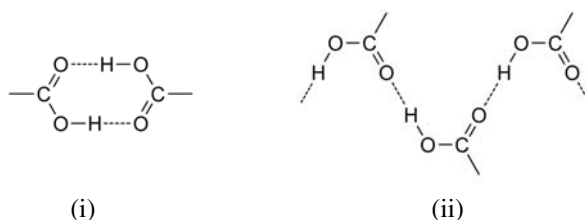
Reaction of pyridine with 1,2- or 1,3-phenylenediacetic acids, denoted as 1,2-phdaH₂ or 1,3-phdaH₂, afforded two crystalline products, [PyH⁺][1,2-dphaH⁻] · 1,2-dphaH₂ (**1**) and [PyH⁺][1,3-dphaH⁻] (**2**) (PyH⁺ = C₅H₅NH⁺, pyridinium cation). Compound **1** contains apart from protonated pyridine molecule also two 1,2-phenylenediacetic acid species, a semi-1,2-phenylenediacetate ion and a neutral acid molecule, one of each per formula unit. As such, it can be classified among co-crystals. The 1,2-phenylenediacetic acid species are assembled into double-chains *via* O–H...O hydrogen bonds. Pyridinium cations are attached to these chains *via* N⁺–H...O⁻(carboxylate) interactions. The X-ray structure analysis of compound **2** revealed a hydrogen bond of moderate strength occurring between the pyridine nitrogen and oxygen atom of one COOH function, N...H...O = 2.539(2) Å. The position of hydrogen is almost half way between the two atoms. Compound **2** can neither be considered as a pure salt nor as a pure co-crystal. As in **1**, the O–H...O interactions link the 1,3-phenylenediacetic acid residues into chains.

Keywords: Dicarboxylic acids, pyridinium salts, co-crystals, hydrogen bonds, crystal structure

1. Introduction

Carboxylic acids have found frequent use in crystal engineering. The latter expression describes the design and syntheses of solid-state structures, based on an understanding and exploitation of intermolecular interactions.¹ The most important interaction type in crystal engineering is hydrogen bonding because it combines strength with directionality.² The solid-state structures of carboxylic acids reveal typical hydrogen bond patterns.³ A centrosymmetric dimer occurs as a dominant recognition motif, whereas a catemer (chain) motif forms only rarely. Both are illustrated in Scheme 1. The interaction of carboxylic acids with nitrogen donor bases can afford either salts or co-crystals. The outcome depends upon the acidity of the carboxylic groups and the basicity of the base.⁴ Scheme 2 illustrates the situation when pyridine acts as a base. The distinction between the salt and the co-crystal can only be made by the experimental location of hydrogen atom by the single-crystal neutron or X-ray diffraction method.

Whereas at the salt end of the spectrum the proton transfer is complete, in co-crystals at the opposite end, there is no proton transfer. The two extremes are connected by a salt-co-crystal continuum. In an alternative definition of the co-crystal, the latter term also defines a multi-component crystal containing a stoichiometric ratio of at least two components that are solid at room temperature and at least one is in an un-ionized state.^{5–7} The co-crystals have recently attracted significant interest because of their potential application in pharmaceutical industry.^{8–15}



Scheme 1. Hydrogen bond synthons of carboxylic acids: a dimer (i) and a catemer (ii).



Scheme 2. The ionic, $\text{COO}^-\cdots\text{H}-\text{N}_{\text{arom}}^+$, and the neutral, $\text{COOH}\cdots\text{N}_{\text{arom}}$, forms of the carboxylic acid–pyridine heterosynthon.

Herein, we report on the reactions of two dicarboxylic acids, 1,2-phenylenediacetic acids (1,2-phdaH₂) and 1,3-phenylenediacetic acid (1,3-phdaH₂) (Scheme 3), with pyridine. Pyridine was chosen because of its structural simplicity and its acid/base properties. The pK_{a} values of the acids and of pyridine conjugate acid do not predict the formation of salt in either case.¹⁶ The generally accepted criterion is that for the formation of salt a pK_{a} difference greater than two units between the acid and the base is required.⁴ A recent database study has shown that recognition of COOH with pyridine is favoured 10 times more through the $\text{O}-\text{H}\cdots\text{N}$ hydrogen bond compared to dimer or catemer motifs with itself.¹⁷ Would our products demonstrate the same? Simple synthetic procedure resulted in two crystalline phases: $[\text{PyH}^+][1,2\text{-dphaH}^-] \cdot 1,2\text{-dphaH}_2$ (**1**) and $[\text{PyH}^+][1,3\text{-dphaH}^-]$ (**2**).¹⁸ Single crystals of both were subjected to the X-ray structure analysis.¹⁹ It is to be noted that the positions of the COOH hydrogen

atoms and of the protonated sites in both compounds were clearly revealed from the residual electron density maps during the structure solution/refinement. Crystallographic data of **1** and **2** are given in Table 1, relevant geometric parameters in Table 2 and hydrogen bonding parameters in Table 3.



Scheme 3. Structural formulae of 1,2-phenylenediacetic (left) and 1,3-phenylenediacetic acid (right).

The asymmetric unit of compound **1** contains a protonated pyridine molecule and two distinctly different species of 1,2-phenylenediacetic acid, a mononeutralized form of the acid, *i.e.*, an 1,2-phdaH[−] ion, and a neutral acid molecule 1,2-phdaH₂ (see Figure 1). Their COOH functions reveal two non-equivalent C–O bonds, a short one suggesting a double bond character, and a long one for protonated oxygens (Table 2).²⁶ Both functions, the carboxylate moiety and the COOH groups, are engaged in an intricate hydrogen bonding pattern (Table 3). As expected, the charged carboxylate moiety is involved in the shorter bonding interactions. A neutral acid molecule is linked *via* two hydrogen bonds with an 1,2-phdaH[−] ion to form a pair: $\text{O}(3)\cdots\text{O}(7) = 2.519(2) \text{ \AA}$ and $\text{O}(5)\cdots\text{O}(2) = 2.680(2) \text{ \AA}$. In graph set notation, the pair may be described as a $R_2^2(18)$ motif.²⁸ Pairs are linked *via* $\text{O}(1)\cdots\text{O}(8)^i = 2.627(2) \text{ \AA}$ [(i) symmetry code: $x-1, -y+0.5, z+0.5$] interactions into chains (Figure 2). The chains propagate along the $[20-1]$ direction. Protonated pyridine molecules are attached to these chains. Pyridinium cation interacts with both oxygen atoms of the carboxylate moiety: a bifurcated hydrogen bond is thus formed. Nevertheless, one of the two contacts in the $R_1^2(4)$ motif is significantly shorter (see Table 3). Ortho hydrogen atom of pyridinium cation forms a weak interaction with carbonyl oxygen $\text{O}(2)$ from an adjacent pair, $\text{C}(15)\cdots\text{O}(2)^{ii} = 3.268(2) \text{ \AA}$ [(ii) symmetry code: $x+1, -y+0.5, z-0.5$].

The asymmetric unit of compound **2** contains two residues which were conveniently formulated as a mononeutralized acid, an 1,3-phdaH[−] ion, and a protonated pyridine molecule (Figure 3). The pair is linked with a hydrogen bond of a moderate strength, $\text{N}(1)\cdots\text{O}(3) = 2.539(2) \text{ \AA}$. It is of interest to note that the position of hydrogen is symmetrical along the $\text{N}1-\text{O}3$ vector. With the hydrogen atom being almost equally shared by the two atoms, the formulation of compound **2** as a pyridinium salt of semi-phenylenediacetate ion, *i.e.*, $[\text{PyH}^+][1,3\text{-dphaH}^-]$, is not strictly correct. The location of hydrogen on oxygen atom, *i.e.*, $\text{N}\cdots\text{H}-\text{O}$, would represent the other extreme, a co-crystal. Our compound cannot be

Table 1. Crystallographic data for $[\text{PyH}^+][1,2\text{-dphaH}^-] \cdot 1,2\text{-dphaH}_2$ (**1**) and $[\text{PyH}^+][1,3\text{-dphaH}^-]$ (**2**).

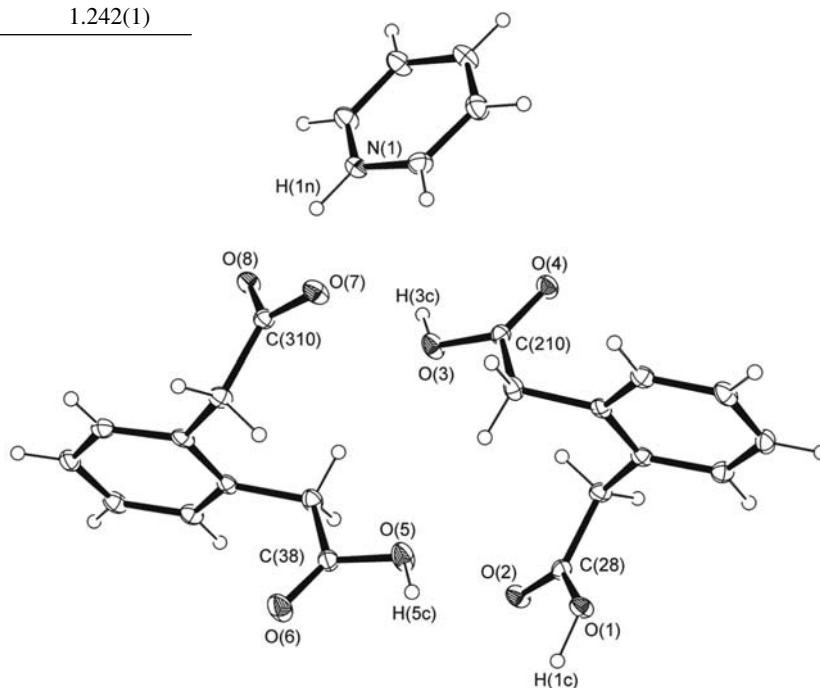
	1	2
Empirical formula	$\text{C}_{25}\text{H}_{25}\text{NO}_8$	$\text{C}_{15}\text{H}_{15}\text{NO}_4$
Formula weight	467.46	273.28
Crystal system	monoclinic	monoclinic
Space group	$P 2_1/c$	$P 2_1/a$
T [K]	150(2)	150(2)
a [Å]	4.9980(1)	6.4623(1)
b [Å]	24.4202(4)	23.5536(6)
c [Å]	18.0866(3)	9.2578(2)
α [°]	90	90
β [°]	92.1970(7)	106.307(1)
γ [°]	90	90
V [Å ³]	2205.89(7)	1352.45(5)
D_{calcd} [g/cm ³]	1.408	1.342
Z	4	4
λ [Å]	0.71073	0.71073
μ [mm ^{−1}]	0.106	0.098
collected reflections	9782	5871
unique reflections, R_{int}	5060, 0.0353	3097, 0.0202
observed reflections	3489	2442
$R1^a$ ($I > 2\sigma(I)$)	0.0427	0.0374
$wR2^b$ (all data)	0.1048	0.0974

^a $R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$. ^b $wR2 = \{ \sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2] \}^{1/2}$.

Table 2. Relevant structural parameters [Å] of [PyH⁺][1,2-dphaH⁻] · 1,2-dphaH₂ (**1**) and [PyH⁺][1,3-dphaH⁻] (**2**).

Compound 1	
1,2-dphaH ₂ molecule	
C(28)–O(1)	1.312(2)
C(28)–O(2)	1.223(2)
C(210)–O(3)	1.314(2)
C(210)–O(4)	1.217(2)
1,2-dphaH ⁻ ion	
C(38)–O(5)	1.324(2)
C(38)–O(6)	1.204(2)
C(310)–O(7)	1.258(2)
C(310)–O(8)	1.267(2)
Compound 2	
C(8)–O(1)	1.327(1)
C(8)–O(2)	1.206(2)
C(10)–O(3)	1.276(1)
C(10)–O(4)	1.242(1)

considered as either of the two cases, neither as a pure salt nor as a pure co-crystal, but something in-between. Nevertheless, we decided for a salt formulation, [PyH⁺][1,3-dphaH⁻], because of the similarity of the C–O bond lengths, *i.e.*, 1.242(1) *vs.* 1.277(1) Å. It is to be noted that the other carboxylic function of the 1,3-phenylenediacetic acid residue displays a non-equivalence of the C–O bonds, *i.e.*, 1.206(2) *vs.* 1.328(1) Å, and as such corroborates its formulation as a COOH group which retained its proton. The orientation of pyridine residue is such that a weak C–H...O interaction is enabled, C(15)...O(4) = 3.194(2) Å. The C–H...O interaction, although not drawn, can be clearly seen upon the inspection of Figure 4. As in **1**, both the carboxylic and the carboxylate groups are engaged in hydrogen bonding interactions. The OH group makes a rather short contact to a carboxylate oxygen from an adjacent anion, O(1)...O(4)ⁱⁱⁱ = 2.598(1) Å

**Figure 1.** ORTEP drawing of the asymmetric unit in **1** with displacement ellipsoids drawn at the 30% probability.**Table 3.** Hydrogen bonding interactions in [PyH⁺][1,2-dphaH⁻] · 1,2-dphaH₂ (**1**) and [PyH⁺][1,3-dphaH⁻] (**2**).

compd	type of the interaction	atom labels ^a	D...A [Å] ^b	D–H [Å]	H...A [Å]	D–H...A [°]
1	COOH...COO ⁻	O(3)–H(3c)...O(7)	2.519(2)	1.00(3)	1.52(3)	177(2)
	COOH...COOH	O(5)–H(5c)...O(2)	2.681(2)	0.95(3)	1.73(3)	174(2)
	COOH...COO ⁻	O(1)–H(1c)...O(8) ⁱ	2.627(2)	0.98(3)	1.65(3)	176(2)
	PyH ⁺ ...COO ⁻	N(1)–H(1n)...O(8)	2.710(2)	0.99(2)	1.72(2)	173(2)
	PyH ⁺ ...COO ⁻	N(1)–H(1n)...O(7)	3.041(2)	0.99(2)	2.39(2)	123(1)
	C–H...O	C(15)–H(15)...O(2) ⁱⁱ	3.268(2)	0.93	2.42	152
2	COOH...COO ⁻	O(1)–H(1c)...O(4) ⁱⁱⁱ	2.598(1)	0.97(2)	1.63(2)	172(2)
	Py...H ⁺ ...COO ⁻	N(1)...H(1n)...O(3)	2.533(1)	1.24(2)	1.29(2)	175(2)
	C–H...O	C(15)–H(15)...O(4)	3.194(2)	0.93	2.57	125

^a See Figures 1 and 3 for the atom labels. Symmetry codes are: (i) $x-1, -y+0.5, z+0.5$; (ii) $x+1, -y+0.5, z-0.5$; (iii) $x-1, y, z-1$.

^b The distances may be compared to the sums of the corresponding van der Waals radii: 3.04 Å for O + O, and 3.07 Å for N + O.²⁷

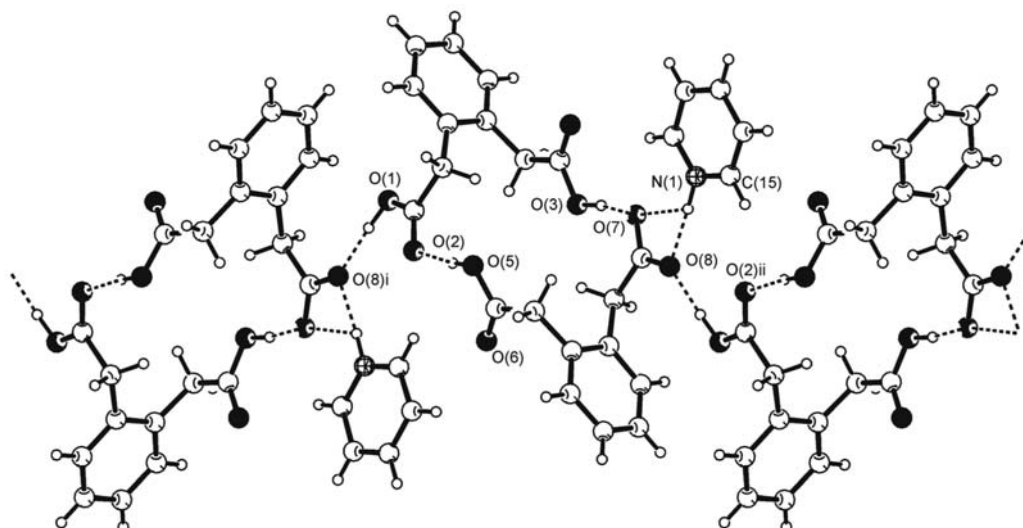


Figure 2. Section of a chain of hydrogen-bonded 1,2-phdaH[−] ions and 1,2-phdaH₂ molecules in **1**. Protonated pyridine molecules are attached to the chains via N⁺–H⁺⋯O[−] contacts.

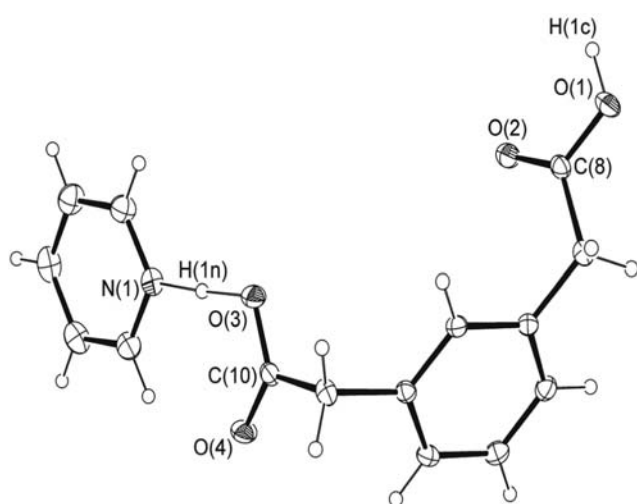


Figure 3. ORTEP drawing of the asymmetric unit in **2** with displacement ellipsoids drawn at the 30% probability.

[(iii) symmetry code = $x-1, y, z-1$]. As a result, the anions are linked into chains which propagate along the [101] direction. In graph set notation, the pattern formed may be described as $C(10)$. The carbonyl oxygen of the non-ionized COOH group, O(2), does not participate in any hydrogen bonds.

The answer to the question posed above is the same for both **1** and **2**: pyridine is engaged in hydrogen bonding interaction with one COOH function. A transfer of proton occurred for **1**, whereas in **2**, the hydrogen atom is equally shared between the two groups. The remaining COOH functions, three for compound **1** and one for compound **2**, are engaged in O–H⁺⋯O interactions. Both compounds demonstrate once again that the predictive ability of pK_a values in defining the hydrogen atom location in hydrogen bond in solid-state is very limited.²⁹ The literature survey reveals that real salts of 1,2- and 1,3-phenylenediacetic acids are scarce.³⁰ The structurally characterized examples, $K^+ [1,2\text{-phdaH}^-]$, $[LH_2^{2+}] [1,2\text{-phda}^{2-}]$ and $[LH_2^{2+}] [1,3\text{-}$

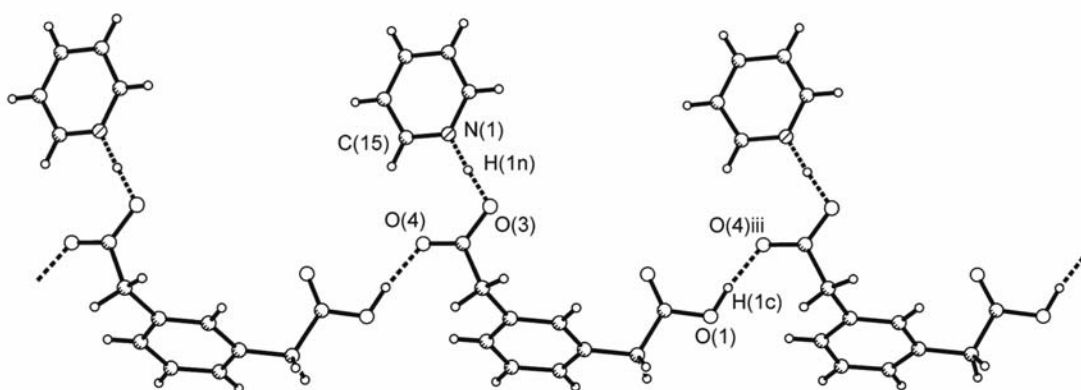


Figure 4. Section of a chain of hydrogen-bonded 1,3-phdaH[−] ions in **2**. Pyridine residues are attached to the chains via N(1)⋯H(1n)⋯O(3) hydrogen bonds.

phda²⁻] [where L stands for (1R,2R)-1,2-diphenylethyl-
nediamine], are all salts of relatively strong bases.^{31–32}

2. Supplementary Material

CCDC- 854118 (1) and - 854119 (2) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3. Acknowledgement

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4. References

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18. Preparation of pyridinium salt of 1,2-phenylenediacetic acid, [PyH⁺][1,2-dphaH⁻] · 1,2-dphaH₂ (1): 2.50 mmol of 1,2-phenylenediacetic acid (485 mg) was dissolved in 2-propanol (10 mL). To this solution, 2.50 mmol of pyridine (0.20 mL) was added. On the following day, the volume of the resulting solution was reduced under vacuum to ca. one half. Within a few hours colourless crystals of **1** started to deposit. The crystals were filtered off. Yield: 340 mg; 58%. Found C, 64.09; H, 5.43; N, 2.96%. C₂₅H₂₅NO₈ requires C, 64.23; H, 5.39; N, 3.00%. Preparation of pyridinium salt of 1,3-phenylenediacetic acid, [PyH⁺][1,3-dphaH⁻] (2): 2.50 mmol of 1,3-phenylenediacetic acid (485 mg) was dissolved in a mixture of methanol (5 mL) and 2-propanol (5 mL). To this solution, 2.50 mmol of pyridine (0.20 mL) was added. The resulting solution was left to stand in an open flask at ambient conditions. Colourless crystals of **2** were filtered off after a week. Yield: 252 mg; 37%. Found C, 65.78; H, 5.60; N, 5.09%. C₁₅H₁₅NO₄ requires C, 65.92; H, 5.53; N, 5.13%.
19. X-ray structure determinations: Data were collected on Nonius Kappa CCD diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data reduction and integration were performed with the software package DENZO-SMN.²⁰ Specific absorption corrections were not applied since the averaging of the symmetry-equivalent reflections largely compensated for any absorption effects. The coordinates of the majority of non-hydrogen atoms were found via direct methods using the structure solution program SHELXS.²¹ The positions of the remaining non-hydrogen atoms were located by use of a combination of least-squares refinement and difference Fourier maps in the SHELXL 97 program.²¹ The positions of COOH hydrogen atoms and pyridinium cation protons in both compounds were unambiguously located from the residual electron density maps. Other hydrogen atoms were placed in geometrically calculated positions and refined using a riding model. All the calculations were performed using WinGX.²² Figures depicting the structures were prepared by Ortep3,²³ SHELXTL,²⁴ and PLATON.²⁵
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Povzetek

Pri reakciji piridina z 1,2- ali 1,3-fenilendiocetno kislino, ki ju označimo 1,2-phdaH₂ ali 1,3-phdaH₂, nastaneta kristalinična produkta, [PyH⁺][1,2-dphaH⁻]·1,2-dphaH₂ (**1**) in [PyH⁺][1,3-dphaH⁻] (**2**) (PyH⁺ = C₅H₅NH⁺, piridinijev kation). V eni formulski enoti spojine **1** sta poleg piridinijevega kationa še dve zvrsti 1,2-fenilendiocetne kisline: vodikovni-1,2-fenilendiocetni ion in nevtralna molekula kisline. Spojino **1** zato razvrščamo med kokristale. Anioni in nevtralne molekule kisline so z vodikovimi vezmi O–H...O povezani v dvojne verige. Na slednje so vezani piridinijevi kationi prek N⁺–H...O (karboksilat) interakcij. Z rentgensko strukturno analizo spojine **2** smo potrdili, da je med piridinskim dušikom in kisikovim atomom iz ene od karboksilnih skupin vodikova vez, N...H...O = 2.539(2) Å. Ker je vodik skoraj na sredini med obema atomoma, spojina **2** ne sodi niti med prave soli in tudi ne med kokristale. Tudi v tej spojinji so anioni 1,3-fenilendiocetne kisline z O–H...O interakcijami povezani v verige.