organic papers

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Key indicators

Single-crystal X-ray study
T = 150 K
Mean σ(C–C) = 0.002 Å
R factor = 0.031
wR factor = 0.086
Data-to-parameter ratio = 7.4

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Redetermination of *para*-aminopyridine (fampridine, EL-970) at 150 K

The structure of fampridine (EL-970) or 4-aminopyridine, $C_5H_6N_2$, has been redetermined at 150 K. The room-temperature structure has been reported previously [Chao & Schempp (1977). *Acta Cryst.* B**33**, 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 N—H···N and N—H···π(pyridine) interactions with N···N and N···π(centroid) distances of 2.9829 (18) and 3.3954 (15) Å, respectively; a C—H···π(pyridine) contact completes the intermolecular interactions [C···π(centroid) = 3.6360 (16) Å].

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, $NC_5H_4NH_2$, (I)–(III), have been reported previously using data collected at room temperature on a Nonius CAD-4 diffractometer with Cu $K\alpha$ radiation (Chao *et al.*, 1975a,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-amino-pyridine (fampridine), (IV), at 150 K with greater precision than reported previously for (III) and comment on the inter-molecular hydrogen bonding for comparison with the related structures (I)–(III).
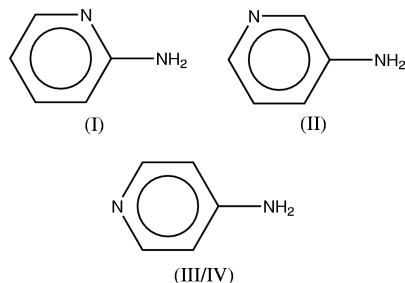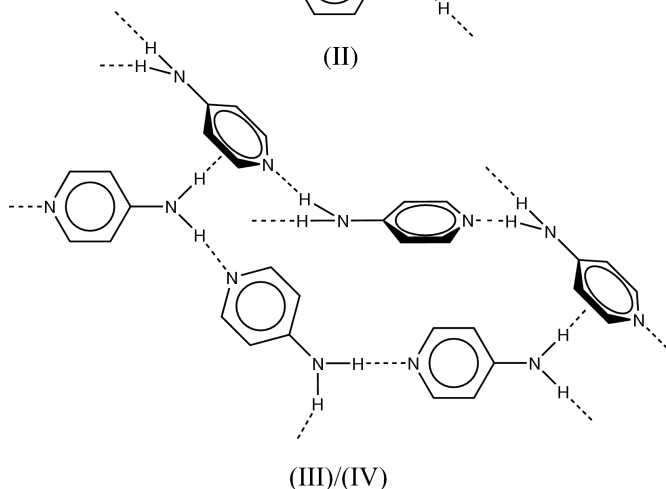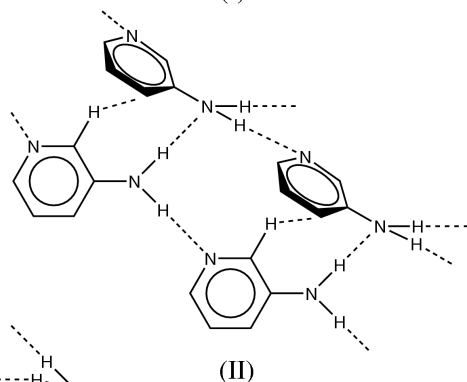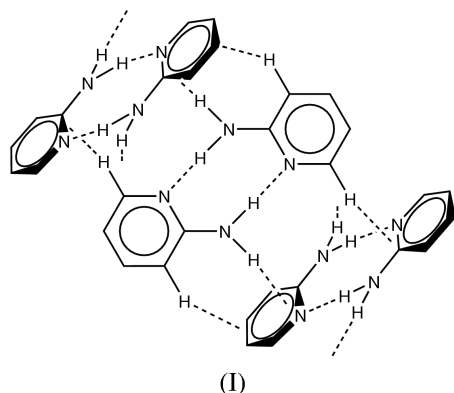

In (I)–(III/IV), the primary donor (*D*) and acceptor (*A*) are the two NH_2 donor H atoms and the pyridine N atom

acceptor. Herein lies a mismatch in the number of strong donor and acceptors 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.

(I)

(II)

(III)/(IV)

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⋯N$_{pyridine}$ hydrogen bonds in a cyclic array about inversion centres, with graph set $R_2^2(8)$ (Bernstein *et al.*, 1995) (H⋯N = 2.20 (3) Å, N⋯N = 3.071 (7) Å and N—H⋯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⋯N$_{pyridine}$ interactions (about a twofold screw axis), forming a herringbone-type packing pattern in the [011] direction (interplanar

angle 58.9°), with H⋯N = 2.63 (3) Å, N⋯N = 3.416 (7) Å and N—H⋯N = 149 (2)°, and augmented by two C—H⋯π(arene) contacts per N—H⋯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⋯N$_{pyridine}$ interactions link molecules along the *a*-axis direction in a head-to-tail fashion, thus generating infinite one-dimensional chains [H⋯N = 2.22 (3) Å, N⋯N = 3.123 (4) Å and N—H⋯N = 168 (2)°]. The second NH donor forms an interaction with the amine N atom (lone pair of electrons), with H⋯N = 2.46 (3) Å, N⋯N = 3.336 (4) Å and N—H⋯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⋯π(arene) interactions per molecule of (II), *e.g.* H⋯C 2.81 and 2.87 Å, only one of which is depicted in the second scheme.

In (III) (Chao & Schempp, 1977), N—H⋯N$_{pyridine}$ interactions link molecules in a head-to-tail manner, forming zigzag chains along the *c*-axis direction, with H⋯N = 2.14 Å, N⋯N = 3.007 Å and N—H⋯N = 159°. The second NH donor atom forms an N—H⋯π(pyridyl) interaction with a symmetry-related chain, stacked antiparallel along the *b*-axis direction, with shortest H⋯C = 2.66 Å and N—H⋯C = 173°. The N—H⋯π(pyridyl) interaction links each chain with two neighbouring chains, each consecutive NH donor alternately donating to either of the two π(pyridyl) groups. Thus, each chain is linked and effectively surrounded by four chains as the π(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
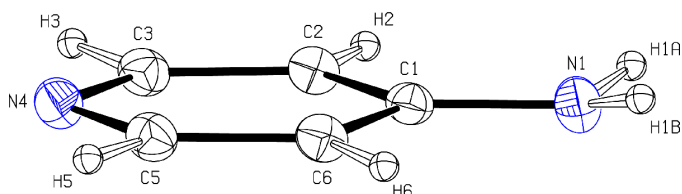A view of (IV), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.. H atom sphere radii are arbitrary.
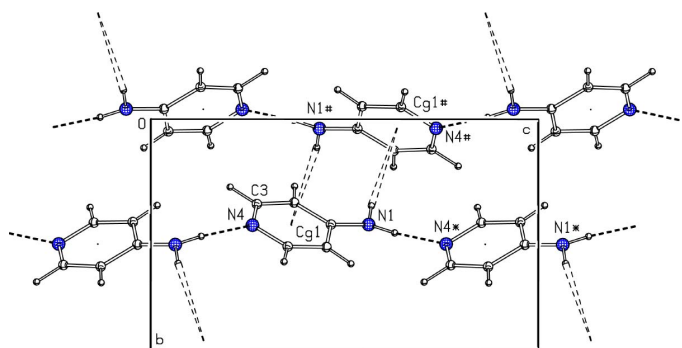

Figure 2
A view of the two primary interactions in (IV). Atoms labelled with the suffixes # and * are at the symmetry-related positions $(-\frac{1}{2} + x, \frac{1}{2} - y, 1 - z)$ and $(\frac{1}{2} - x, 1 - y, \frac{1}{2} + z)$, respectively.
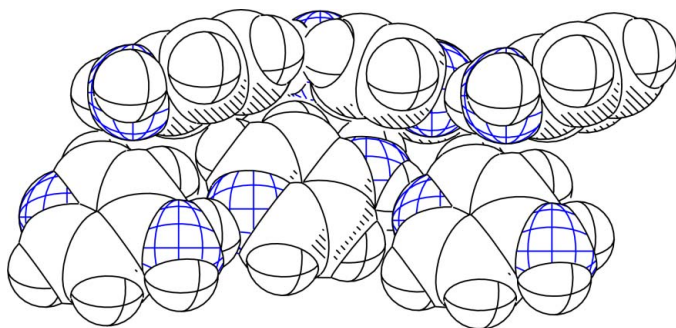
Figure 3
A view of the hydrogen-bonded chain generated by N—H···N hydrogen bonds and N—H···π(arene) interactions with a neighbouring chain.

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, H1*A* and H1*B*; this pyramidalization can also be observed by the three angles about N1 summing to 355.3°. The amine N1/H1*A*/H1*B* and the pyridyl NC$_5$ group are twisted from coplanarity by 21 (2)°, while atom N1 is coplanar with the pyridine ring system; the H1*A*/H1*B* 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, $C_6H_5NH_2$, (aminobenzene), 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···$\pi(Cg)$ = 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 CH_2Cl_2 prior to analysis.

Crystal data

$C_5H_6N_2$	Mo $K\alpha$ radiation
$M_r = 94.12$	Cell parameters from 2026
Orthorhombic, $P2_12_12_1$	reflections
$a = 5.5138$ (4) Å	$\theta = 2.6$–27.5°
$b = 7.1866$ (5) Å	$\mu = 0.08$ mm^{-1}
$c = 12.0459$ (4) Å	$T = 150$ (1) K
$V = 477.32$ (5) Å^3	Block, colourless
$Z = 4$	$0.25 \times 0.20 \times 0.15$ mm
$D_x = 1.310$ 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	$\theta_{max} = 27.5°$
(*SORTAV*; Blessing, 1995)	$h = -6 \rightarrow 7$
$T_{min} = 0.979$, $T_{max} = 0.988$	$k = -9 \rightarrow 9$
3217 measured reflections	$l = -15 \rightarrow 15$
662 independent reflections	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0587P)^2$
$R[F^2 > 2\sigma(F^2)] = 0.031$	$+ 0.0044P]$
$wR(F^2) = 0.086$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.10$	$(\Delta/\sigma)_{max} < 0.001$
662 reflections	$\Delta\rho_{max} = 0.17$ e Å^{-3}
89 parameters	$\Delta\rho_{min} = -0.13$ e Å^{-3}
All H-atom parameters refined	Extinction correction: *SHELXL97*
	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—H1*A*	0.95 (2)
C2—C3	1.378 (2)	N1—H1*B*	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···A	D—H	H···A	D···A	D—H···A
N1—H1*B*···N4^i	0.94 (2)	2.06 (2)	2.9829 (18)	167 (2)
N1—H1*A*···$Cg1^{ii}$	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.

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supporting information

Redetermination of *para*-aminopyridine (fampridine, EL-970) at 150 K

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4-aminopyridine

Crystal data

$C_5H_6N_2$	? #Insert any comments here.
$M_r = 94.12$	$D_x = 1.310$ Mg m^{-3}
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Hall symbol: P 2ac 2ab	Cell parameters from 2026 reflections
$a = 5.5138$ (4) Å	$\theta = 2.6$–27.5°
$b = 7.1866$ (5) Å	$\mu = 0.08$ mm^{-1}
$c = 12.0459$ (4) Å	$T = 150$ K
$V = 477.32$ (5) Å^3	Block, colourless
$Z = 4$	$0.25 \times 0.20 \times 0.15$ mm
$F(000) = 200$	

Data collection

Nonius KappaCCD diffractometer	3217 measured reflections
Radiation source: fine-focus sealed X-ray tube	662 independent reflections
Graphite monochromator	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)	$\theta_{max} = 27.5°$, $\theta_{min} = 3.3°$
$T_{min} = 0.979$, $T_{max} = 0.988$	$h = -6 \rightarrow 7$
	$k = -9 \rightarrow 9$
	$l = -15 \rightarrow 15$

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	All H-atom parameters refined
$R[F^2 > 2\sigma(F^2)] = 0.031$	$w = 1/[\sigma^2(F_o^2) + (0.0587P)^2 + 0.0044P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.086$	
$S = 1.10$	$(\Delta/\sigma)_{max} < 0.001$
662 reflections	$\Delta\rho_{max} = 0.17$ e Å^{-3}
89 parameters	$\Delta\rho_{min} = -0.13$ e Å^{-3}
0 restraints	Extinction correction: SHELXL97, Fc*=kFc[1+0.001xFc$^2\lambda^3$/sin(2θ)]$^{-1/4}$
Primary atom site location: structure-invariant direct methods	Extinction coefficient: 0.13 (4)
Secondary atom site location: difference Fourier map	

Special details

Experimental. ? #Insert any special details here.

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Planes data ###########

Least-squares planes (*x*,*y*,*z* in crystal coordinates) and deviations from them (* indicates atom used to define plane)

$-2.7639(0.0029)x + 5.8598(0.0027)y - 3.4889(0.0068)z = 0.9722(0.0035)$

* -0.0048 (0.0010) C1 * 0.0023 (0.0011) C2 * 0.0036 (0.0010) C3 * -0.0072 (0.0010) N4 * 0.0047 (0.0011) C5 * 0.0013 (0.0010) C6 0.0000 (0.0021) N1 - 0.1285 (0.0181) H1A -0.2253 (0.0231) H1B

Rms deviation of fitted atoms = 0.0044

$-3.3817(0.0787)x + 5.6625(0.0835)y + 0.6624(0.3484)z = 3.2778(0.1869)$

Angle to previous plane (with approximate e.s.d.) = 20.9(1.6)

* 0.0000 (0.0000) N1 * 0.0000 (0.0000) H1A * 0.0000 (0.0000) H1B

Rms deviation of fitted atoms = 0.0000

$- 2.7837(0.0740)x + 6.0631(0.0710)y - 2.1990(0.1424)z = 1.6604(0.0959)$

Angle to previous plane (with approximate e.s.d.) = 15.3(2.1)

* 0.0000 (0.0000) C1 * 0.0000 (0.0000) H1A * 0.0000 (0.0000) H1B 0.1331 (0.0106) N1 - 0.2686 (0.0221) N4

Rms deviation of fitted atoms = 0.0000

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
N1	−0.0935 (2)	0.45712 (19)	0.56319 (10)	0.0302 (4)
C1	0.0307 (3)	0.4568 (2)	0.46567 (11)	0.0244 (4)
C2	−0.0533 (3)	0.3619 (2)	0.37080 (11)	0.0259 (4)
C3	0.0811 (3)	0.3682 (2)	0.27448 (13)	0.0285 (4)
N4	0.2927 (2)	0.4593 (2)	0.26288 (10)	0.0295 (4)
C5	0.3692 (3)	0.5515 (2)	0.35369 (12)	0.0284 (4)
C6	0.2497 (3)	0.5542 (2)	0.45390 (12)	0.0274 (4)
H1A	−0.228 (3)	0.376 (3)	0.5703 (14)	0.034 (5)*
H1B	−0.020 (4)	0.493 (3)	0.6301 (18)	0.054 (6)*
H2	−0.204 (3)	0.292 (3)	0.3720 (12)	0.030 (4)*
H3	0.026 (3)	0.295 (3)	0.2055 (15)	0.036 (5)*
H5	0.523 (3)	0.617 (3)	0.3440 (14)	0.031 (4)*
H6	0.309 (4)	0.626 (3)	0.5168 (15)	0.037 (5)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0328 (7)	0.0322 (7)	0.0257 (7)	−0.0054 (7)	0.0031 (5)	−0.0009 (6)
C1	0.0269 (7)	0.0217 (7)	0.0246 (7)	0.0022 (7)	−0.0016 (5)	0.0025 (6)
C2	0.0257 (7)	0.0253 (7)	0.0268 (7)	−0.0019 (7)	−0.0041 (6)	0.0005 (6)
C3	0.0332 (8)	0.0269 (7)	0.0254 (7)	0.0015 (8)	−0.0042 (6)	0.0012 (6)
N4	0.0309 (7)	0.0310 (7)	0.0267 (6)	0.0009 (6)	0.0010 (5)	0.0031 (5)
C5	0.0266 (7)	0.0274 (7)	0.0313 (8)	−0.0013 (7)	−0.0001 (6)	0.0035 (6)
C6	0.0297 (8)	0.0255 (7)	0.0270 (7)	−0.0013 (8)	−0.0044 (6)	0.0005 (6)

Geometric parameters (Å, º)

N1—C1	1.3597 (18)	N1—H1A	0.95 (2)
C1—C2	1.409 (2)	N1—H1B	0.94 (2)
C1—C6	1.403 (2)	C2—H2	0.971 (19)
C2—C3	1.378 (2)	C3—H3	1.028 (18)
C3—N4	1.345 (2)	C5—H5	0.978 (19)
N4—C5	1.346 (2)	C6—H6	0.973 (19)
C5—C6	1.375 (2)		
N1—C1—C2	122.41 (13)	C1—N1—H1B	121.7 (14)
N1—C1—C6	121.33 (13)	C1—C2—H2	121.3 (9)
C2—C1—C6	116.25 (13)	C3—C2—H2	119.4 (9)
C1—C2—C3	119.37 (14)	C2—C3—H3	120.4 (10)
N4—C3—C2	124.77 (15)	N4—C3—H3	114.8 (10)
C3—N4—C5	115.25 (13)	N4—C5—H5	114.4 (10)
N4—C5—C6	124.74 (14)	C6—C5—H5	120.9 (10)
C5—C6—C1	119.61 (13)	C1—C6—H6	118.4 (11)
H1A—N1—H1B	115.5 (16)	C5—C6—H6	121.9 (11)
C1—N1—H1A	118.1 (10)		
N1—C1—C2—C3	179.68 (13)	C3—N4—C5—C6	1.3 (2)
C6—C1—C2—C3	0.5 (2)	N4—C5—C6—C1	−0.5 (2)
C1—C2—C3—N4	0.3 (2)	N1—C1—C6—C5	−179.59 (14)
C2—C3—N4—C5	−1.2 (2)	C2—C1—C6—C5	−0.4 (2)

Hydrogen-bond geometry (Å, º)

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1B···N4ⁱ	0.94 (2)	2.06 (2)	2.9829 (18)	167 (2)
N1—H1A···Cg1ⁱⁱ	0.95 (2)	2.61 (2)	3.3954 (15)	141.1 (15)
C3—H3···Cg1ⁱⁱⁱ	1.028 (18)	2.76 (2)	3.6360 (16)	143.3 (15)

Symmetry codes: (i) −*x*+1/2, −*y*+1, *z*+1/2; (ii) *x*−1/2, −*y*+1/2, −*z*+1; (iii) −*x*, *y*−1/2, −*z*+1/2.