

Redetermination of *para*-aminopyridine
(fampridine, EL-970) at 150 KFrankie P. Anderson,^a John F.
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Key indicators

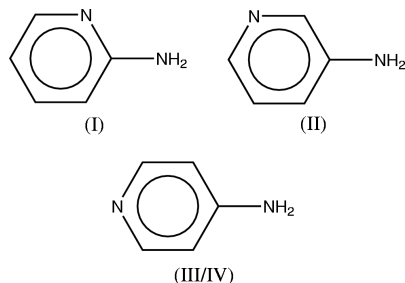
Single-crystal X-ray study
T = 150 K
Mean $\sigma(\text{C}-\text{C}) = 0.002 \text{ \AA}$
R factor = 0.031
wR factor = 0.086
Data-to-parameter ratio = 7.4For details of how these key indicators were
automatically derived from the article, see
<http://journals.iucr.org/e>.

The structure of fampridine (EL-970) or 4-aminopyridine, $\text{C}_5\text{H}_6\text{N}_2$, has been redetermined at 150 K. The room-temperature structure has been reported previously [Chao & Schempp (1977). *Acta Cryst.* B33, 1557–1564]. Pyramidalization at the amine N atom occurs in fampridine, with the N atom 0.133 (11) Å from the plane of the three C/H/H atoms to which it is bonded; the interplanar angle between the pyridyl ring and NH_2 group is 21 (2)°. Aggregation in the solid state occurs by $\text{N}-\text{H}\cdots\text{N}$ and $\text{N}-\text{H}\cdots\pi(\text{pyridine})$ interactions with $\text{N}\cdots\text{N}$ and $\text{N}\cdots\pi(\text{centroid})$ distances of 2.9829 (18) and 3.3954 (15) Å, respectively; a $\text{C}-\text{H}\cdots\pi(\text{pyridine})$ contact completes the intermolecular interactions [$\text{C}\cdots\pi(\text{centroid}) = 3.6360 (16) \text{ \AA}$].

Comment

4-Aminopyridine (fampridine) is used in the treatment of neurological ailments, such as multiple sclerosis (MS), with tests showing that fampridine improves motor function in MS patients (Schwid *et al.*, 1997). Related studies have utilized this small molecule on episodic ataxia type 2 (EA2), as it functions as a potassium channel blocker (Strupp *et al.*, 2004). Our interest in *para*-aminopyridine is to react it with aromatic carboxylic acids and acyl chlorides to generate new series of amide-based aromatic systems.

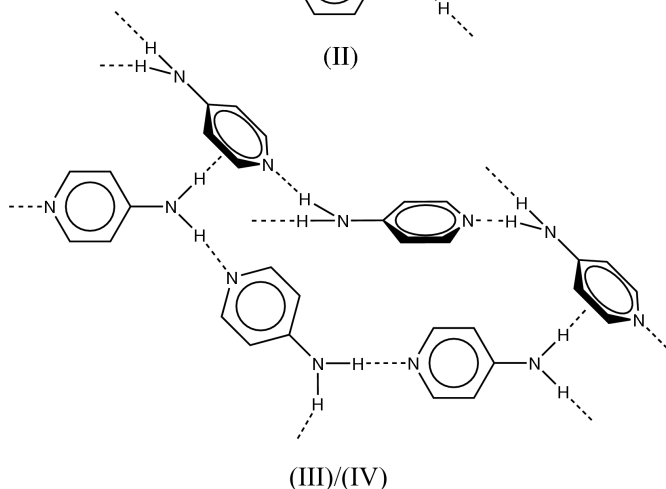
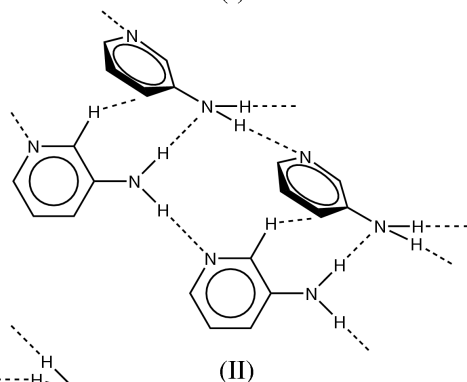
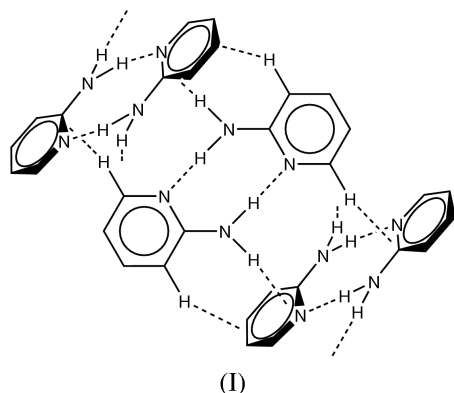
The structures of 2-, 3- and 4-aminopyridine, $\text{NC}_5\text{H}_4\text{NH}_2$, (I)–(III), have been reported previously using data collected at room temperature on a Nonius CAD-4 diffractometer with $\text{Cu K}\alpha$ radiation (Chao *et al.*, 1975*a,b*; Chao & Schempp, 1977), with corresponding Cambridge Structural Database (CSD; Version V6.26, February 2005 release; Allen, 2002) refcodes of AMPYRD, AMIPYR and AMPYRE. In the present study, we report the crystal structure of 4-aminopyridine (fampridine), (IV), at 150 K with greater precision than reported previously for (III) and comment on the intermolecular hydrogen bonding for comparison with the related structures (I)–(III).



In (I)–(III/IV), the primary donor (*D*) and acceptor (*A*) are the two NH_2 donor H atoms and the pyridine N atom

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acceptor. Herein lies a mismatch in the number of strong donor and acceptor groups, although the aromatic CH groups (*D*) and the π -pyridyl system (*A*) can redress this imbalance and participate as weaker donor and acceptor groups in the hydrogen-bonding process.



Primary interactions in (I) to (IV)

In (I) (Chao *et al.*, 1975*a*), the primary hydrogen bonding consists of pairs of molecules forming $N-H \cdots N_{\text{pyridine}}$ hydrogen bonds in a cyclic array about inversion centres, with graph set $R_2^2(8)$ (Bernstein *et al.*, 1995) ($H \cdots N = 2.20$ (3) Å, $N \cdots N = 3.071$ (7) Å and $N-H \cdots N = 171$ (2)°). Dimers stack into columns along the *b* axis direction, although there are no π - π stacking interactions of note. Further association of the dimers occurs *via* the second $N-H$ donor as $N-H \cdots N_{\text{pyridine}}$ interactions (about a twofold screw axis), forming a herringbone-type packing pattern in the [011] direction (interplanar

angle 58.9°), with $H \cdots N = 2.63$ (3) Å, $N \cdots N = 3.416$ (7) Å and $N-H \cdots N = 149$ (2)°, and augmented by two $C-H \cdots \pi(\text{arene})$ contacts per $N-H \cdots N$ interaction. There are no other interactions of note apart from normal van der Waals contacts.

In (II) (Chao *et al.*, 1975*b*), $N-H \cdots N_{\text{pyridine}}$ interactions link molecules along the *a*-axis direction in a head-to-tail fashion, thus generating infinite one-dimensional chains [$H \cdots N = 2.22$ (3) Å, $N \cdots N = 3.123$ (4) Å and $N-H \cdots N = 168$ (2)°]. The second NH donor forms an interaction with the amine N atom (lone pair of electrons), with $H \cdots N = 2.46$ (3) Å, $N \cdots N = 3.336$ (4) Å and $N-H \cdots N = 162$ (2)°, thus linking the chains into a three-dimensional herringbone pattern, where each chain is surrounded by six others, and this process is augmented by two $C-H \cdots \pi(\text{arene})$ interactions per molecule of (II), *e.g.* $H \cdots C = 2.81$ and 2.87 Å, only one of which is depicted in the second scheme.

In (III) (Chao & Schempp, 1977), $N-H \cdots N_{\text{pyridine}}$ interactions link molecules in a head-to-tail manner, forming zigzag chains along the *c*-axis direction, with $H \cdots N = 2.14$ Å, $N \cdots N = 3.007$ Å and $N-H \cdots N = 159$ °. The second NH donor atom forms an $N-H \cdots \pi(\text{pyridyl})$ interaction with a symmetry-related chain, stacked antiparallel along the *b*-axis direction, with shortest $H \cdots C = 2.66$ Å and $N-H \cdots C = 173$ °. The $N-H \cdots \pi(\text{pyridyl})$ interaction links each chain with two neighbouring chains, each consecutive NH donor alternately donating to either of the two $\pi(\text{pyridyl})$ groups. Thus, each chain is linked and effectively surrounded by four chains as the $\pi(\text{pyridyl})$ is also an acceptor of $N-H$ interactions from two extra chains. Of note is that pyramidalization occurs at the amine N atom.

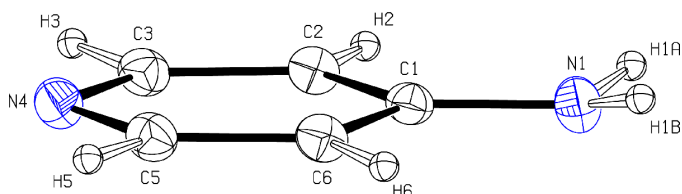


Figure 1

A view of (IV), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atom sphere radii are arbitrary.

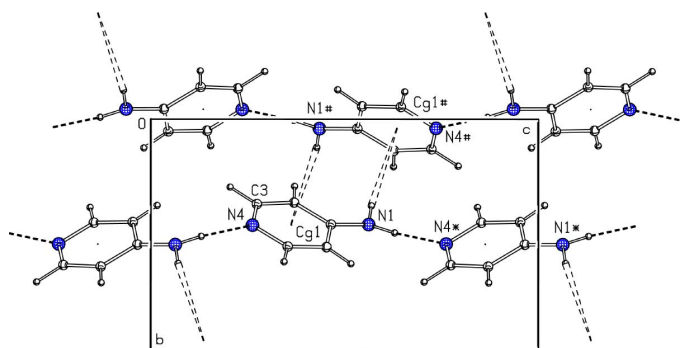


Figure 2

A view of the two primary interactions in (IV). Atoms labelled with the suffixes # and * are at the symmetry-related positions $(-\frac{1}{2} + x, \frac{1}{2} - y, 1 - z)$ and $(\frac{1}{2} - x, 1 - y, \frac{1}{2} + z)$, respectively.

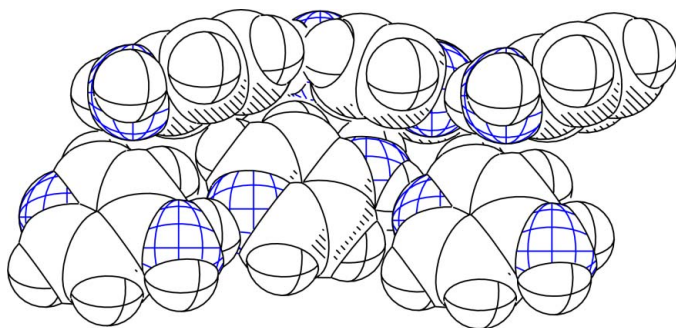


Figure 3
A view of the hydrogen-bonded chain generated by N–H...N hydrogen bonds and N–H... π (arene) interactions with a neighbouring chain.

Thus, in structures (I)–(III), an N_{amine}–H...N_{pyridine} hydrogen bond forms and the remaining amine H-atom donor interacts in the crystal structure in one of three different ways, either *via* herringbone-type N–H...N_{pyridine} interactions in (I), by N–H...N_{amine} interactions in (II) or as N–H... π (pyridyl) interactions in (III), as depicted in the second scheme above. It is pertinent to note that in the original reports the primary hydrogen bonding involving N_{amine}–H...N_{pyridine} was comprehensively discussed. However, only in (II) was the remaining (second) amine NH donor implicated in an interaction and with the lone pair of electrons on the amine N atom. The authors further qualify this with the statement ‘although these distances are too long to be recognized as hydrogen bonds’.

In the present study of (IV), the low-temperature structure of (III), the corresponding data are detailed in Tables 1 and 2. Bond lengths and angles are similar but are determined to a higher degree of precision than reported for (III). In (IV), amine atom N1 lies 0.133 (11) Å from the plane of atoms C1, H1A and H1B; this pyramidalization can also be observed by the three angles about N1 summing to 355.3°. The amine N1/H1A/H1B and the pyridyl NC₅ group are twisted from coplanarity by 21 (2)°, while atom N1 is coplanar with the pyridine ring system; the H1A/H1B atoms lie 0.12 (2) and 0.22 (2) Å from this aromatic plane. The hydrogen-bonding distances in (IV) (Table 2) [values for (III) in brackets] are N...N 2.9829 (18) Å [3.007 Å], N... π (pyridyl) 3.3954 (15) Å [3.460 Å], and a contact between atom C3 and a neighbouring π (pyridyl) of 3.6360 (16) Å [3.704 Å].

In the isoelectronic compound aniline, C₆H₅NH₂, (amino-benzene), studied at 252 K (CSD refcode BAZGOY), two strong donor groups and no strong acceptors are present (Fukuyo *et al.*, 1982). Aggregation in the solid state utilizes both NH donor groups as N–H...N_{amine} [N...N = 3.180 (6) and 3.373 (5) Å] and N–H... π (phenyl) interactions [N...Cg = 3.41 and 3.49 Å, H...N = 2.70 and 2.64 Å, and N–H... π (Cg) = 154 and 150°, where Cg represents the aromatic ring centroids]. The former two N–H...N_{amine} interactions are similar to that observed in (II) above: the latter two are described as having H atoms that are ‘free from hydrogen bonding’ (Fukuyo *et al.*, 1982). Such N–H... π (aromatic) interactions have received considerable attention in recent years both in chemistry and in biology (Desiraju & Steiner,

1999). The distances and angles associated with these type of interactions in (III) and (IV) are typical of the values reported in the literature.

Experimental

4-Aminopyridine was purchased from Aldrich Chemical Company Ltd and recrystallized from CH₂Cl₂ prior to analysis.

Crystal data

C ₅ H ₆ N ₂	Mo K α radiation
$M_r = 94.12$	Cell parameters from 2026 reflections
Orthorhombic, $P2_12_12_1$	$\theta = 2.6$ – 27.5°
$a = 5.5138$ (4) Å	$\mu = 0.08$ mm ⁻¹
$b = 7.1866$ (5) Å	$T = 150$ (1) K
$c = 12.0459$ (4) Å	Block, colourless
$V = 477.32$ (5) Å ³	0.25 × 0.20 × 0.15 mm
$Z = 4$	
$D_x = 1.310$ Mg m ⁻³	

Data collection

Nonius KappaCCD diffractometer	591 reflections with $I > 2\sigma(I)$
φ scan and ω scans with κ offsets	$R_{int} = 0.030$
Absorption correction: multi-scan (SORTAV; Blessing, 1995)	$\theta_{max} = 27.5^\circ$
$T_{min} = 0.979$, $T_{max} = 0.988$	$h = -6 \rightarrow 7$
3217 measured reflections	$k = -9 \rightarrow 9$
662 independent reflections	$l = -15 \rightarrow 15$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0587P)^2 + 0.0044P]$
$R[F^2 > 2\sigma(F^2)] = 0.031$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.086$	$(\Delta/\sigma)_{max} < 0.001$
$S = 1.10$	$\Delta\rho_{max} = 0.17$ e Å ⁻³
662 reflections	$\Delta\rho_{min} = -0.13$ e Å ⁻³
89 parameters	Extinction correction: SHELXL97
All H-atom parameters refined	Extinction coefficient: 0.13 (4)

Table 1

Selected geometric parameters (Å, °).

N1–C1	1.3597 (18)	N4–C5	1.346 (2)
C1–C2	1.409 (2)	C5–C6	1.375 (2)
C1–C6	1.403 (2)	N1–H1A	0.95 (2)
C2–C3	1.378 (2)	N1–H1B	0.94 (2)
C3–N4	1.345 (2)		
N1–C1–C2	122.41 (13)	N4–C3–C2	124.77 (15)
N1–C1–C6	121.33 (13)	C3–N4–C5	115.25 (13)
C2–C1–C6	116.25 (13)	N4–C5–C6	124.74 (14)
C1–C2–C3	119.37 (14)	C5–C6–C1	119.61 (13)

Table 2

Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N1–H1B...N4 ⁱ	0.94 (2)	2.06 (2)	2.9829 (18)	167 (2)
N1–H1A...Cg1 ⁱⁱ	0.95 (2)	2.61 (2)	3.3954 (15)	141 (2)
C3–H3...Cg1 ⁱⁱⁱ	1.03 (2)	2.76 (2)	3.6360 (16)	143 (2)

Symmetry codes: (i) $-x + \frac{1}{2}, -y + 1, z + \frac{1}{2}$; (ii) $x - \frac{1}{2}, -y + \frac{1}{2}, -z + 1$; (iii) $-x, y - \frac{1}{2}, -z + \frac{1}{2}$.

All six H atoms bound to C and N were refined with isotropic displacement parameters with the four C–H bond lengths in the range 0.971 (19) to 1.028 (18) Å. Examination of the structure with PLATON (Spek, 2003) showed that there were no solvent-accessible voids in the crystal structure. In the absence of significant anomalous

scattering, Friedel pairs were merged prior to the final refinement cycles.

Data collection: *KappaCCD Server Software* (Nonius, 1997); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*, *ORTEX* (McArdle, 1995) and *PREP8* (Ferguson, 1998).

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