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Structure of 4-Nitroimidazole

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Abstract. $C_3H_3N_3O_2$, $M_r = 113.08$, monoclinic, $P2_1/c$, $a = 7.093$ (1), $b = 9.926$ (1), $c = 7.3474$ (9) Å, $\beta = 119.02$ (1)°, $V = 452.3$ (1) Å³, $Z = 4$, D_m (293 K) = 1.63, $D_x = 1.66$ Mg m⁻³, $\lambda(\text{Cu } K\alpha) = 1.54178$ Å, $\mu = 1.18$ mm⁻¹, $F(000) = 232$, $T = 293$ K, final $R = 0.048$ for 702 unique observed reflections. Planar molecules of the 4-nitro tautomer (nitro group α to unprotonated N) are connected into ribbons along the **b** direction by N—H \cdots N hydrogen bonds.

Introduction. Nitroimidazoles are known to be effective radiosensitizers either as uncoordinated groups (Farrell, 1989; Adams, Clarke, Flockhart, Jacobs, Sehmi, Stratford, Wardman, Watts, Parrick, Wallace & Smithen, 1979; Brown, Yu, Brown & Lee, 1984) or when incorporated in Pt, Ru and Rh complexes (Bales, Mazid, Sadler, Aggarwal, Kuroda, Neidle, Gilmour, Peart & Ramsden, 1985; Farrell, Carneiro, Einstein, Jones & Skov, 1984; Chan, Skov, James & Farrell, 1986; Goodgame, Lawrence, Slawin, Williams & Stratford, 1986). The influence of nitro groups on the coordinating properties of these ligands has so far received little attention. As part of our ongoing interest in metal complexes with nitroimidazoles, we first determined the structure of the free 4-nitro derivative. In contrast with other simple imidazoles, this compound does not readily form good crystalline material. Since disordering related to tautomeric forms coexisting in the crystal could not be ruled out as a possible explanation for this peculiarity, efforts were made to obtain a suitable material with which this question could be examined by X-ray diffraction.

Experimental. The compound was purchased from Aldrich Chemicals. It is much less soluble in all

common solvents than imidazole and most of its derivatives. Attempts to grow crystals from water, dilute acids (HCl, HNO₃, H₂SO₄), alcohols, nitromethane and ethyl acetate, either by slow cooling of hot solutions or by slow evaporation of saturated solutions at room temperature, repeatedly produced microcrystalline or twinned materials. One crystallization in ethyl acetate yielded larger crystals, but oscillation photographs of many of them invariably showed twinning. With one specimen, the minor twin component appeared to be small enough not to give critical interference. The X-ray work was performed with this specimen.

Crystal size (pair of hkl faces): 0.14 (010/0 $\bar{1}0$) \times 0.19 (10 $\bar{1}$ /101) \times 0.24 (100/100) mm. D_m measured by flotation in benzene–1,2-dibromoethane. Data collected on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromatized Cu $K\alpha$ radiation. Unit-cell dimensions determined from 25 centered reflections ($20 \leq 2\theta \leq 25^\circ$). Laue symmetry and cell dimensions checked with long-exposure axial photographs along the three axes. No higher symmetry consistent with Niggli matrix. ω – 2θ scan, $\omega = (0.80 + 0.14 \tan \theta)^\circ$, $2\theta_{\max} = 140^\circ$. Orientation monitored every 200 measurements, intensity checked every hour with six standard reflections, fluctuations within $\pm 1.9\%$. 3355 reflections (eight octants) measured ($-8 \leq h \leq 8$, $-12 \leq k \leq 12$, $-8 \leq l \leq 8$). 853 independent hkl and $hk\bar{l}$ reflections after octant averaging ($R_{\text{av}} = 0.048$), 702 with $I \geq 1.96\sigma(I)$ retained for structure determination and refinement. Data corrected for Lp. No absorption correction applied.

Space group $P2_1/c$ uniquely defined by monoclinic Laue symmetry and systematic absences ($0k0$ $k \neq 2n$, $h0l$ $l \neq 2n$). All non-H atoms found by direct methods using *MULTAN80* (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). H atoms located from difference Fourier (ΔF) map.

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Since the compound was a good candidate for disorder, special care was taken to unambiguously identify the N and C atoms in the imidazole unit. Initially, the five ring atoms were defined as carbons (C*) and refined isotropically. Lower B_{iso} values provided a first indication that C*(1) and C*(3) were N atoms: C*(1), 2.68; C*(2), 3.94; C*(3), 2.67; C*(4), 3.42; C*(5), 3.70 Å². This was also consistent with an intermolecular N...N separation of 2.85 Å and favorable angles for hydrogen bonding. The non-H atoms were then refined anisotropically. H atoms attached to N(1), C(2) and C(5) were located on the next ΔF synthesis. The absence of significant residual electron density around N(3) and the different C—N—C angles (see *Discussion*) definitely support the presence of a single, ordered N(1)—H tautomer.

Full-matrix least-squares refinement on $|F|$, isotropic for H, anisotropic for non-H atoms. Function minimized: $\sum w(|F_o| - |F_c|)^2$, weights based on counting statistics [$w = 1/\sigma^2(F) + 0.001F^2$]. Five reflections (020, 040, 080, 100, 202) with large $|F_o| - |F_c|$ differences, affected by secondary extinction or twinning, were assigned zero weight. Final $R = 0.048$, $wR = 0.056$, $S = 2.35$ for 85 parameters refined. Maximum $(\Delta/\sigma) = 0.04$, average $(\Delta/\sigma) = 0.01$, background in final ΔF synthesis below $\pm 0.47 e \text{ \AA}^{-3}$. Scattering factors from Cromer & Mann (1968), except for H, from Stewart, Davidson & Simpson (1965). Refined coordinates are given in Table 1.†

Discussion. The crystal contains well ordered molecules of the 4-nitroimidazole tautomer (Fig. 1), which is the form also present in crystals of 2-methyl-4-nitroimidazole (Kálmán, Van Meurs & Tóth, 1980) and found to predominate in aqueous solution (Jimenez, Laynez, Claramunt, Sanz, Fayet, Vertut, Catalán, de Paz, Pfister-Guillouzo, Guimon, Flammang, Maquestiau & Elguero, 1989). The molecule, including the nitro group, is planar: the maximum deviation from the weighted least-squares plane through all non-H atoms is only 0.004 (3) Å (details in supplementary material). The dihedral angle between the five-membered ring and the nitro unit is 0.5 (4)°.

The bond lengths in the imidazole ring (Table 2) are in good agreement with those of 2-methyl-4-nitroimidazole (Kálmán *et al.*, 1980). As expected, C(2)—N(3) [1.318 (3) Å] shows greater double-bond

Table 1. Final coordinates ($\times 10^4$; H $\times 10^3$) and equivalent isotropic temperature factors ($\text{Å}^2 \times 10^3$)

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	U_{eq}
N(1)	4365 (3)	5083 (2)	1966 (3)	39
C(2)	5434 (4)	3968 (2)	2998 (4)	42
N(3)	4403 (3)	2856 (2)	2060 (3)	39
C(4)	2606 (4)	3320 (2)	354 (3)	34
C(5)	2547 (4)	4690 (2)	255 (4)	39
N(4)	1049 (3)	2412 (2)	-1086 (3)	40
O(1)	1365 (3)	1196 (2)	-767 (3)	56
O(2)	-540 (3)	2878 (2)	-2600 (3)	62
H(1)	489 (5)	583 (3)	239 (5)	67 (9)*
H(2)	684 (4)	408 (3)	432 (4)	52 (7)*
H(5)	160 (5)	525 (3)	-77 (4)	60 (8)*

* Isotropic temperature factors.

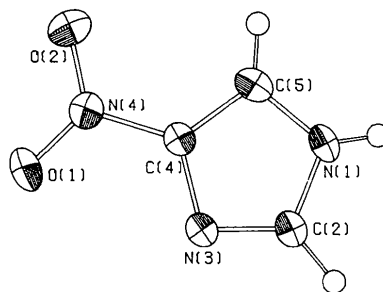


Fig. 1. Structure and numbering scheme of the 4-nitroimidazole molecule. Ellipsoids correspond to 50% probability.

character than N(1)—C(2) [1.348 (3) Å]. The geometry of a series of nitro derivatives is compared with that of unsubstituted imidazole in the supplementary material. No systematic influence of nitration on the ring bond lengths can be detected. The angles, however, are affected to a greater extent. Two effects discussed by other workers (Larsen, 1984; Craven, McMullan, Bell & Freeman, 1977) are superimposed. Nitration at C(2) (Larsen, 1984; Jenkins & Walton, 1988) or C(4) (Kálmán *et al.*, 1980; Solans & Font-Altaba, 1981, 1982) opens the internal angle at the substituted C atom by 2.1–2.4°, whereas the adjacent angles decrease by 1.1–2.5°. For nitration at C(5), a similar pattern is found, but the changes are only half as large (Blaton, Peeters & De Ranter, 1979a,b; Germain, Declercq, Van Meerssche & Koch, 1977). On the other hand, in absence of a nitro group, the lone pair makes the C—N—C angle 1.8° smaller than the angle at the N—H or N-alkyl site (Hsu & Craven, 1974; Craven *et al.*, 1977; McMullan, Epstein, Ruble & Craven, 1979; Wang & Craven, 1979). The large difference between C(2)—N(3)—C(4) and C(2)—N(1)—C(5) in this and other 4-nitroimidazole units (Kálmán *et al.*, 1980; Solans & Font-Altaba, 1981, 1982) results from the cooperative effects of the N lone pair and α -nitration. For

† A stereoview of the unit cell and lists of observed and calculated structure-factor amplitudes, anisotropic thermal parameters, distances to least-squares planes, and literature data on the geometry of nitroimidazoles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54430 (11 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Intramolecular distances (Å), bond angles (°) and intermolecular contacts (Å, °)*

N(1)—C(2)	1.348 (3)	C(5)—N(1)	1.349 (3)
C(2)—N(3)	1.318 (3)	C(4)—N(4)	1.420 (3)
N(3)—C(4)	1.363 (3)	N(4)—O(1)	1.229 (2)
C(4)—C(5)	1.361 (3)	N(4)—O(2)	1.227 (3)
N(1)—H(1)	0.82 (3)	C(5)—H(5)	0.91 (3)
C(2)—H(2)	1.00 (3)		
C(2)—N(1)—C(5)	108.0 (2)	N(3)—C(4)—N(4)	120.8 (2)
N(1)—C(2)—N(3)	112.0 (2)	C(5)—C(4)—N(4)	126.9 (2)
C(2)—N(3)—C(4)	103.4 (2)	C(4)—N(4)—O(1)	118.5 (2)
N(3)—C(4)—C(5)	112.1 (2)	C(4)—N(4)—O(2)	118.4 (2)
C(4)—C(5)—N(1)	104.4 (2)	O(1)—N(4)—O(2)	123.0 (2)
C(2)—N(1)—H(1)	120 (2)	N(3)—C(2)—H(2)	129 (1)
C(5)—N(1)—H(1)	132 (2)	N(1)—C(5)—H(5)	125 (2)
N(1)—C(2)—H(2)	118 (1)	C(4)—C(5)—H(5)	130 (2)
<i>A—H...B</i>	<i>A...B</i>	<i>H...B</i>	<i>A—H...B</i>
N(1)—H(1)...N(3)	2.871 (3)	2.06 (3)	167 (3)
N(1)—H(1)...O(2)	3.160 (3)	2.64 (3)	123 (3)
C(2)—H(2)...O(1)	3.115 (3)	2.42 (3)	125 (2)
C(5)—H(5)...O(1 ⁱⁱ)	3.454 (3)	2.57 (3)	163 (2)
C(2)—H(2)...O(2 ⁱⁱ)	3.290 (3)	2.43 (3)	143 (2)

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

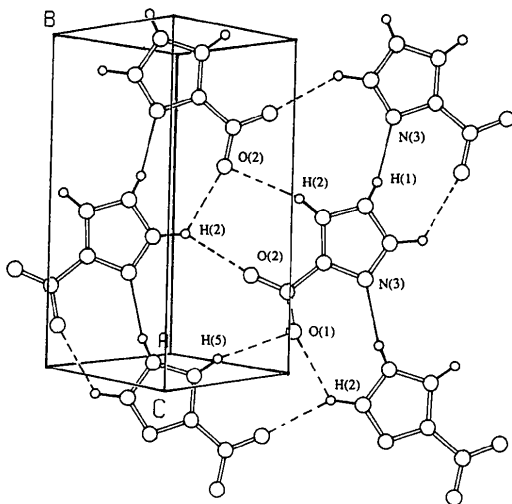


Fig. 2. Molecular layer parallel to the *b* axis and the *ac* diagonal. The unlabeled atoms can be identified by comparison with Fig. 1. Continuous lines correspond to hydrogen bonds and dashed lines to C—H...O contacts.

the 5-nitro compounds, these two effects are in opposite directions, making the two angles roughly equal (Blaton *et al.*, 1979*a,b*; Germain *et al.*, 1977). The nitro group itself shows no unusual features, its bond lengths and angles being similar to those found in the other nitroimidazoles.

Molecular packing (Fig. 2 and supplementary material) follows a pattern found in 2-nitro- (Larsen, 1984), 2-methyl-4-nitro- (Kálmán *et al.*, 1980) and unsubstituted imidazole (McMullan *et al.*, 1979): infinite chains of molecules are linked by N—H...N bonds along the *b* direction. The N...N separation

(Table 2) is typical of such systems and indicates moderately strong hydrogen bonding. A peculiarity of the 2-nitro and 4-nitro compounds is that the molecules along the chain are all coplanar. Cohesion along the resulting ribbon is helped by a dipolar interaction giving a short intermolecular contact of 2.42 (3) Å between H(2) and the nitro oxygen O(1). The ribbons define layers parallel to the *b* axis and the *ac* diagonal. Short C(2)—H(2)...O(1) and C(5)—H(5)...O(1) contacts of 2.43 (3) and 2.57 (3) Å, respectively, are found between molecules in adjacent ribbons. As suggested by Larsen (1984), the relatively high melting point and low solubility of this compound are probably related to these dipolar interactions. The interlayer separation of 3.12 Å corresponds to strong π interactions between aromatic rings.

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Structure of 1,1'-(5-Methyl-2,4-pyrimidinediyl)dipyridinium Dichloride Dihydrate

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Abstract. $C_{15}H_{14}N_4^{2+} \cdot 2Cl^- \cdot 2H_2O$, $M_r = 357.2$, triclinic, $P\bar{1}$, $a = 9.322$ (1), $b = 14.268$ (2), $c = 7.5902$ (9) Å, $\alpha = 94.22$ (1), $\beta = 113.867$ (8), $\gamma = 109.695$ (9)°, $V = 843.0$ (2) Å³, $Z = 2$, $D_x = 1.407$ g cm⁻³, $\lambda(Cu K\alpha) = 1.54178$ Å, $\mu = 36.49$ cm⁻¹, $F(000) = 372$, $T = 291$ K, $R = 0.035$, $wR = 0.038$ for 2092 observed reflexions. The methyl group influences the conformation of the dication. The pyrimidine (I) and two pyridinium (II and III) rings composing the dication are nearly planar but are strongly twisted with respect to each other [I/II 24.7 (4), I/III 53.5 (3), II/III 134.7 (4)°]. The two water molecules are hydrogen bonded to both Cl⁻ anions, forming clusters.

Introduction. Nucleic acid bases such as hypoxanthine, guanine, 1-methyluracil, 1-methylthymine and related *O*-protected nucleosides undergo a quantitative transformation into fluorescent monopyridinium salts when treated with various phosphorylating agents in the presence of pyridine (Adamiak, Biała & Skalski, 1985; Adamiak, Biała, Gdaniec, Mielewczyk & Skalski, 1986). Under analogous conditions xanthine, uracil and thymine are transformed into dipyridinium cations.

Unlike most of the monopyridinium derivatives (Jaskólski, Skalski, Adamiak & Adamiak, 1987) the dipyridinium compounds form crystals stable enough for X-ray analysis. Of particular interest in these structures is the spatial arrangement of the three rings composing the dication. Recently we have

reported the crystallographic structure of uracil-derived dipyridinium dichloride monohydrate which appeared to be nearly planar with only slight deviations from strict planarity for the two pyridinium rings (Jaskólski, Skalski & Adamiak, 1988). In this paper we present the structure of the thymine-derived analog, *i.e.* 1,1'-(5-methyl-2,4-pyrimidinediyl)dipyridinium dichloride dihydrate. It will be shown that the methyl substituent in the 5-position of the pyrimidine moiety of this salt imposes a significant steric hindrance which results in severe distortion from coplanarity of the three-ring system.

Experimental. The synthesis of the title compound is described elsewhere (Skalski, Wenska, Gdaniec & Adamiak, 1991). Suitable crystals were obtained from water. Space group from de Jong–Bouman photographs; crystal size 0.3 × 0.35 × 0.40 mm; Syntex P2₁ diffractometer, graphite monochromator, CuK α radiation. Cell parameters from least-squares treatment of setting angles of 15 reflexions ($40.2 \leq 2\theta \leq 87.5^\circ$). θ - 2θ profiles measured for 2269 unique $+h \pm k \pm l$ reflexions with $2\theta \leq 115^\circ$ [$\max. (\sin\theta/\lambda) = 0.547 \text{ \AA}^{-1}$] and with $0 \leq h \leq 10$, $-15 \leq k \leq 14$, $-8 \leq l \leq 7$; profile analysis according to Lehmann & Larsen (1974). No significant intensity variation for two standard reflexions recorded every 100 reflexions. No absorption correction. 2092 observed reflexions with $I \geq 2\sigma(I)$. Structure solved by direct methods using *SHELXS86* (Sheldrick, 1986). Full-matrix least-squares refinement on F , $w = \sigma^{-2}(F)$. All H atoms located in ΔF map and included in the refinement, anisotropic thermal parameters for

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