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Where Did All the bpy Go? – Synthesis, Crystal and Molecular Structure of 4-Nitropicolinic Acid Monohydrate

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The conversion of 2,2′-bipyridine (bpy) to 4,4′-disubstituted derivatives is commonly achieved by a route involving preparation of the *N,N′*-dioxide and subsequent nitration with HNO_3/H_2SO_4. The yields in the latter reaction are of the order of 50% and we now show that a competing ring oxidation process leads to the formation of 4-nitropicolinic acid. The solid state structure of the monohydrate of 4-nitropicolinic acid is reported, which exhibits a series of interesting packing motifs arising from hydrogen bonding networks.

Keywords: 2,2-Bipyridine; Nitration; Oxidation; Crystal structure

INTRODUCTION

Ever since its first preparation by Blau in the 1880's [1–3], 2,2′-bipyridine (bpy, **1**) has played a seminal role in the development of understanding and models in coordination chemistry. More recently, bpy has become one of the most favoured motifs for use as a metal-binding domain in metallosupramolecular chemistry [4,5]. Although a large number of synthetic approaches to substituted bpy derivatives have been developed, one of the simplest and most popular is that originally developed by Haginiwa [6–8] and Murase [9] and more accessibly described by Case [10] for the preparation of 4,4′-disubstituted derivatives. The key reaction involves the nitration of 2,2′-bipyridine *N,N′*-dioxide under classical mixed acid conditions. We now show why the yields in this reaction are relatively low and present the structural characterisation of the unexpected oxidation product, 4-nitropicolinic acid.

RESULTS AND DISCUSSION

Although bpy, like most pyridines, is relatively inert to attack by electrophiles, conversion to the *N*-oxide or *N,N′*-dioxide **2** activates the 4-position(s) towards electrophilic attack [6–12]. The desired *N,N′*-dioxide **2** is obtained in essentially quantitative yield by the reaction of bpy with 30% hydrogen peroxide in acetic acid and is conveniently precipitated analytically pure by quenching the reaction mixture in acetone [13]. The nitration of **2** occurs smoothly upon reaction with fuming nitric acid in sulfuric acid solution. Typical yields of 4,4′-dinitro-2,2′-bipyridine *N,N′*-dioxide **3** in this reaction are in the range 40–50% and, to date, no information is available as to the fate of the remaining bpy in this reaction. In the course of a routine preparation we investigated the material present in the aqueous mother liquor after the water-insoluble 4,4′-dinitro-2,2′-bipyridine *N,N′*-dioxide **3** had been separated. After cooling to 0°C overnight, a yellow crystalline material was obtained. Additional material could be obtained by concentrating the solution.

Spectroscopic characterisation showed the yellow material to be 4-nitropicolinic acid **4** (Scheme 1). The acid **4** has previously been obtained by the oxidation of 4-nitropicoline [14] or hydrolysis of 2-cyano-4-nitropyridine [15]. The ^1H NMR spectrum of a CD_3SOCD_3 solution of the compound exhibits resonances at δ 9.08, 8.53 and 8.37 ppm corresponding to the literature values reported for the aromatic protons [15]. A parent ion is observed in the mass spectrum. Although the oxidation of alkyl substituents on pyridines to carboxylic acids is

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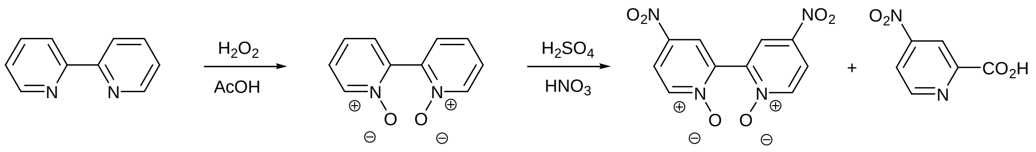

1 **2** **3** **4**

SCHEME 1 Synthesis of 4,4′-disubstituted 2,2′-bipyridine derivatives and of 4-nitropicolinic acid, **4**

well-established, very few examples are known of the oxidation of arylpyridines to picolinic acids have been reported [16] and only two cases are known in which a pyridine ring is oxidised [6,17].

Structural Characterisation of 4·H_2O

We have determined the solid state crystal structure of the monohydrate of **4** which is obtained upon recrystallisation from aqueous conditions (Tables I and II). Fig. 1 shows the structure of a molecule of **4** together with the numbering scheme adopted. The parent compound, 2-picolinic acid has been structurally characterised and forms a lattice with equal numbers of 2-pyridinecarboxylic acid and Zwitterionic pyridinio-2-carboxylate molecules [18–20].

As expected, the presence of the water molecule in the lattice of **4** results in a perturbation of the structure and in this case no Zwitterion is observed in the lattice. All bond lengths and angles are typical and the molecule is close to planar with the planes of the nitro and carboxylic acid groups making least squares planes angles with the plane of the pyridine ring of 8.37 and 6.16°respectively The basic structural unit in the packing is a tight tetramolecular package of two water molecules and two molecules of **4** (Fig. 2a). Each water molecule is hydrogen-bonded to a pyridine nitrogen atom (O5…N1, 2.928 Å, ∠O5-H5a-N1, 164.21°) and the OH group of a carboxylic acid (O5…O2C, 2.542 Å, ∠O5–H1C–O2c, 168.42°). The dimeric assemblies are then assembled into ribbons with short O…H contacts of 2.562 Å between nitro O4 and C4–H4 of the next dimer (Fig. 2b). The ribbons are then stacked in a coplanar manner with a 3.23 Å distance between adjacent least squares planes. Hydrogen bonding data are presented in Table III.

TABLE I Crystallographic data, data collection and refinement parameters for **4**·H_2O.

Empirical formula	$C_6H_4N_2O_4.H_2O$
Formula weight	186.13 g mol^{-1}
Temperature	296(2)K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	$P\,2\,1/n$
Unit cell dimensions	
$a = 12.7538(18)$	$\alpha = 90°$
$b = 5.5141(7)$	$\beta = 116.515(2)°$
$c = 12.762(2)$	$\gamma = 90°$
Volume, Z	803.1(2)$Å^3$, 4
Density (calculated)	1.539 mg m^{-3}
Absorption coefficient	0.137 mm^{-1}
$F(000)$	384
Crystal size	0.50 × 0.20 × 0.20 mm
θ range for data collection	3.57–25.18°
Index ranges	$-15 \le h \le 15$, $-6 \le k \le 6$, $-15 \le l \le 15$
Reflections collected	4480
Independent reflections	1370
Data/restraints/parameters	1370/0/130
Goodness-of-fit on F^2 (all data)	1.112
Final R indices [$I > 2\sigma I$]	$R1 =$, 0.0455, $wR2 =$, 0.1067
R indices (all data)	$R1 =$, 0.0477, $wR2 =$, 0.1083
Largest diff. peak and hole	0.177, − 0.135 $eÅ^3$

TABLE II Selected bond distances (Å) and angles (°) in **4**·H_2O with esds in parentheses.

O1-C1 1.208(2)	O2–C1 1.302(2)
O2–H1 0.95(3)	O3–N2 1.216(2)
O4–N2 1.216(2)	O5–H5A 0.89(3)
O5–H5B 0.86(3)	N1–C3 1.339(2)
N1–C2 1.341(2)	N2–C5 1.478(2)
C1–C2 1.503(2)	C2–C6 1.379(2)
C3–C4 1.381(3)	C4–C5 1.372(3)
C5–C6 1.374(3)	
H5A–O5–H5B 105(2)	C3–N1–C2 117.20(16)
O3–N2–O4 124.27(19)	O3–N2–C5 117.78(17)
O4–N2–C5 117.95(19)	O1–C1–O2 125.16(16)
O1–C1–C2 120.96(16)	O2–C1–C2 113.88(14)
N1–C2–C6 123.53(15)	N1–C2–C1 117.64(15)
C6-C2-C1 118.81(14)	N1–C3–C4 123.70(18)
C4–C5–C6 121.43(18)	C4–C5–N2 119.74(17)
C6–C5–N2 118.84(17)	C5–C6–C2 117.13(16)

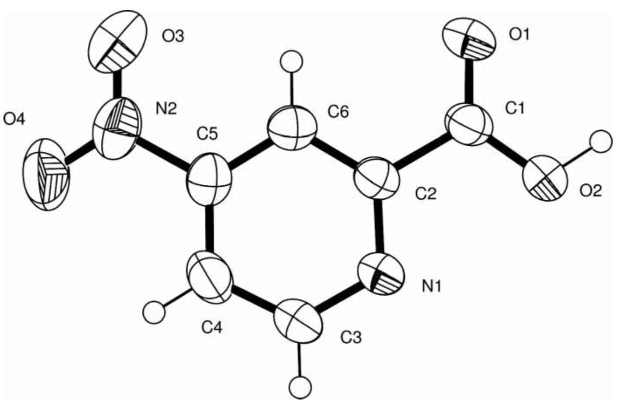

FIGURE 1 ORTEP representation of a single molecule of **4** present in the lattice of **4**. H_2O showing the numbering scheme adopted (50% probability thermal ellipsoids).

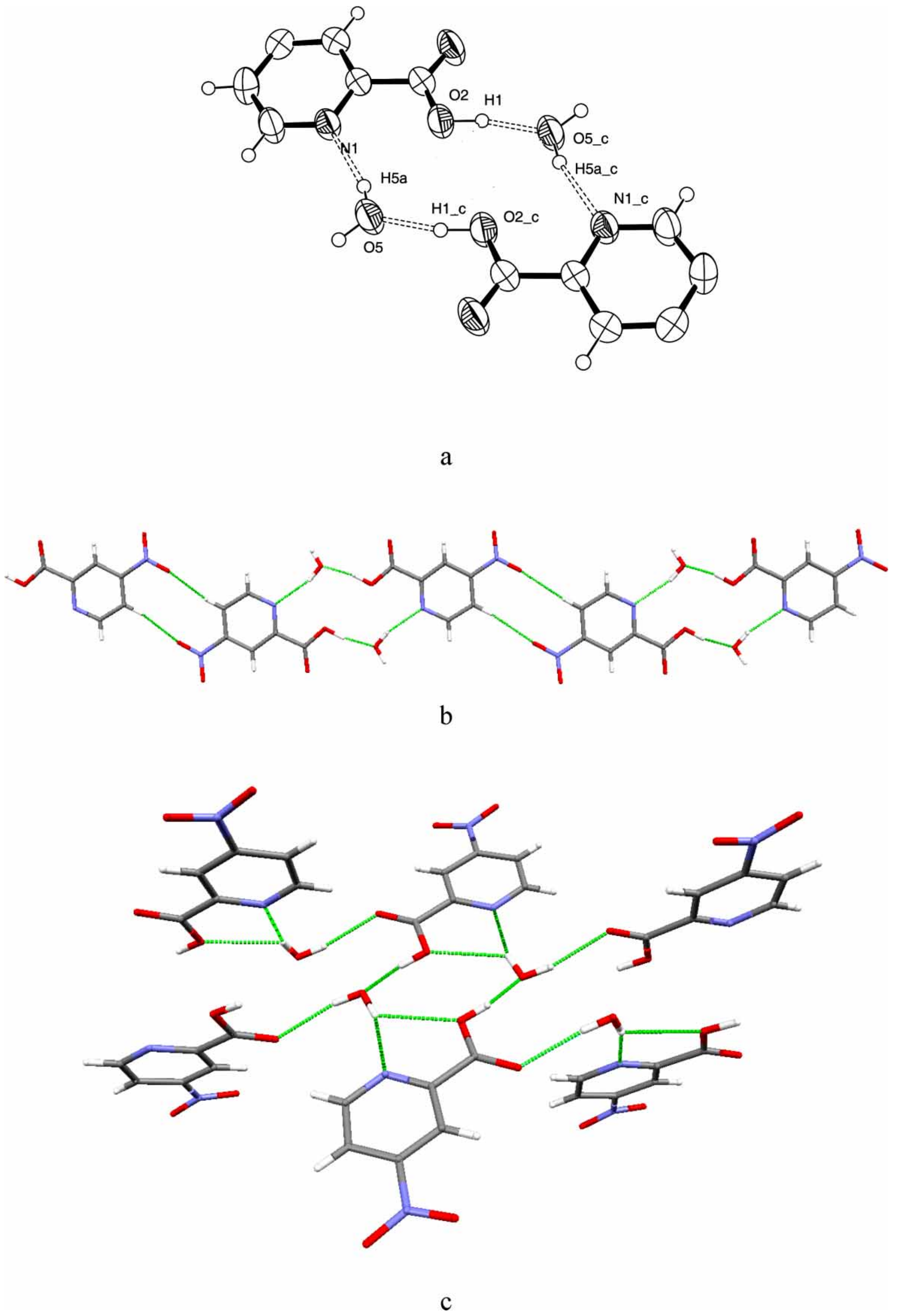

FIGURE 2 (a) ORTEP representation of a the tetramolecular package of two water molecules and two molecules of **4** present in the lattice of **4**. H_2O (50% probability thermal ellipsoids). Atoms with the symmetry label _c are generated by the symmetry operation -x, -y, -z; (b) Additional interactions between nitro oxygen atoms and pyridine CH bonds assemble the tetramolecular units into approximately planar ribbons; (c) Additional hydrogen bonds between ribbons construct the full three-dimensional array.

Each tetramolecular packet has one remaining hydrogen bond donor and hydrogen bond acceptor per water molecule, together with a carbonyl hydrogen bond acceptor. Ribbons are packed by the formation of a hydrogen bond O5−H5b…O1 (O1…O15, 2.832 Å, ∠O5−H5b−O1, 165.48°) between the carbonyl oxygen and the water molecule hydrogen bonded to the pyridine nitrogen atom (Fig. 2c). The ribbons are oriented at 72.11° with respect to the hydrogen-bonded neighbour.

TABLE III Distances (Å) and angles (°) of hydrogen bond-type interactions in **4**·H_2O.

		Distance		
D–H...A	Symmetry	D...A	H...A	Angle D–H...A
O2–H1...O5	$1 - x, - y,1 - z$	2.542(2)	1.60(3)	168(3)
O5–H5A...O2	$x, - 1 + y,z$	2.989(2)	2.41(3)	123(2)
O5–H5A...N1	x, − 1 + y,z	2.928(2)	2.06(3)	164(3)
O5–H5B...O1	$-1/2 + x, - 1/2 - y, - 1/2 + z$	2.832(2)	1.99(4)	166(3)
C4–H4...O4	$-x, - 1 - y,1 - z$	3.445(3)	2.5600	159.00

CONCLUSIONS

We have shown that the low yield of the key intermediate **3** for the synthesis of 4,4′-disubstituted 2,2′-bipyridines is a result of oxidation of one of the pyridine rings of 2,2′-bipyridine *N,N*′-dioxide under the nitration conditions. We have structurally characterised the oxidation product, 4-nitropicolinic acid as its monohydrate and shown an interesting hydrogen bonding network is present in the lattice.

EXPERIMENTAL

General

2,2′-Bipyridine *N,N*′-dioxide **2** was prepared by the literature method [5,6].

4,4′-Dinitro-2,2′-Bipyridine N,N′-Dioxide and 4-Nitropicolinic Acid

A solution of **2** (12.7 g, 67.5 mmol) in concentrated H_2SO_4 (42 mL) was cooled to 5°C and then fuming nitric acid (26 mL) was added dropwise. The brownish solution was then heated at 120°C for 5 h (Caution – nitrogen oxides copiously evolved). The reaction mixture was then allowed to cool to room temperature and then quenched by pouring it onto an ice-water (500 g/500 mL) mixture to give a pale yellow precipitate. This was collected by filtration, washed several times with water and acetone (128 mL) and dried to give 4,4′-dinitro-2,2′-bipyridine *N,N*′-dioxide **3** as a yellow solid (7.38 g, 39.0%). The aqueous and acetone filtrates were combined and left in a refrigerator at 0°C overnight, to give yellow needles of 4-nitropicolinic acid monohydrate **4** which were filtered and dried under high vacuum (2.08 g, 18.5%). Concentration of the mother liquor allowed the recovery of a further 1.7 g of less pure material. M.p.: 150–151°C (lit. 150–155°C) [14,21–26] FTIR: ν_{max} (neat, cm^{-1}) 3110 (w), 1882 (b), 1705 (s), 1589 (w), 1528 (s), 1443 (m), 1350 (s), 1234 (m). δ_H/ppm (CD_3SOCD_3, 300 MHz, 297K): 9.08 (H^{B6}, d, 2H, $J = 5.4$ Hz), 8.52 (H^{B3}, d, 2H, $J = 2.1$ Hz), 8.36 (H^{B5}, dd, 2H, $J = 2.3$, 5.3 Hz). MS (EI): m/z 169 $[M + H]^+$.

Single-Crystal X-ray Structure Analysis of 4·H_2O

Details of crystal data, data collection and refinement are given in Table I. X-Ray data were collected on a Rigaku R-axis iic diffractometer using Mo Kα radiation ($\lambda = 0.71069$ Å). A total of 4480 reflections were collected, of which 1370 were independent reflections and 1324 observed reflections [$I > 2\sigma I$]. The structure was solved by direct methods (SHELXS-86) [27] and refined with full-matrix least squares procedures on all data using SHELXL-97 [28]. All non hydrogen atoms were refined anisotropically. A riding model was used for the ring protons with ADPs 1.2 times those of the atoms to which they are bonded. The water and carboxylic acid proton have been refined unrestrained isotropically. Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic data Centre (CCDC 280145). Copies of the data can be obtained free of charge at www.ccdc.cam.ac.uk/products/csd/request/ or from the CCDC, 12 Union Road, Cambridge CB2 1EW, UK; fax: (44)1223-336-033; orE-mail: deposit@ccdc.cam.ac.uk.

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