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The Crystal Structure of 2-Amino-4,6-dihydroxypyrimidine Determined from Powder X-Ray Synchrotron Diffraction

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The crystal structure of $C_4H_5N_3O_2$ (2-amino-4,6-dihydroxypyrimidine and tautomers) has been solved and refined from synchrotron X-ray powder data. The unit cell is monoclinic, with unit cell parameters at 15 K: $a = 6.9123(2)$, $b = 9.5658(3)$, $c = 3.5698(1)$ Å and $\beta = 93.218(2)°$; $Z = 2$. The space group is $P2_1/m$. The essentially planar molecules are arranged in sheets running in parallel with the {101} lattice planes. Whereas the contact between sheets is limited, extensive hydrogen-bridge bonding exists between the molecules within the sheet. The molecule itself is highly symmetrical with conjugated bonds between non-hydrogen atoms. An attempt to locate the hydrogen atoms has been made and the result indicates a disorder of the main tautomers: an '-ol' form with hydrogens at the oxygen atoms, a 'zwitterion' form with hydrogens at the heterocycle nitrogens, and/or less probable '-on' forms.

The small molecule derived from guanidine by condensation with malonic acid forms a remarkably stable solid phase, practically insoluble in organic solvents and water, having a melting point above 330 °C. The bonding in this heterocycle is highly symmetrical, particularly when the 2-amino-4,6-dihydroxypyrimidine tautomer is considered. The decreased nucleophile character of the N and O atoms due to the aromatic ring is reflected in the increased acidity of the hydroxy group and decreased basicity of the 'guanidine' nitrogens. Soluble salts are hence formed with both strong aqueous acids and bases,[1] but no single crystals suitable for structural determination have been obtained in this way. The high stability of this solid suggests the strong participation of hydrogen bonding in the molecular packing of the crystal structure. Several tautomers are feasible depending on the actual location of the 'protonic' hydrogens. In order to facilitate the determination of the crystal structure from powder data, synchrotron radiation has been employed and data were collected at low temperature in order to decrease temperature factors so that the location of the hydrogen atoms might be possible. The compound is an intermediate in an agrochemical process but the small size and flake-like habit of the crystals have led to processing problems which may be overcome through crystal growth modifications once the crystal structure is known.

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Experimental

The compound is obtained as a microcrystalline precipitate upon reaction of guanidine carbonate and diethyl malonate in ethanol.[1] This powder was ground and loaded into a 1.5 mm glass capillary which was then mounted in a cryostat which cooled the sample to 15 K. Three sets of diffraction data were collected at the x7a beamline at the National Synchrotron Light Source using the high resolution mode as described by Cox *et al.*[2] (wavelength $\lambda = 0.6993$ Å): (i) overall pattern from $4 < 2\theta < 54°$ in 0.01° steps and a count time of 4 s per point (see Fig. 1); (ii) low-angle pattern $4 < 2\theta < 20°$, 0.005° steps, 6 s per point; (iii) a high-angle region $20 < 2\theta < 54°$, 0.01° steps, 8 s per point. In all cases, the sample was oscillated by 4° during each data point.

An approximate unit cell for this compound had been previously obtained from an analysis of a room-temperature (RT) diffraction pattern assisted by parameters obtained from an electron diffraction study. The RT structure was solved (non-hydrogen atoms only) from this initial pattern by a combination of direct methods and computer modelling. Rietveld refinement of the 'low-temperature' structure was now carried out using GSAS[3] with the data provided by the three patterns noted above (11 600 data points).

The powder data were indexed on a monoclinic lattice and showed systematic absences for the condition $0k0$,

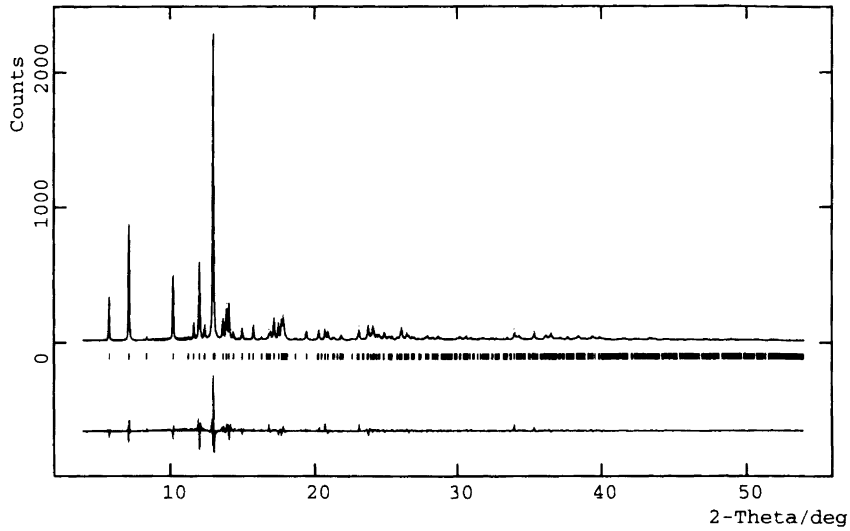


Fig. 1. Observed (dots) and calculated (curve) intensities of one of the three diffraction patterns collected at 15 K. The difference plot I(obs) − I(calc) is shown in the lower part of the illustration. The short vertical bars indicate the Bragg angle at which the reflections occur.

$k = 2n$ only, suggesting a $P2_1$ or $P2_1/m$ space group. The latter was chosen because it seemed to describe the structure adequately enough, although its use means that two H atoms per molecule must be disordered across the inversion centres. The other space group, $P2_1$, might allow for an ordered structure, but its refinement would certainly be burdened by high correlations, and was hence considered not feasible based on the powder data.

The molecular packing is characterized by the formation of sheets of the practically planar molecular rings. These sheets run parallel to the {101} lattice planes. The individual molecules are slightly tilted from this plane and occur in two orientations, one slightly above the sheet, one slightly below (Fig. 2). The average distance between the sheets of the molecules corresponds to d_{101} = 3.0967 Å, and these sheets are shifted against each other by approximately the C–N distance, in an arrangement distantly reminiscent of graphite. The perpendicular view upon the sheets of the non-hydrogen atoms (Fig. 3) reveals that all the nucleophile (Lewis basic) atoms of the neighbouring molecules face each other, and

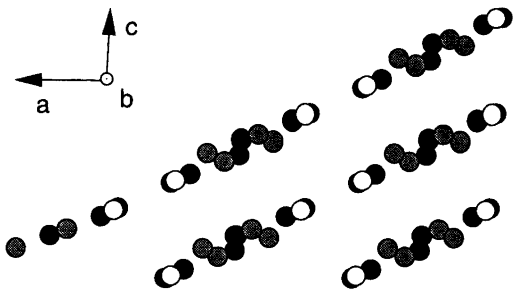


Fig. 2. Orientation of the planar molecules (without hydrogens) across the sheets. Atoms are represented as arbitrary circles: carbon, dark; nitrogen, shaded; oxygen, empty. Note the single molecule on the left, where the partially obstructing other molecule has been deleted.

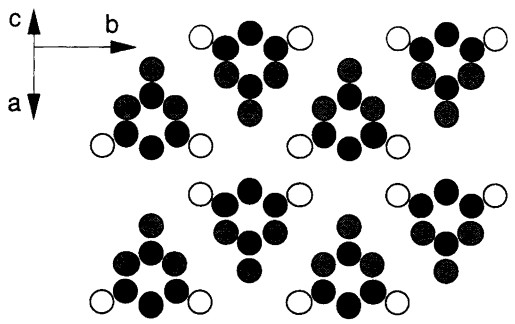


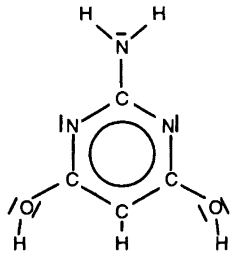
Fig. 3. Arrangement of the molecules (without hydrogens) within the sheet. Atoms are represented as arbitrary circles: carbon, dark; nitrogen, shaded; oxygen, empty.

this suggests intermolecular hydrogen-bonding (bridge) interactions.

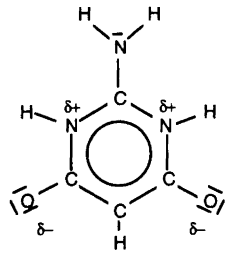
The bond distances (*vide infra* for final data) suggest that the molecule of the heterocycle is fully conjugated, and that situates two hydrogens in the amino group and one hydrogen in the CH group. The remaining two hydrogens can be regarded as proton precursors, and will hence assume positions at the remaining most basic (Lewis) centres of the molecule. There are three candidates for such a center: the oxygen, the heterocyclic nitrogen and the amino nitrogen. Due to the presence of the amino group and conjugation, all N atoms are weakly basic, comparably to the (keto) oxygens, and the conclusion is not *a priori* straightforward. This leaves the location of these two hydrogen atoms to the crystal structure refinements.

Difference Fourier maps based on the model of non-hydrogen atoms are calculated for finely scaled slices parallel with the sheet of the molecules. Peaks at the height of some 0.7 e Å^{-3} are clearly seen and assigned to the hydrogens of the amino group and hydrogen of

the CH group. No peak is seen at the possible locations in the vicinity of the lone pair position of the amino group, but maxima at some 0.3–0.4 e $Å^{-3}$ occur both in the vicinity of the heterocycle nitrogen and the oxygen atoms. On assumption of the fully conjugated ring, two tautomers occur as candidates for the solid state, *viz.*, the '-ol' form (**I**) with hydrogens situated at the oxygen atoms, and the 'zwitterion' form (**II**) with hydrogens at the heterocycle nitrogens.

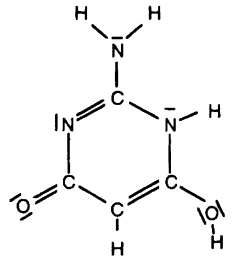


(I)

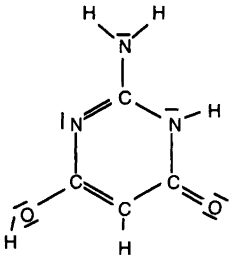


(II)

These two tautomers have the two hydrogen atoms in question distributed symmetrically according to the mirror plane of the $P2_1/m$ space group. Two other tautomers are possible, where the hydrogen atoms are distributed asymmetrically with respect to this mirror plane. This means that **III** and **IV** cannot be distinguished in the present space-group symmetry, as each of them would appear as a combination of **I** and **II**.



(III)



(IV)

In the subsequent refinements, several of the rejected possibilities were also tested, such as a CH_2 group, or a quaternary ammonium group NH_3^+, with clearly negative result. The tautomers **I** and **II** were hence assumed to be present in equal amounts, *viz.*, with the site occupancy of one half for the hydrogens in question. After the thermal parameters had also been refined for all atoms, both the coordinates and the unconstrained occupancy of these two 'protons' were refined, resulting in 0.54(2) for the '-ol' form and 0.47(2) for the 'zwitterion' form. Refinement also converged to the same result when each of these forms was chosen as a starting point, *viz.*, with initial site occupancies of 0.0 and 1.0, respectively. This distribution of hydrogen atoms is hence consistent with the equimolar mixture of tautomers **I** and **II**, or with the presence of tautomer **III** or **IV**.

The final crystal structure parameters, refined on the primitive monoclinic lattice and symmetry of the space group $P2_1/m$ (No. 11) with unique *b* axis, are listed in Table 1. The unit cell volume is 235.67(1) $Å^3$ and $Z = 2$, which gives a calculated density of 1.791 g cm^{-3}. Since the three sets of the raw data contained different proportions of the background and scattered intensity, the figures of merit of the refinement were different for these subpatterns, varying from $R(\text{Bragg}) = 0.032$ for the first 32 reflections [pattern (ii)] to 0.098 for 576 reflections [pattern (i)]. The total values were: $wRp = 0.131$, $Rp = 0.113$ and $DWd = 0.203$.

Discussion

The bond lengths (Fig. 4) between the non-hydrogen atoms of the heterocycle (calculated standard deviations are between 0.003 and 0.004 Å) conform to a fully aromatic ring, which is essentially planar. Only the C(3) atom (of the CH group) appears 0.024 Å off the C(2),C(1),C(2) plane of the ring and 0.048 Å off the N(1),N(2),N(1) plane. The slightly enhanced U_{iso} for this C(3) atom may reflect some orientational disorder; however, for the even larger U_{iso} of the C(1) 'guanidine' carbon there is no such simple explanation.

The distinction between the tautomers is constrained by the imposed mirror symmetry, but the bond lengths give some clues when compared with single-crystal-based data on similar pyrimidine-ring compounds with the guanidine segment. The refined bond lengths in Fig. 4

Table 1. Refined atomic coordinates, occupational and thermal parameters for 2-amino-4,6-dihydroxypyrimidine at 15 K. Space group $P2_1/m$, unit cell parameters: $a = 6.9123(2)$, $b = 9.5658(3)$ and $c = 3.5698(1)$ Å, $\beta = 93.218(2)°$. Isotropic thermal factors are used, defined as $T'' = \exp[-8\pi^2 U_{iso} \sin^2\theta/\lambda^2]$.

Atom	Site	Occupancy	*x*	*y*	*z*	$U_{iso}/Å^2$
O(1)	4*f*	1	0.1618(2)	−0.0004(2)	0.3521(5)	0.0106(8)
N(1)	4*f*	1	0.4122(3)	0.1267(2)	0.1400(7)	0.0104(9)
N(2)	2*e*	1	0.6758(5)	1/4	−0.0620(9)	0.0168(14)
C(1)	2*e*	1	0.4978(7)	1/4	0.0863(14)	0.0221(17)
C(2)	4*f*	1	0.2342(4)	0.1237(3)	0.2851(5)	0.0074(10)
C(3)	2*e*	1	0.1373(6)	1/4	0.3654(12)	0.0136(15)
H(1)	4*f*	1	0.740(3)	0.174(3)	−0.211(10)	0.239(16)
H(2)	2*e*	1	−0.006(4)	1/4	0.547(8)	0.008(10)
H(3)	4*f*	0.47(2)	0.449(5)	0.050(4)	0.067(11)	0.001(15)
H(4)	4*f*	0.54(2)	−0.023(5)	−0.024(4)	0.277(7)	0.005(15)

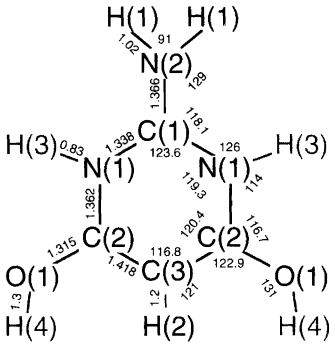


Fig. 4. Interatomic distances (Å) and bond angles (°) calculated from the refined structure data.

comply better with the highly symmetrical 2,4,6-triaminopyrimidine[4] than with isocytosine,[5] which is derived from the tautomer **III** by replacing the OH group by H. In particular, the C(2)–O(1) distance is longer than the 1.25 Å double bond seen in isocytosine. The N(2)–C(1) bond length is consistent with the conjugation typical of the amino nitrogen in aminopyrimidines.[4,6–8] The problem with the mirror symmetry constraint notwithstanding, these data could suggest that the tautomers **I** and **II** prevail in the present structure.

Other tautomers than **I**–**IV** are clearly excluded by the refined bond lengths. As an example, the C(2)–C(3) distance of 1.418 Å is clearly shorter than 1.49 Å for such a bond in the OC–CH_2–CO section of a pyrimidine-type ring,[9] and is close to the HC–CH–CH distance of 1.39 Å (at 271 K)[10] in the pyrimidine itself.

The bond lengths towards the hydrogen atoms are associated with largest errors (calculated standard deviations are between 0.03 and 0.04 Å). In particular, the H(2)–C(3) distance of the CH group is too long, and this could be associated with orientational disorder following the slight displacement of the C(3) atom. These H(2) atoms are also displaced some 0.26 Å from the C(2),C(1),C(2) plane of the ring. Also in the difference Fourier maps, the quite sharp maximum associated with the H(2) atoms seems to extend somewhat more above and below the molecular plane than for the other hydrogens. Nevertheless, this possible disorder did not refine successfully and also U_{iso} of the H(2) atom is quite normal. The H(3)–N(1) bond distance is practically identical with that for an analogously situated bond in uracil,[11] whereas the H(1)–N(2) bond of 1.02 Å in the amino group is somewhat long. However, the H(4) atom of the hydroxy group appears too distant from the O(1) atom. Both the amino- and particularly the hydroxy-group hydrogens clearly lie outside the plane [H(1) is 0.32 Å off the N(1),N(2),N(1) and H(4) is 0.66 Å off the C(2),C(1),C(2) plane, respectively] and it is possible that hydrogen-bridging effects have some influence on the actual bond distances. Otherwise, the structure refinements are surprisingly stable for these two hydrogen atoms. Refinements attempted with a hypothetical mirror disorder for the off-the-plane H(1) amino- and H(4) hydroxy-hydrogens do not support this kind of disorder and confirm the previous location. The three bonds at the amino N(2) atom seem to conform with the essentially sp^2 hybridization due to conjugation. The triangle is slightly tetrahedrally deformed in order to accommodate what remains of the lone pair on nitrogen. However, as seen in the following, the out-of-the-plane displacement of the amino- and hydroxy-group seems also to conform with the occurring hydrogen bonding.

Hydrogen-bond interactions are the most significant features of the intermolecular contacts in this crystal structure. All nitrogen and oxygen atoms seem to participate (cf. Fig. 3), and their orientation suggests that they (at least on average) both donate and accept hydrogen bonds. The list of the assumed intermolecular hydrogen-bonding interactions between these nucleophile atoms is given in Table 2. To a first approximation, the distances and angles are feasible except for the unusual geometry concerning the O(1)–H(4)···O(1) interactions. On closer analysis, however, it appears that the O(1) atoms are the only ones which participate (locally, not just on average) in two sets of hydrogen-bond interactions: (i) as an active O(1)–H(4) group with an H-bond donation towards the adjacent molecule's O(1), and (ii), as a Lewis base with an H-bond acceptance from the H(1) atom of the amino group of a third molecule in the same layer. These two interactions lie approximately in the same plane (different from the ring plane) with the conjugated O(1)–C(2) bond, and this suggests (deformed) sp^2 hybridization at O(1). The corresponding nearly triangular geometry of these three interactions at O(1) in turn imposes the unusual H-bond angle at the H(4) atom. The H-bond interactions seem to have another directional implication: the H(1) atoms of the amino group, which appear somewhat out of the plane of the ring, are displaced in such a manner that the N(2)–H(1)···O(1) intermolecular H-bond interactions are all approximately *in one plane* joining those respective molecules which lie slightly above and below in the molecular sheet of the structure packing. On the other hand, no H-bond interactions seem to occur between these sheets, as the closest interatomic distance, which by chance is the distance between an H(4) and an O(1) atom, is 2.40 Å.

Some other isomer molecules also arrange into similar structural sheets, like 6-azathymine[12] with density of 1.513 g cm^{-3}, but none of them is so efficiently packed as the presently investigated most symmetrical isomer of $C_4H_5N_3O_2$ having density of 1.791 g cm^{-3}. Its layered structure could indeed be dubbed a 'hydrogen-bond

Table 2. Intermolecular A–H···B hydrogen bonds (Å).

A	H	B	A···B	A–H	H···B	A–H···B
N(2)	H(1)	O(1)	2.86	1.02	1.88	161°
N(1)	H(3)	N(1)	2.91	0.83	2.10	170°
O(1)	H(4)	O(1)	2.53	1.31	1.69	114°

graphite'. However, in order to locate these hydrogen-bond interactions precisely, a neutron diffraction study of a deuteriated version is necessary.

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