#### Journal of Molecular Structure 991 (2011) 97-102



Contents lists available at ScienceDirect

## Journal of Molecular Structure



journal homepage: www.elsevier.com/locate/molstruc

# Crystalline forms of 1,3,5-benzene-tri(pyridinyl)carboxamides: Isolated site hydrates as polymorphs and solvates

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#### ARTICLE INFO

Article history: Received 12 November 2010 Received in revised form 5 February 2011 Accepted 7 February 2011 Available online 4 March 2011

Keywords: Amides Hydrates Polymorphs Solvates Conformations Hydrogen bonds

#### ABSTRACT

The crystallization of 3-pyridyl (1) and 4-pyridyl (2) analogues of the title compound results in different crystalline hydrates and polymorphs and their crystal structures reveal that 1 and 2 exhibit conformational isomerism. The molecule 1 forms three crystalline forms from MeOH solution depending on concentration of the solution. Among these three forms, two are polymorphic monohydrates. However, the crystallization of 2 was found to be dependent on the solvent of crystallization and resulted in new crystalline form from DMF as a dihydrate. The hydrates of both 1 and 2 can be classified as isolated site hydrates. In these crystal structures, water molecules found to exhibit three types of coordination environments with regard to hydrogen bonds.

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#### 1. Introduction

Prediction of periodic arrangements of organic molecules in the crystal lattice via anticipated supramolecular synthons is always a challenge [1]. This is due to the dependency of the resultant structure on several factors such as solvent, concentration, temperature and technique of crystallization [2]. The existence of several polymorphs or solvates for any given compound is probably the most convincing example of this aspect [3]. Generally it is well accepted that the misbalance of number of acceptors and donors increases the probability of formation of solvates or hydrates such that the balance between acceptors and donors is achieved in the crystal lattice [4]. In such situations the inclusion of water into the crystal lattice is more frequent due to its abundance in the atmosphere and in some organic solvents, small size and versatile hydrogen bonding ability. It has been suggested that almost 33% of organic compounds form hydrates, whereas inclusion of other solvents occurs only in 10% of organic compounds [5]. In pharmaceutical industry almost 1/3rd of the APIs are found to exhibit the tendency to form crystalline hydrates [6].

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1,3,5- benzene-tricarboxamide (**BTA**)

Hydrates are classified into three types: isolated site hydrates, channel hydrates and metal-ion coordinated hydrates [7]. In isolated site hydrates, the water molecules are not directly hydrogen bonded to each other. Channel hydrates are the ones where water molecules are hydrogen bonded to each other to form clusters or networks within the channels formed by some other chemical component(s). In metal-ion coordinated hydrates, water molecules are coordinated to the metal ion. The Cambridge Structural Database (CSD) analysis by Gillion et al. reveals that water molecules exhibit eight different possible hydrogen bonding environments in the crystal structures of hydrates [8]. In some cases, formation of hydrate helps in stabilizing the crystal structures by the formation of diverse set of supramolecular synthons. In our previous study we have observed that the compound **1** crystallizes in three different forms (one unstable methanol solvate and two stable monohydrates) [9]. Out of these three, only two crystal structures (Form **1A** and **1B**) were reported as the third form (Form **1C**) did not form suitable crystals for single crystal X-ray diffraction analysis. However, in the previous report the existence of the third form was proved by TGA, DSC, powder-XRD and elemental analysis [9,10]. Herein we report successful efforts in obtaining the single crystals of the third form of 1 and also of a dihydrate of related analogue **2** [11]. In case of **1** the three crystalline forms were obtained from the same solvent such as MeOH at different initial concentrations. While in case of **2** the crystallization did not exhibit any such concentration dependency. Further, the compounds containing multiple pyridine or carboxylic acids have been well known to form versatile coordination polymers [12]. One of the primary goals in engineering such structures is to incorporate catalytic centres in crystal lattices with channels for solvents and substrates [13].

#### 2. Experimental section

#### 2.1. General

FTIR spectra were recorded with an NEXUS-870 instrument, Thermo Nicolet Corporation. Elemental analyses were obtained with a Perkin–Elmer instrument, series II, CHNS/O analyzer 2400. TGA data were recorded with a Perkin–Elmer instrument, Pyris Diamond TG/DTA. Powder XRD data were recorded with a XPERT-PRO PW3050/60 diffractometer.

#### 2.2. Synthesis of 1

The THF solution of 1,3,5-benzenetricarbonyl chloride (0.5310 g, 2 mmol) was added drop wise to the THF solution (25 mL) of 3-aminopyridine (0.5647 g, 6 mmol) and triethylamine (1.0119 g, 10 mmol) at 0 °C with continuous stirring under nitrogen atmosphere. The solution was stirred overnight. THF was distilled off and the solid product thus obtained was washed with water and recrystallized from MeOH. Yield: 85%. This product was crystallized from MeOH as described in the results and discussion and obtained the crystals of three forms.

The elemental analysis of A-form is not reproducible as mentioned in the earlier report.

**1**·*H*<sub>2</sub>*O* (**1B**): Calculated: C, 62.91%; H, 4.94%; N, 18.26%; found: C, 63.1%; H, 4.38%, N, 18.42%.

 $1 \cdot H_2O$  (**1C**): Layering 25 mg of **1** in 3 mL MeOH over 6 mL of  $H_2O$  in a sealed test tube resulted into diffractable quality crystals.

Calculated: C, 62.91%; H, 4.94%; N, 18.26%; found: C, 63.14%; H, 4.57%; N, 18.54%.

#### 2.3. Synthesis of 2

Similar procedure was adopted as of **1** and the product was recrystallized from DMF. Yield: 78.37%.

**2**·2H<sub>2</sub>O (**2B**): Calculated: C, 60.75%; H, 4.67%; N, 17.71%; Found: C, 60.82%; H, 4.24%, N, 17.60%.

#### 2.4. X-ray crystal structure determination

The single crystal data was collected on Bruker APEX-2 CCD Xray diffractometer that uses graphite monochromated Mo K $\alpha$  radiation ( $\lambda$  = 0.71073 Å) by hemisphere method. The structures are solved by direct methods and refined by least square methods on  $F^2$  using SHELX-97 [14]. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were fixed at calculated positions and refined using a riding model.

#### 3. Results and discussion

The compounds **1** and **2** are of our interest to understand the interference of pyridine group in amide-to-amide hydrogen bond formation [15]. These classes of compounds are also useful for the construction of coordination polymers where amide-to-amide

Table 1	
Crystallographic parameters for compounds <b>1C</b> and <b>2B</b> .	

Compound	10	2B
Formula	$C_{24}H_{20}N_6O_4$	C24H22N6O5
M.wt.	456.46	474.48
T (K)	293(2)	293(2)
System	Orthorhombic	Orthorhombic
Space group	Pbca	Pbca
a (Å)	8.1324(6)	7.593(4)
b (Å)	22.0796(2)	15.736(7)
c (Å)	24.1286(2)	36.327 (2)
α (°)	90	90
β (°)	90	90
γ (°)	90	90
V (Å <sup>3</sup> )	4332.5(6)	4340 (3)
Ζ	8	8
$D_{\text{calc}}$ (Mg/m <sup>3</sup> )	1.400	1.452
$R_1 (I > 2\sigma(I))$	0.0499	0.0628
$wR_2$ (on $F^2$ , all data)	0.1213	0.1903



Fig. 1. Honeycomb network via N-H···N hydrogen bonds observed in: (a) 1A and (b) 2A.



**Fig. 2.** Illustrations for the crystal structure of **1B**: (a) interaction of water with **1**, 1D-chain formed *via* amide-to-amide N—H…O hydrogen bonds along *c*-axis; (b) side view and (c) top view; (d) 2D-layer formed *via* C—H…O and C—H…N hydrogen bonds involving water molecules; (e) packing of the 2D-layers through water and amide-to-amide hydrogen bonds.



**Fig. 3.** Illustrations for the crystal structure of **1C**: (a) interaction of water with **1**; (b) amide-to-amide hydrogen bonded column; (b) side view and (c) top view; (d) 2D-layer formed *via* N–H···N, C–H···O hydrogen bonds and through water molecules and (e) joining of the zig-zag layers through water molecules.

recognition provides more control over the network geometries [16]. Both the compounds have more number of acceptors (six) than donors (three). To compensate such misbalance between donors and acceptors these molecules tend to include solvent molecules in their crystal lattice.

During the crystallization of **1** from MeOH, initially hexagonal shaped crystals were formed and subsequently rectangular block shaped crystals were observed in the same crystallization flask. To understand this process in detail the crystallization studies for **1** and **2** were carried out by varying the concentration and/or sol-



**Fig. 4.** Illustrations for the crystal structure of **2B**: (a) Interaction of water molecules with **2**; (b) amide-to-amide hydrogen bonded 1D-chain, 2D-layer formed *via* N-H···O and N-H···N hydrogen bonds; (c) top view and (d) side view; (1D-chains via amide-to-amide hydrogen bonds molecules are shown in one colour) and joining of the 2D-layers through water molecules; (e) top view and (f) side view.

vent of crystallization. In case of **1**, we have observed that high concentrations of **1** in MeOH (5–37.5 mg/ml) results in MeOH solvate of **1** (**1A**, **1**·3MeOH) which is unstable at room temperature, crystal structure of this form was reported by Palmans et al. (Fig. 1a) [10]. The moderate (3.5-4.2 mg/ml) and low concentrations (0.5-3.5 mg/ml) of **1** in MeOH resulted in the crystals of two stable forms **1B** (**1**·H<sub>2</sub>O) and **1C** (**1**·H<sub>2</sub>O) respectively. However the crystals of **1C** which were grown in this procedure are fibrous in nature and not suitable for single crystal X-ray diffraction. Therefore, good quality crystals of **1C** were obtained by layering MeOH solution of **1** over the H<sub>2</sub>O in a sealed test tube (Table 1).

The compound **2** earlier was reported by Dastidar et al. to form single crystals (**2A**, **2**·0.16DMSO·0.33MeOH) from DMSO, the crystal structure contains assembling of the molecules *via* N—H···N hydrogen bonds to form a network containing continuous channels similar to the form **1A** (Fig. 1b) [11]. Our studies by varying the concentrations of **2** in DMSO always resulted in the crystals of same form (**2A**) indicating that the formation of crystal forms does not depend on the concentration. However, our efforts are successful in obtaining another crystalline form (**2B**, **2**·2H<sub>2</sub>O) of **2** by choosing a different solvent such as DMF.

In the crystal structure of form **1B**, the molecule adopts T-shape geometry and includes one water molecule in its asymmetric unit. Water exhibits three coordination via hydrogen bonding: one to amide – NH (N–H···O: 1.980 Å, 152.09°, 2.770 Å) and two with N-atoms of two pyridyl units (O–H···N: 2.037 Å, 175.57°, 2.873 Å; 2.109 Å, 165.74°, 2.852 Å) (Fig. 2a). The other two N–H groups of **1** are involved in amide-to-amide hydrogen bonds with neighbouring molecules along *c*-axis such that it forms a linear chain (Fig. 2b-c). One of the three pyridine units which is not involved in O-H...N hydrogen bond with water forms a C-H...N hydrogen bond (Fig. 2d). Overall each unit of 1 is hydrogen bonded to three water molecules. In brief, the structure can be best described as joining of 2D-layers, which are formed via C-H--O and C-H...N hydrogen bonds, through water molecules and amide-to-amide hydrogen bonds along c-axis (Fig. 2e). We note here that the water molecules are present in between the layers and no other significant weak interactions were observed between 1 and water molecules.

Form **1C** is a polymorph of **1B** and molecules in the crystal structure of **1C** exhibit similar T-shape as that of **1B**. However the inter-planar angles between amide and central  $C_6$ -rings signif-

icantly differ from those of form 1B (29.5° in 1A; 30°, 33.1°, 34.4 in 1B and 1.09°, 25.49°, 36.99° in 1C). These differences in the geometry also reflected in their supramolecular aggregation with itself and also with water. In this form water molecule exhibits five coordination with respect to hydrogen bonds (Fig. 3a). The five hydrogen bonds include one N–H···O (2.180 Å; 159.25°, 3.000 Å), two O—H····N (1.881 Å; 174.31°, 2.774 Å; 2.131 Å; 172.16°, 2.950 Å), two C-H...O hydrogen bonds one each of with C-H of central phenyl (2.455 Å; 171.64°, 3.378 Å) and C–H of pyridine (2.619 Å; 129.17°, 3.287 Å). The molecules interact with each other via a single amide-to-amide N—H···O (2.223 Å, 150.89°, 3.006 Å) hydrogen bond along *a*-axis (Fig. 3b-c) to form an offset stacks between central C<sub>6</sub> rings. These stacks are further connected with the adjacent stacks in *bc*-plane *via* N–H···N (2.300 Å, 160.69°, 3.125 Å), C—H···O (2.470 Å; 169.59°, 3.389 Å; 2.453 Å 137.57°, 3.201 Å) hydrogen bonds and through water molecules (Fig. 3d). The 2D lavers are linked along *a*-axis through water molecules, that are present within the layer, and amide-to-amide hydrogen bonds (Fig. 3e). It is important to note here that the single crystals suitable for X-ray diffraction analysis for form-1C were obtained by using different conditions from the initially reported ones [9]. However, the calculated powder X-ray pattern of 1C found to match exactly with the initially reported experimental powder pattern of 1C.

Compound **2** has poor solubility in common organic solvents and soluble only in DMF or DMSO. The reported form 2A was obtained from DMSO-MeOH solvent mixture [11]. We have obtained the second form **2B** by crystallizing **2** from DMF. The compound **2** crystallizes as a dihydrate from DMF. In the crystal structure of 2B, the molecule exhibits T-shape geometry similar to the geometry of 1 in 1B or 1C. The water molecules have different coordination through hydrogen bonding (Fig. 4a). One of the two exhibits five coordination similar to the one observed in 1C: one N-H--O (2.043 Å; 164.10°, 2.880 Å) and two O-H···N (2.015 Å; 170.42°, 2.927 Å; 2.093 Å, 166.21°, 2.777 Å) and two C–H···O (with phenyl 2.402 Å; 140.50°, 3.175 Å and with pyridine 2.463 Å, 137.41°, 3.210 Å) hydrogen bonds. The second water molecule involved in four significant interactions: one  $O-H \cdots O$  hydrogen bond with amide carbonyl ( $0 \cdots 0$  distance 2.906 Å), one  $0 - H \cdots \pi$  interaction  $(O \cdots C \text{ distance } 3.341 \text{ Å})$  and two  $C - H \cdots O$  hydrogen bonds with pyridine – CH (2.586 Å; 129.41°, 3.257 Å; 2.705 Å, 141.17°, 3.478 Å).

The inter-planar angles between amide and central C<sub>6</sub>-rings of 2B (9.04°, 21.99°, 32.19°) differ from those in 2A (38.47°, 41.55°, 46.86°). The crystal structure of **2B** is constituted by combination of N-H···N and N-H···O hydrogen bonds while that of **2A** is fully constituted via N–H···N hydrogen bonds. The molecules assemble via amide-to-amide N–H···O (2.42Å, 140.50°, 3.128Å) hydrogen bonds to form 1D-chain along b-axis (Fig. 4b). These 1D-chains are inter-connected through N-H-...N (2.388 Å, 168.38°, 3.235 Å) hydrogen bonds between amide --NH and pyridine to form a 2D-layer in *ab*-plane (Fig. 4c-d) with a thickness of 18.18 Å. Remaining two pyridyl units are hydrogen bonded to water to link the 2D layers in bc-plane (Fig. 4e-f). The second water molecule also joins the 2D-layers in bc-plane via O-H···O hydrogen bonds with amide carbonyl and C-H···O hydrogen bonds with pyridine --CH group. Compared to 1C, the packing of 2B is observed to be highly corrugated. TGA analysis of 2B shows that the gradual loss of two water molecules occurs up to 346 °C.

#### 4. Conclusion

Our study confirms that the molecules **1** and **2** exhibit the tendency to include solvent molecules in the crystal lattice to compensate the mis-match of donor acceptor ratio. Both the molecules

show conformational isomerism which results in different crystalline forms. The stable crystalline forms were observed when the molecules are including water in their crystal lattice compared to other solvents. In the hydrate structures three different coordination environments for water are observed depending upon the position of water with respect to the molecular plane. The three forms of **1** can be selectively achieved depending on its concentration in MeOH, whereas of **2** based on the solvent of crystallization.

#### Supporting information

The IR spectra, TGA and Powder XRD patterns of compounds. CCDC 800565 and CCDC 800566 contain the supplementary crystallographic data for this paper for **1C** and **2B** respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data\_request/cif.

#### Acknowledgement

We gratefully acknowledge DST for financial support and DST-FIST for single crystal X-ray facility. L.R. thanks IIT (Kharagpur) for research fellowship.

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