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# Hydrogen Bond Studies. CXXI. Structure Determination of 2-Amino-4-methylpyridine by Molecular-Packing Analysis and X-ray Diffraction*

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The crystal and molecular structure of 2-amino-4-methylpyridine, $C_6N_2H_8$, has been determined from X-ray diffractometer data (Cu $K\alpha$) at 100 K. The crystals are orthorhombic, space group *Pbca*, with eight formula units in a cell with $a = 27{\cdot}060\ (1)$, $b = 7{\cdot}3092\ (6)$, $c = 5{\cdot}8494\ (3)$ Å (100 K). The preliminary crystal structure was determined from an automated packing analysis, and subsequently refined from the X-ray data with a least-squares procedure. The parameters for all atoms, including H atoms, were included in the final refinement, which converged at a discrepancy index $R(F)$ of 0·041. The preliminary structure was in good agreement with the final structure. The molecules link *via* two N–H···N hydrogen bonds [2·996 (2) Å] to produce centrosymmetric dimers which, in turn, pack in a herring-bone fashion.

## Introduction

This work is part of a systematic investigation of organic compounds which utilize hydrogen bonding to provide simple analogs to biologically interesting systems. Several substituted hydroxy- and aminopyridines have been studied earlier and are summarized by Kvick (1974). The present compound also served as a test case for solving crystal structures *ab initio* employing molecular-packing analysis. We present here the results from the molecular-packing analysis, and the final structure determination of 2-amino-4-methylpyridine based on single-crystal X-ray diffraction data collected at 100 K. The crystal structure of 2-aminopyridine has earlier been reported by Chao, Schempp & Rosenstein (1975, 1976).

### *Crystal data*

2-Amino-4-methylpyridine, $C_6N_2H_8$. FW 108·144. Orthorhombic $a = 27{\cdot}060\ (1)$,‡ $b = 7{\cdot}3092\ (6)$, $c = 5{\cdot}8494\ (3)$ Å, $V = 1156{\cdot}93$ Å$^3$ at 100 K, $Z = 8$, $D_x = 1{\cdot}241$ g cm$^{-3}$. Space group *Pbca*. The cell dimensions were determined at 100 K by least-squares refinement using the $2\theta$ values of 32 reflexions measured with graphite-monochromatized Cu $K\alpha$ radiation ($\lambda = 1{\cdot}5418$ Å) on a Stoe–Philips Weissenberg diffractometer.

## Experimental

Commercial 2-amino-4-methylpyridine was recrystallized several times from an aqueous solution. Prismatic crystals, bounded by faces of the forms {100}, {010} and {111}, were isolated, and two crystals with dimensions 0·14 × 0·27 × 0·27 mm (crystal I) and 0·17 × 0·21 × 0·29 mm (crystal II) were selected for the data collection. The intensity data were collected with graphite-monochromatized Cu $K\alpha$ radiation on a Stoe–Philips two-circle diffractometer modified for low-temperature studies. The cooling apparatus has been described by Olovsson (1960).

Two independent sets of data were obtained by collecting one set from crystal I rotating around the [010] direction and one set from crystal II rotating around the [001] direction. The data sets included data for layers *h*0*l* to *h*6*l* and *hk*0 to *hk*5 respectively. The measurements were made with the equi-inclination $\omega$-scan mode with a variable scan range calculated according to expressions given by Freeman, Guss, Nockolds, Page & Webster (1970). The variation in scan range was based on wavelength dispersion, divergence of the X-ray beam, crystal mosaicity and estimation of maximal errors in the settings of the crystal and instrument. Intensity data set I included 972 independent reflexions and set II 1034 reflexions out to $\sin\theta/\lambda = 0{\cdot}62$ Å$^{-1}$. Three standard reflexions were monitored at regular intervals within each layer

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‡ Numbers in parentheses here and throughout this paper are estimated standard deviations in the last given digit.

and no divergence from the expected variance in the intensities was found.

The two data sets were used to determine the relative interlayer scale factors, which were fixed at the obtained values in all subsequent calculations.

The raw intensities for each data set were corrected for Lorentz, polarization and absorption effects with the program *DATAPW*.* The crystals were described by ten rational boundary planes; a grid of 216 sampling points was used in a Gaussian integration method. The linear absorption coefficient for Cu $K\alpha$ radiation was 5·82 $\text{cm}^{-1}$.

The resulting two data sets were analysed by means of $\delta m$ normal probability plots (Abrahams & Keve, 1971) comparing 910 common, observed structure factors. The analysis indicated that each reflexion should be assigned a weight $w$, inversely proportional to the estimated variance of the observation: $w^{-1} = \sigma^2(|F_o|^2) = \sigma_c^2(|F_o|^2) + (0{\cdot}045|F_o|^2)^2$ where $\sigma_c(|F_o|^2)$ is based on counting statistics. The above weighting scheme gave a $\delta m$ plot with a slope of 1·0 and with only four differences more than $4\sigma$ away from the expected values. These weights were used in all subsequent calculations.

## Determination of the structure

The phase problem was solved by molecular-packing analysis. The atomic connectivities of the molecule were known, and we assumed the molecule to be planar, leaving no intramolecular degrees of freedom. A prototype structure was 2-amino-5-chloropyridine (Kvick & Backéus, 1974), where the planar molecules form hydrogen-bonded dimers in which the two molecules are related by a centre of symmetry.

For our trial molecular model we used a similar hydrogen-bonded dimer with bond angles close to 120° and the following bond lengths: in the pyridine ring 1·38 Å for C—C bonds and 1·35 Å for C—N bonds, 1·53 Å for the C—$CH_3$ distance, 1·36 Å for the C—$NH_2$ distance, 1·09 Å for C—H bonds and 0·9 Å for N—H bonds. The hydrogen-bonded N···N distance was taken as 3·06 Å. The dimer constructed in this way had approximate dimensions 6·5 × 12 Å. To conform with the unit-cell dimensions, the initial angular orientation of this trial model was chosen as follows: the dimer was placed on a centre of symmetry (0,0,0) in the *ac* plane with the hydrogen bond parallel to the crystallographic *a* axis.

Table 1. *Nonbonded potential parameters*

| Type | $d_0$ | $w$ |
|---|---|---|
| Me···Me* | 3·89 | 6·90 |
| Me···C | 3·65 | 3·69 |
| Me···N | 3·65 | 3·69 |
| Me···H | 3·07 | 5·50 |
| C···C | 3·47 | 2·42 |
| C···N | 3·47 | 2·42 |
| C···H | 2·86 | 3·45 |
| N···N | 3·47 | 2·42 |
| N···H | 2·86 | 3·45 |
| H···H | 2·36 | 3·23 |

* Me = methyl group, considered to be one 'atom' centred on the C position.

Table 2. *Final coordinates after least-squares refinement with X-ray data compared with results from molecular-packing analysis and MULTAN*

| | FINAL | WMIN | *MULTAN* | FINAL | WMIN | *MULTAN* | FINAL | WMIN | *MULTAN* |
|---|---|---|---|---|---|---|---|---|---|
| | | $x(\times 10^5)$ | | | $y(\times 10^4)$ | | | $z(\times 10^4)$ | |
| N(1) | 6757 (4) | 7000 | 6600 | −294 (2) | −330 | −360 | 71 (2) | −80 | −160 |
| C(2) | 6601 (5) | 6800 | 6700 | 582 (2) | 450 | 500 | 2095 (3) | 2000 | 2150 |
| C(3) | 10874 (5) | 11100 | 10900 | 863 (2) | 740 | 840 | 3430 (3) | 3260 | 3380 |
| C(4) | 15414 (5) | 15500 | 15300 | 277 (2) | 270 | 340 | 2627 (3) | 2480 | 2540 |
| C(5) | 15584 (5) | 15800 | 15400 | −596 (2) | −520 | −520 | 504 (3) | 410 | 580 |
| C(6) | 11216 (5) | 11500 | 11000 | −856 (2) | −810 | −850 | −678 (3) | −850 | −560 |
| C(Me) | 20035 (6) | 20300 | 19800 | 578 (2) | 560 | 550 | 4017 (3) | 3820 | 3890 |
| N(2) | 2118 (5) | 2400 | 2300 | 1252 (2) | 950 | 1030 | 2747 (3) | 2830 | 2900 |
| | | $x(\times 10^4)$ | | | $y(\times 10^3)$ | | | $z(\times 10^3)$ | |
| H(1) | −54 (8) | −70 | — | 87 (3) | 75 | — | 187 (4) | 193 | — |
| H(2) | 182 (7) | 220 | 17 | 171 (3) | 151 | 50 | 417 (4) | 432 | 451 |
| H(3) | 1055 (6) | 1090 | — | 144 (3) | 136 | — | 486 (3) | 490 | — |
| H(5) | 1896 (7) | 1920 | — | −104 (3) | −94 | — | −12 (3) | −32 | — |
| H(6) | 1123 (6) | 1170 | — | −143 (3) | −144 | — | −213 (4) | −253 | — |
| H(Me1) | 1942 (9) | — | — | 86 (4) | — | — | 554 (5) | — | — |
| H(Me2) | 2223 (10) | — | — | −37 (4) | — | — | 379 (6) | — | — |
| H(Me3) | 2169 (10) | — | — | 171 (4) | — | — | 353 (6) | — | — |

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* All crystallographic computer programs are described by Lundgren (1975).

Starting with this trial molecular orientation, the repulsion energy between molecules in the crystal was minimized according to the method of Williams (1969), which consists basically of moving a rigid molecule together with its symmetry-related mates within the fixed unit cell until a position of minimum energy is found. For this calculation the computer program *WMIN* (Busing, 1972) was used. The interatomic nonbonded repulsion energy of a pair of atoms was approximated by (Williams, 1969): $E_r = w(d_0 - d_{ij})^2$, $d_{ij} < d_0$, where $d_{ij}$ is a calculated interatomic distance for the model, and $d_0$ and $w$ are nonbonded potential parameters. These parameters were calculated by fitting quadratic functions with a well-documented set of (exp – 6) functions (Dentini, De Santis, Morosetti & Piantanida, 1972) and are given in Table 1. In the molecular-packing analysis the quantity minimized was $E_t = \frac{1}{2}\sum E_r$, where the sum is over all nonbonded interatomic distances between the reference molecule and the surrounding molecules. The variables in the minimization were the three rotations about the crystallographic axes, denoted by $R_x$, $R_y$ and $R_z$. The observed space group and unit-cell dimensions were used.

Two of the minimization techniques available within the program *WMIN* (the Rosenbrock search and the Newton minimization) were applied. The first resulted in a straightforward convergence of the trial model to a structure with a minimum energy $E_t = 0{\cdot}5$ (arbitrary units). A structure-factor calculation based on this model, using the 26 lowest-angle reflexions from the room-temperature data, resulted in a crystallographic discrepancy index $R = 0{\cdot}22$. Successful structure-factor least-squares refinement of the model proved it to be correct. Final values for the parameters $R_x$,$R_y$ and $R_z$ resulting from the energy minimization were 29·8, 32·4 and –10·4° respectively. These rotations gave rise to atomic shifts as large as 3·5 Å from the positions in the starting model.

Application of the Newton minimization technique to the initial trial model, as well as to a number of models with different initial angular orientations (up to 10° in $R_x$, $R_y$ and $R_z$), invariably resulted in a false minimum with $E_t = 9{\cdot}9$ (arbitrary units). Only models with $R_x$, $R_y$ and $R_z$ within about 15° of the correct value converged to the correct structure with this minimization technique.

In Table 2, the final structure models obtained by molecular-packing analysis, *MULTAN* (Declercq, Germain, Main & Woolfson, 1973)[*] and the least-squares refinement from X-ray data are compared.

## Structure refinement

The starting parameters for refinement of the structure of 2-amino-4-methylpyridine from the X-ray data were the parameters for the C and N atoms obtained in the molecular-packing analysis (Table 2). The structure was refined with the full-matrix least-squares program *UPALS*.

The function minimized was $\sum w(|F_o|^2 - |F_c|^2)^2$ where each reflexion was assigned a weight $w$ described above. The choice of this weighting scheme has been discussed above. After a few cycles of refinement, all the H atoms could be located from a difference Fourier synthesis. In the final cycles, one scale factor, one isotropic extinction parameter, 48 positional, 48 anisotropic and 8 isotropic thermal parameters were varied (in all 106 parameters). In order not to bias the refinement, all reflexions, even very weak ones, were included. Refinements using the two different data sets (I and II) gave almost identical results. No parameters differed more than 3$\sigma$ when independently determined from each of the two data sets. The data set II was somewhat arbitrarily chosen as the final set. The refined atomic coordinates are found in Table 2.[*] The final agreement factors are $R(F^2) = 0{\cdot}069$ and $R_w(F^2) = 0{\cdot}120$. The corresponding $R(F)$ is 0·041 if the 283 reflexions with $|F_o|^2 < 3\sigma(|F_o|^2)$ are excluded from the calculations. Atomic scattering factors for C and N were taken from *International Tables for X-ray Crystallography* (1974), and for H from Stewart, Davidson & Simpson (1965). Anomalous-scattering corrections were included for C and N atoms (Cromer & Liberman, 1970). One reflexion, 220, was excluded because of errors in the measurement.

## Discussion

### Packing arrangements and molecular structure

The packing in the structure is illustrated in Fig. 1.[†] The hydrogen-bonded dimeric units pack in layers perpendicular to the *a* axis. The two sets of dimers

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[*] It may be noted here that, although in general the molecular-packing analysis method is not competitive with other methods commonly used for the solution of the phase problem (*e.g.* *MULTAN*) because of the large amounts of computing time involved, in this particular case it is. The computing time required to converge the initial trial model to the correct structure model was 10 s of CDC 7600 time, with the very time-consuming Rosenbrock search technique. (The Newton minimization is about five times faster.) For comparison, the phase problem was also solved with the fully automated tangent-formula procedure *MULTAN*, which required 20 s CDC 7600 time to generate 16 solutions, to calculate an $E$ map and to do a peak search for the most probable (correct) solution.

[*] Lists of structure factors, anisotropic thermal parameters and r.m.s. components of thermal vibration along the major axes of the thermal ellipsoids have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32594 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

[†] All illustrations have been prepared with the plotting program *ORTEP* (Johnson, 1965).

within a layer have an angle of 56·8° between their respective planes. The shortest interdimeric contact is $N(2)(x,y,z)\cdots H(2)(x, \frac{1}{2}-y, -\frac{1}{2}+z)$, 2·57 (2) Å, with a corresponding $N(2)\cdots N(2)$ distance of 3·447 (2) Å and a $N(2)\cdots H(2)-N(2)$ angle of 164 (2)°. It is interesting to note that the H atom H(2) points towards the expected electron-lone-pair region of the amino N atom (*i.e.* perpendicular to the plane of the pyridine ring). The $C(3)-N(2)\cdots H(2)$ angle is 90 (1)° and the interaction is apparently strong enough to pull the N(2) atom 0·104 (1) Å out of the plane of the molecule (Table 3). The geometry of the interaction is close to that expected for a weak hydrogen bond (Kvick, 1974).

Table 3. *Deviations* (Å) *of the atoms from the least-squares plane through the six atoms marked with an asterisk*

The equation of the least-squares plane is

$$3{\cdot}662606x + 6{\cdot}428410y - 2{\cdot}668809z = 0{\cdot}044767.$$

| | | | |
|---|---|---|---|
| N(1)* | −0·005 (1) | H(1) | −0·006 (22) |
| C(2)* | 0·012 (1) | H(2) | 0·004 (20) |
| C(3)* | −0·007 (1) | H(3) | −0·029 (19) |
| C(4)* | −0·003 (1) | H(5) | 0·017 (20) |
| C(5)* | 0·008 (1) | H(6) | 0·019 (20) |
| C(6)* | −0·003 (2) | H(Me1) | −0·260 (30) |
| C(Me) | −0·012 (2) | H(Me2) | −0·477 (31) |
| N(2) | 0·104 (1) | H(Me3) | 0·907 (30) |

The layers are held together by van der Waals interactions between the methyl groups, which cluster together in non-polar zones also perpendicular to the *a* axis. The crystal structure of alternating hydrogen-bonded and van der Waals-bonded zones is very similar to that found in 2-amino-5-chloropyridine (Kvick & Backéus, 1974). The shortest distances between methyl H atoms are $H(Me1)(x,y,z)$ and $H(Me3)(x, \frac{1}{2}-y, \frac{1}{2}+z)$ 2·57 (4) Å and $H(Me2)(x,y,z)$ and $H(Me3)(\frac{1}{2}-x, -\frac{1}{2}+y, z)$ 2·70 (4) Å. The molecular geometry of 2-amino-4-methylpyridine is given in Fig. 2. The standard deviations have been estimated from the uncertainties in the atomic coordinates obtained in the form of a variance–covariance matrix from the last cycle of refinement. The effects of the uncertainties in the cell dimensions have also been taken into account.

Details of the mean plane through the skeleton of the pyridine ring are given in Table 3. The pyridine ring itself appears to deviate slightly from planarity with the largest out-of-plane displacement for atom C(2) [0·012 (1) Å]. The largest deviation for exocyclic atoms occurs for N(2) [0·104 (1) Å] except, obviously, for the methyl H atoms.

The dihedral angles across the C(4)–C(Me) bond looking from C(Me) towards C(4) are, in order, −16·8,

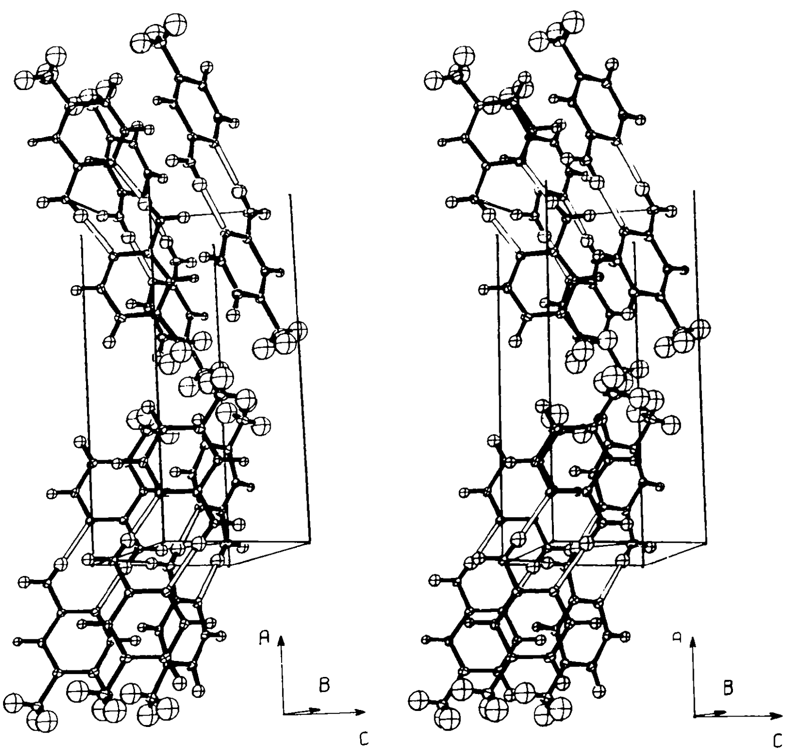

Fig. 1. Stereoscopic illustration of the crystal structure of 2-amino-4-methylpyridine. Covalent bonds are filled and hydrogen bonds are open; other short intermolecular contacts are represented by thin lines. The thermal ellipsoids are scaled to 50% probability.

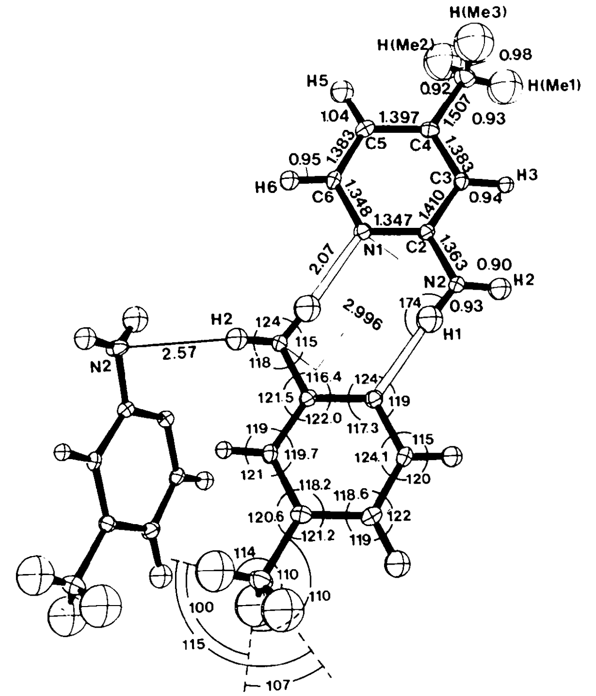

Fig. 2. Bond distances and angles. Estimated standard deviations are, for bond lengths, $\sigma_{X-X} = 0{\cdot}002$, $\sigma_{X-\mathrm{H}} = 0{\cdot}02$–$0{\cdot}03$ Å; for bond angles, $\sigma_{X-X\cdots X} = 0{\cdot}1$, $\sigma_{X-X-\mathrm{H}} = 1$, $\sigma_{X-X-\mathrm{H(Me)}} = 2$, $\sigma_{\mathrm{H(Me)}-X-\mathrm{H(Me)}} = 3°$. Covalent bonds are filled and hydrogen bonds are open; one short contact is represented by a thin line.

−147·5 and 94·5° when calculated from planes defined by C(3), C(4), C(Me) and C(4), C(Me), H(Me) where H(Me) was H(Me1), H(Me2) and H(Me3) respectively.

The molecular geometry of the six-membered ring is very similar to that found for 2-amino-5-chloropyridine (Kvick & Backéus, 1974). The double-bond character in the C(3)–C(4) [1·383 (2) Å] and C(5)–C(6) [1·383 (2) Å] bonds is more pronounced than in the C(2)–C(3) [1·410 (2) Å] and C(4)–C(5) [1·397 (2) Å] bonds. The two C–N bonds in the ring are shorter [1·347 (2), 1·348 (2) Å] than the bond to the amino group [1·363 (2) Å].

The C(2)–N(1)–C(6) angle [117·3 (1)°] is, as expected for a non-protonated ring N atom, smaller than 120°, and the N(1)–C(2)–C(3) [122·0 (1)°] and N(1)–C(6)–C(5) [124·1 (1)°] angles are enlarged.

## The hydrogen bond

Dimers are formed by hydrogen bonding between the N atoms. The N···N distance is 2·996 (2) Å and the bond is almost linear [N(2)–H(1)···N(1) = 174 (2)°]. The distance N(2)–H(1) is 0·93 (2) Å and H(1)···N(2) is 2·07 (2) Å, distances which also are affected by the non-spherical charge density for the H atoms. The accepted N(2)–H(1) distance should be about 0·1 Å longer.

The hydrogen bond appears to be slightly shorter than the N···N bond [N···N = 3·058 (3) Å] in 2-amino-5-chloropyridine, but longer than the N···N bond in the dimer of 6-chloro-2-hydroxypyridine: 2-pyridone [N···N = 2·904 (4) Å] (Almlöf, Kvick & Olovsson, 1971) where pyridine N atoms serve as both donor and acceptor atoms.

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