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Crystal Structure Determination and Hydrogen-Bonding Patterns in 2-Pyridinecarboxamide

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ABSTRACT

The title compound, 2-pyridinecarboxamide, $C_6H_6N_2O$, crystallize in the monoclinic system with space group $P2_1/n$ (N˚14), Z = 4, and unit cell parameters a = 5.2074(1) Å, b = 7.1004(1) Å, c = 16.2531(3) Å, β = 100.260(1)˚. The crystal structure of the title compound, was reported previously from Weissenberg photographic data with R = 0.127. It has now been redetermined, providing a significant increase in the precision of the derived geometric parameters. The crystal packing is governed by N--H···O hydrogen bond-type intermolecular interactions, forming infinite one-dimensional chains with graph-set notation C(4), $R^2_2(8)$ and $R^2_4(8)$.

Keywords: Pyridinecarboxamides; Picolinamide; X-Ray Crystal Structure; Hydrogen Bonding

1. Introduction

The three isomers of pyridinecarboxamide; 2-pyridine carboxamide or picolinamide, 3-pyridinecarboxamide or nicotinamide and 4-pyridinecarboxamide or isonicotinamide are a class of medicinal agents which can be classified as GRAS (generally regarded as safe) compounds. In particular, nicotinamide (niacinamide, Vitamin B3) and picolinamide show important biological activity with a coenzyme called NAD (nicotinamide adenine dinucleotide), which plays important roles in more than 200 amino acid and carbohydrate metabolic reactions [1]. In general pyridinecarboxamides are excellent co-crystallizing compound. The amide group has two hydrogen bond donors and two lone pairs on the carbonyl O atom. A second hydrogen bond acceptor is the lone pair on the N atom of the pyridine ring. This makes these molecules very versatile for a variety of hydrogen bonded interactions, especially in pharmaceutical co-crystals [2-13]. The molecular structures and vibrational spectra of the three isomers has been the subject of recent theoretical studies [14,15], and from the crystal structure point of view, all isomer compounds exhibit polymorphism [12]. Nicotinamide has four polymorphs, the most stable crystallize in a monoclinic form [16], Isonicotinamide has three polymorphs in monoclinic and orthorhombic forms [17], and Picolinamide exists under two polymorphic structures [18]. The polymorph form with crystal structure in the Crystal Structure Database [19], was reported using Weissenberg photographic data and R = 0.127 [18].

The present paper reports a redetermination of the crystal structure of 2-pyridinecarboxamide (picolinamide), with greater precision and accuracy. An analysis of the hydrogen-bonding patterns is also included.

2. Experimental

2.1. Crystallization of the Title Compound

Picolinamide crystals were obtained in an attempt to prepare 2-pyridinecarboxamide—amino acid co-crystals, in a 1:1 ethanol-water solution. Colorless crystals suitable for X-ray diffraction analysis were grown by slow evaporation from this solution (m.p. 375 K).

2.2. FT-IR and NMR Analysis

Melting point was determined on an Electrothermal Model 9100 apparatus. The FT-IR absorption spectrum was obtained as KBr pellet using a Perkin-Elmer 1600 spectrometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker Avance 400 model spectrometer.

FT-IR: 1392 cm^{-1} (t, C-N), 1666 cm^{-1} (t, C = O), 3419 cm^{-1} (t, N-H)]. ^{1}H NMR (400 MHz, DMSO d_6): δ 8.63 (d, H6, J = 4.8 Hz), 8.12 (s, H3), 8.05 (d, H1A, J= 7.9 Hz), 7.98 (dt, H4, J1= 15.4 Hz, J2 = 7.6 Hz, J3 = 1.7 Hz), 7.65 (s, H5), 7.55 - 7.61 (m, H1B). ^{13}C NMR (100 MHz, DMSO d_6): δ 166.0 (C1), 150.3 (C2), 148.4 (C6), 137.6 (C4), 126.4 (C5), 121.9 (C3).

2.3. X-Ray Powder Diffraction

X-ray powder diffraction pattern was collected, at room

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temperature, in a Phillips PW-1250 goniometer using monocromatized CuKα radiation (λ = 1.5418 Å). A small quantity of picolinamide was ground mechanically in an agate mortar and pestle and mounted on a flat holder covered with a thin layer of grease. The specimen was scanned from 10˚ - 60˚ 2θ, with a step size of 0.02˚ and counting time of 15 s. Silicon was used as an external standard.

X-ray powder pattern of picolinamide is shown in **Figure 1**. The 20 first measured reflections were completely indexed using the program Dicvol04 [20], which gave a unique solution in a monoclinic cell with parameters a = 5.19 Å, b = 7.09 Å, c = 16.41 Å, β = 100.26˚. In order to confirm the unit cell parameters, a Le Bail refinement [21] of the whole diffraction pattern without structural was carried out using the Fullprof program [22]. **Figure 1** shows a very good fit between the observed and calculated patterns.

2.4. X-Ray Single-Crystal Crystallography

Colorless rectangular crystal (0.37 × 0.20 × 0.20 mm^3) was used for data collection. Diffraction data were collected at 298(2) K by ω-scan technique on a Bruker SMART APEX II CCD diffractometer [23] equipped with CuKα radiation (λ = 1.5418 Å). The unit cell parameters were determined by the least-squares methods using 1292 reflections in the 2θ range 5.5˚ - 55.6˚. The data were corrected for Lorentz-polarization and absorption effects [24]. The structure was solved by direct methods using the SHELXS program [25] and refined by a full-matrix least-squares calculation on F^2 using SHELXL [25].

All H atoms were placed at calculated positions and treated using a riding model, fixing the C-H distances at 0.96 Å and $U_{iso}(H) = 1.2U_{eq}(C)$], the N-H distance at 0.86 Å and $U_{iso}(H) = 1.2U_{eq}(N)$]. The final Fourier maps showed no peaks of chemical significance.

Figure 2 shows the molecular structure and the atom-labeling scheme of picolinamide. **Table 1** shows the crystallographic data and structure refinement parameters. Selected bond distances, bond and torsion angles are listed in **Table 2**. Hydrogen bonds geometry is listed in **Table 3**.

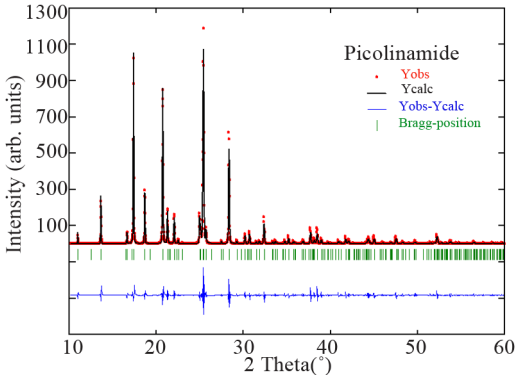

Figure 1. X-ray powder diffraction data for Picolinamide. The powder pattern was refined without structural model to confirm the unit cell parameters.

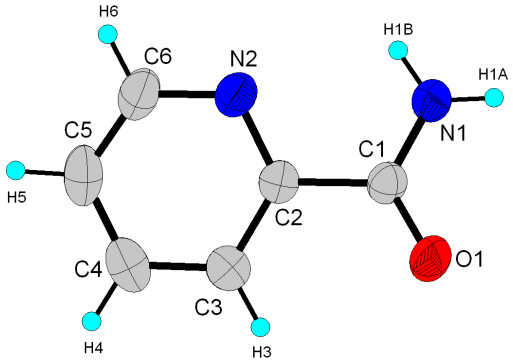

Figure 2. Molecular structure of the title compound showing the atomic numbering scheme. Displacement ellipsoids are drawn at 30% probability level. H atoms are shown as spheres of arbitrary radii.

Table 1. Crystal data, data collection and structure refinement.

Chemical formula	$C_6H_6N_2O$
Formula weight	122.13
Temperature (K)	296
Radiation (Å)	CuK$_\alpha$ (1.5418)
Crystal system	Monoclinic
Space group	P2$_1$/n(14)
a (Å)	5.2074(1)
b (Å)	7.1004(1)
c (Å)	16.2531(3)
β (˚)	100.260(1)
V (Å^3)	591.34(2)
Z	4
d$_x$ (g cm^{-3})	1.372
F(000)	256
μ (mm^{-1}) CuK$_\alpha$	0.807
Crystal size (mm^3)	0.37 × 0.20 × 0.20
θ range for data collection(˚)	5.5 - 57.4
hkl range	$-5 \le h \le 4$; $-7 \le k \le 7$; $-17 \le l \le 17$
Reflections	
Collected	2946
Unique (R$_{int}$)	777 (0.015)
With I > 2σ(I)	663
Refinement method	Full-matrix least-squares on F^2
Number of parameters	83
R(F^2) [I > 2σ(I)]	0.0389
*w*R(F^2) [I > 2σ(I)]	0.1119
Goodness of fit on F^2	1.06
Max/min $\Delta\rho$ (e·Å^{-3})	0.15/–0.12

Table 2. Selected geometrical parameters (Å, °).

C1-O1	1.253(2)	C1-N1	1.317(2)
C1-C2	1.496(2)	C2-C3	1.386(2)
C2-N2	1.370(2)	C6-N2	1.334(2)
O1-C1-N1	124.0(1)	O1-C1-C2	120.7(1)
N1-C1-C2	115.4(1)	C1-C2-N2	117.2(1)
N1-C1-C2-N2	–18.1(2)	O1-C1-C2-N2	162.4(2)
N1-C1-C2-C3	162.0(2)	O1-C1-C2-C3	–17.5(2)

Table 3. Hydrogen bonds geometry (Å, °).

D--H···A	D--H	H···A	D···A	D--H···A
N1---H1A···O1(i)	0.86	2.08	2.923 (2)	166
N1---H1B···O1(ii)	0.86	2.41	3.033 (2)	130

Symmetry codes: (i) 1 – x, 2 – y, 1 – z; (ii) 1 + x, y, z.

Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (Deposition No. CCDC-913526). The data can be obtained free of charge via http://www.ccdc.cam.ac.uk/perl/catreq.cgi.

3. Results and Discussion

A search in the Cambridge Structural Database (Version 5.33, August 2012) [19] shows only 5 structures with the picolinamide moiety. In the structures with code EYIXAL [26], FUGDER [27] and POVZEF [28] the picolinamide is a cation forming salts, and in EXAPEZ [29] picolinamide is a neutral molecule forming a co-crystal. PICAMD [18] corresponds with the earlier determination of the single amide molecule.

In our study, the pyridine ring is essentially planar, with maximum deviations of 0.010 in C4 and –0.010 in N2 (**Figure 2**). The dihedral angle formed between the pyridine ring and the amide plane is 18.26(9)°. This value is similar with the observed in the other picolinamide cations EYIXAL, FUGDER and POVZEF, but higher that 6.4(2) Å observed in the neutral molecule of co-crystal EXAPEZ.

Picolinamide molecule adopts a *syn* conformation with the heterocyclic N and amide N on same sides of the molecule [torsion angle N1-C1-C2-N2 = –18.1 (2)°]. This conformation is also observed only in the co-crystal EXAPEZ. When picolinamide is in cations form, EYIXAL, FUGDER and POVZEF, the molecule adopts an anticonformation.

The crystal structure of picolinamide displays an extended hydrogen-bond network generated by amide-amide synthons. Each picolinamide molecule is involved in two intermolecular N--O···H hydrogen bonds (**Figure 3**).

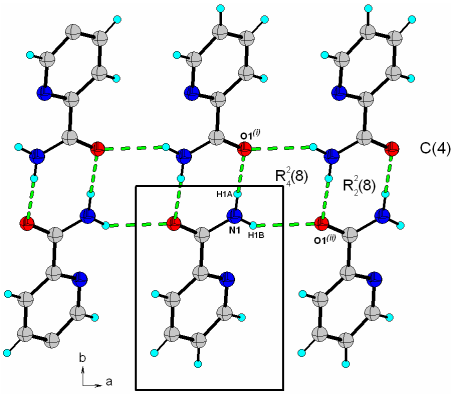

Figure 3. A portion of the crystal packing viewed in the ba plane. Intermolecular hydrogen bonds, N--H···O with symmetry (i) 1 – x, 2 – y, 1 – z and (ii) 1 + x, y, z, are indicated by dashed lines.

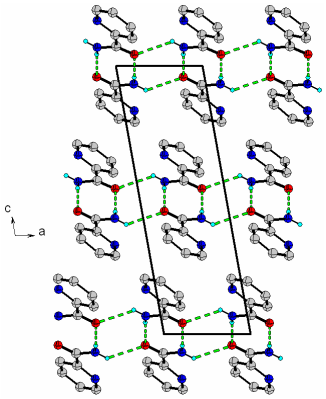

Figure 4. Crystal packing diagram in the ca plane. Intermolecular hydrogen bonds, N--H···O, are indicated by dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity.

These units are linked together through a complementary amide dimer $R^2_2(8)$ motif [30,31], formed by N1--H1A···O1 at (1 – x, 2 – y, 1 – z). The chains are linked through a second complementary interaction formed by N1--H1B···O1 at (1 + x, y, z), resulting in the formation of ladders of alternating $R^2_4(8)$ rings, and chain running in the [100] direction with graph-set C(4). The combination of these interactions generates an extended corrugated hydrogen-bonded sheet in the *ca* plane (**Figure 4**).

4. Conclusion

Crystal structure of picolinamide has been redetermined with greater precision and accuracy. The molecular structure and crystal packing are stabilized by intermolecular N--O···H hydrogen bonds into an infinite one-dimensional network.

5. Acknowledgements

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