

# The Crystal Structure of Imidazole by Neutron Diffraction at 20°C and –150°C

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Imidazole,  $C_3H_4N_2$ , monoclinic space group  $P2_1/c$  with four molecules per cell, has lattice parameters  $a = 7.732$  (4),  $b = 5.458$  (2),  $c = 9.779$  (4) Å,  $\beta = 117.26$  (3)° at 20°C, and  $a = 7.582$  (2),  $b = 5.371$  (2),  $c = 9.790$  (3) Å,  $\beta = 118.98$  (2)° at –150°C. The neutron structure determinations were based on 835 reflections at 20°C and 590 reflections at –150°C. The final  $R$  values were  $R(F^2) = 0.046$  for 20°C and  $R(F) = 0.074$  for –150°C. Distances and angles in the strong hydrogen bond (N...N, 2.86 Å) are similar at both temperatures. No evidence was found for disorder of the hydrogen-bonding proton. Rigid-body thermal analysis gave appreciable bond-length and angle corrections even at –150°C.

## Introduction

Imidazole (Fig. 1) is a constituent of histamine and of the histidine residues of proteins. The strong N(1)H(1)···N(3) hydrogen bond which is formed in the crystal structure of imidazole is of interest because it may be representative of a state preparatory to the addition of a proton at N(3) or the exchange of a proton from N(1) to N(3). Such proton migrations involving histidine have been implicated in the enzyme mechanism of chymotrypsin (Blow, Birktoft & Hartley,

1969; Blow, 1976). The crystal structure of imidazole has been determined from photographic X-ray diffraction data at room temperature (Will, 1969) and at –150°C (Martínez-Carrera, 1966). Neutron determinations have now been carried out in order to obtain more accurate structure parameters, particularly for the H atoms. The neutron structure at –150°C has been described by Bell (1969) in greater detail.

## Experimental

### The structure at –150°C

An almost equidimensional crystal (2.5 mm) exhibiting the forms {100}, {110}, {001} was grown by slow (0.1°C/3 h) cooling of a saturated aqueous solution over the range 28 to 24°C. For data collection, the crystal was mounted on a vanadium pin with  $a^*$  along the diffractometer  $\varphi$  axis. The crystal was enclosed in an evacuated aluminum cryostat so that the vanadium pin was in contact with a hollow copper block which could be filled repeatedly with approximately 80 ml of liquid nitrogen. The temperature ( $-150 \pm 2^\circ\text{C}$ ) was monitored by means of a copper–constantan thermocouple touching the crystal. Lattice parameters for imidazole at –150°C (Table 1) were assumed to be those reported by Martínez-Carrera (1966). The neutron data were collected by  $\theta$ – $2\theta$  step scans on a four-circle diffractometer using the HIFAR reactor at the Australian Atomic Energy Establishment, Lucas Heights, NSW. A neutron beam of wavelength 1.075 Å

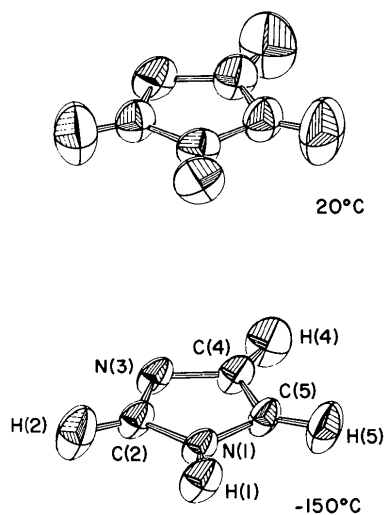


Fig. 1. Atomic nomenclature and 50% probability thermal ellipsoids for imidazole.

Table 1. *Crystal data for imidazole*

Monoclinic, $P2_1/c$ ; $Z = 4(C_3H_4N_2)$ /unit cell.		
	20°C, neutron	-150°C, X-ray*
$a$	7.732 (4) Å	7.582 (2) Å
$b$	5.458 (2)	5.371 (2)
$c$	9.779 (4)	9.790 (3)
$\beta$	117.26 (3)°	118.98 (2)°
$\lambda$	1.1690 (4) Å	1.5418 Å (Cu $K\alpha$ )

\* Values reported by Martinez-Carrera (1966).

was obtained by the (111) diffraction from a copper monochromating crystal. The data were corrected for absorption ( $\mu = 1.67 \text{ cm}^{-1}$ ) calculated from the mass absorption coefficient of  $23.9 \text{ cm}^2 \text{ g}^{-1}$  for hydrogen (Koetzle, 1976), and for the powder diffraction by the aluminum cryostat. Intensities were measured for 590 independent reflections with  $\sin \theta/\lambda < 0.57 \text{ \AA}^{-1}$  of which 90 were unobservably weak [ $I < 2\sigma(I)$ ]. The variance in an intensity was assumed to be  $\sigma^2(I) = I + B + (I_{\min} + 0.04I)^2$ , where  $I$  is the integrated intensity and  $B$  the total background, and  $I_{\min} = 200$  is an arbitrarily chosen small count.

The X-ray atomic parameter values (Martinez-Carrera, 1966) were used as initial values for full-matrix least-squares refinement in which the function to be minimized was  $\sum_h w(|F_o| - |F_c|)^2$ . The weak reflections [ $I < \sigma(I)$ ] were excluded from the refinement. The assumed nuclear scattering lengths ( $\times 10^{-12} \text{ cm}$ ) were C 0.665, H -0.372, and N 0.940. After the last four cycles of refinement, in which all atoms were assigned anisotropic temperature factors, all parameter changes were less than  $0.3\sigma$ . The final agreement indices† were  $R(F) = 0.074$ ,  $R_w(F) = 0.088$  excluding the 90 weak reflections, and  $R(F) = 0.082$ ,  $R_w(F) = 0.089$  for all data.

### The structure at 20°C

An almost equidimensional crystal (2.0 mm, 7.2 mg) was grown in one week by slowly cooling (33 to 29°C) a saturated benzene solution containing a trace of unidentified additives.‡ For data collection, the crystal was mounted on a silica glass fiber with  $c^*$  along the diffractometer  $\phi$  axis. The neutron data were collected using a four-circle diffractometer at the High Flux Beam Reactor of the Brookhaven National Laboratory.

†  $R(F) = \sum_h |A|/\sum_h |F_o|$ ;  $R_w(F) = \{(\sum_h wA^2)/\sum_h w|F_o|^2\}^{1/2}$ , where  $A = |F_o| - |F_c|$  and  $w = 1/\sigma^2(F_o)$ .

‡ The residual tar of a reaction mixture for preparing *N*-acetylpyrrole (Reddy, 1965) was found to contain large (5.0 mm) equidimensional crystals of imidazole (Schempp, 1976). A trace of this tar was added to the crystal growing solution in order to modify the habit of imidazole, which otherwise tends to form thin laths elongated on  $c$ .

The neutron wavelength, 1.1690 (4) Å, was determined by measuring the lattice parameters for a standard KBr crystal. Lattice parameters for imidazole (Table 1) were then calculated by a best least-squares fit to the angle settings for 25 reflections. There was a slow sublimation of the imidazole crystal as shown by the uniform decrease (12%) in the intensities of two monitoring reflections over the 108 h of data collection. The data were corrected for this and also for neutron absorption. Integrated intensities were measured by  $\theta$ - $2\theta$  step scans for 835 independent reflections ( $\sin \theta/\lambda < 0.65 \text{ \AA}^{-1}$ ) of which there were 58 with small but not significantly negative values. The variance in an integrated intensity was assumed to be  $\sigma^2(I) = I + B + (0.015I)^2$ .

The initial atomic positional parameters were taken from the structure determination at -150°C with an overall isotropic temperature factor which was assumed to be  $B = 3 \text{ \AA}^2$ . The assumed nuclear scattering lengths ( $\times 10^{-12} \text{ cm}$ ) were C 0.668, H -0.374 and N 0.940 (Shull, 1972, unpublished). The function  $\sum_h w(F_o^2 - F_c^2)^2$  was minimized by a full-matrix least-squares refinement. After introduction of anisotropic temperature factors, the refinement converged at  $R_w(F^2) = 0.15$ .\* At this stage, the strong-intensity reflections at small Bragg angles were found to have observed structure amplitudes consistently smaller than the calculated values. An isotropic secondary extinction

$$* R_w(F^2) = \{ \sum_h w(|F_o|^2 - |F_c|^2)^2 / \sum_h w|F_o|^2 \}^{1/2}, w = 1/\sigma^2(F^2).$$

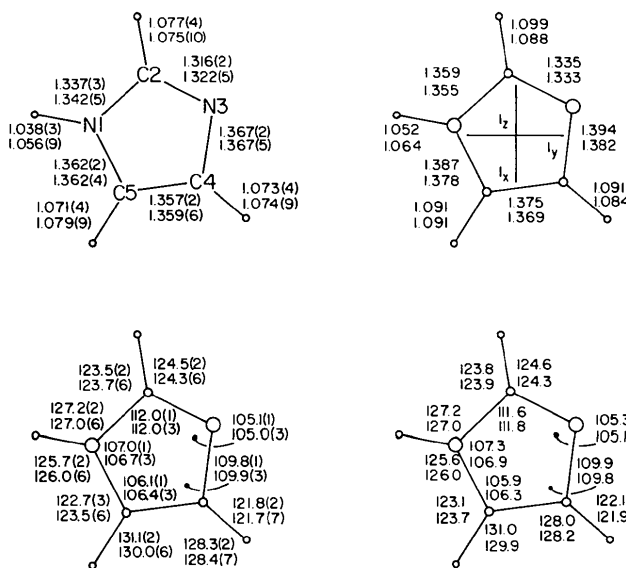


Fig. 2. Bond lengths (Å) and angles (°) for imidazole. The top value of each parameter is for the determination at 20°C. E.s.d.'s are given in parentheses. The right half of the figure contains distances and angles corrected for rigid-body librational motion. The axes shown on the molecule at top right are in the directions of the principal moments of inertia (see Table 3).

parameter was included (Coppens & Hamilton, 1970) and the refinement was completed. The final values of  $R(F^2)$  and  $R_w(F^2)$  were 0.046 and 0.058 respectively, and the final quadratic mean error\* was 1.026.

The pseudosymmetry of the imidazole ring (see Fig. 2 and *Discussion*) led to a concern that the crystal structure might contain molecules with H(1) bonded at N(3) as well as N(1). If the unit cell contained two hydrogen-bonded ribbons which were parallel rather than antiparallel as in Fig. 3(b), then the neutron space group would be  $Pc$  with reflections  $0k0$  no longer required to be absent for  $k$  odd. However, the measured intensities of such reflections ( $k \leq 7$ ) gave  $I < 0.6\sigma(I)$ , consistent with the assumed space group  $P2_1/c$ . After the refinement in space group  $P2_1/c$ , a final Fourier difference map showed no significant residual neutron scattering density. If there is a disordering of the hydrogen-bonding proton, it must involve less than about 5% of the molecules.

The final atomic parameters for both structure determinations are in Table 2.† It is of interest that extinction corrections were not needed in the low-temperature structure determination, whereas at room temperature, with the final extinction parameter  $g = 6220$  (400), some intensities were severely affected. The largest corrections were  $Y = 0.34, 0.45$  for reflections 200 and 002 respectively. Extinction effects may have been minimized in the low-temperature work by the

$$* \text{QME} = \{\sum w(|F_o|^2 - |F_c|^2)^2 / (n_{\text{obs}} - n_{\text{par}})\}^{1/2}.$$

† Structure factor and extinction factor tables and the anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32527 (21 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CHI 1NZ, England.

Table 2. Atomic parameters with *e.s.d.*'s

For each parameter, the first value is for 20°C and the second for -150°C. All parameters are  $\times 10^4$ . *E.s.d.*'s, given in brackets, refer to the least significant digit in the parameter value.

	<i>x</i>	<i>y</i>	<i>z</i>
N(1)	2192 (1) 2189 (4)	3304 (2) 3328 (5)	884 (1) 874 (5)
H(1)	2043 (4) 2046 (13)	2656 (5) 2659 (16)	-162 (3) -189 (9)
C(2)	1589 (2) 1578 (6)	2215 (2) 2196 (7)	1815 (1) 1795 (4)
H(2)	798 (5) 785 (19)	511 (6) 451 (18)	1544 (3) 1514 (11)
N(3)	2093 (1) 2085 (4)	3460 (2) 3468 (5)	3094 (1) 3089 (3)
C(4)	3084 (2) 3083 (6)	5453 (2) 5515 (7)	2970 (1) 2984 (4)
H(4)	3704 (6) 3713 (17)	6791 (7) 6881 (18)	3869 (4) 3898 (10)
C(5)	3155 (2) 3164 (6)	5379 (2) 5445 (7)	1609 (1) 1628 (4)
H(5)	3814 (6) 3871 (15)	6594 (7) 6710 (18)	1124 (4) 1183 (11)

differences in crystal-growing conditions and by the repeated warming and cooling of the crystal which was involved in the development of satisfactory operating conditions for the cryostat.

## Discussion

Hsu & Craven (1974) have pointed to some apparent differences in previously reported bond lengths and angles for imidazole. It now appears that these could be due to thermal motion effects for which X-ray structure determinations do not provide the usual rigid-body corrections (Schomaker & Trueblood, 1968). Difficulties arise in the case of imidazole because the ring atoms lie almost on an ellipse (Johnson, 1970) and because accurate X-ray anisotropic thermal parameters for the remaining H atoms cannot be obtained. However, there is a good fit of the rigid-body model to the neutron atomic thermal parameters (Table 3). The resulting r.m.s. librational amplitudes, which are largest (9.9° at 20°C, 8.0° at -150°C) about an axis nearly parallel to the N(1)→N(3) vector, give rise to appreciable thermal motion corrections, even at -150°C. The corrected distances and angles for the two neutron determinations are not significantly different (Fig. 2).\*

The ring atoms are coplanar (Table 4) with the H atoms all slightly displaced from this plane on the same side. The largest displacement (0.05 Å) involves H(1) and leads to a more nearly collinear N(1)–H(1)···N(3) hydrogen bond than would otherwise occur. It is noteworthy that the C(4)–H(4) and C(5)–H(5) bonds are subject to considerable in-plane bending away from the direction of the bisector of the ring angles at C(4) and C(5). The H–C–C angles (130°) are greater than the H–C–N angles (123°). A similar effect was reported for imidazole in the X-ray determination (Martinez-Carrera, 1966), in the 1:1 complex with barbital (Hsu & Craven, 1974), and in the imidazolium ion in imidazolium phosphate (Blessing & McGandy, 1972).

The presence of the NH bond at atom N(1) but not at N(3) gives rise to a perturbation from point symmetry  $2mm$  in the rest of the imidazole molecule. The internal ring angles at N(1) and N(3) differ by about 2°, the internal ring angles at C(4) and C(5) differ by almost 4°, and the N(1)–C(2) and N(3)–C(2) bond lengths differ by 0.02 Å. This perturbation is absent in the imidazolium ion in which both N atoms form NH bonds (Blessing & McGandy, 1972; Freeman, Huq, Rosalky & Taylor, 1975, and references cited therein). The most significant differences between imidazole and the imidazolium ion

\* A minor computational error which affected the dimensions of imidazole at -150°C as reported by Bell (1969) and quoted in Table 3 of the paper by Freeman, Huq, Rosalky & Taylor (1975) has been corrected in Fig. 2.

Table 3. *Rigid-body analysis of imidazole thermal motion*(1) Tensor components referred to the crystal axes  $a, b, c^*$ 

	20°C			-150°C		
Translational tensor, $T$ ( $\text{\AA}^2 \times 10^4$ )	424 (20)	61 (16) 493 (16)	76 (16) 15 (16) 336 (16)	509 (21)	69 (17) 242 (17)	93 (18) 38 (16) 222 (17)
Librational tensor, $L$ [ $(^\circ)^2$ ]	51 (2)	5 (2) 46 (5)	-21 (2) 12 (3) 86 (3)	27 (3)	6 (2) 28 (5)	-16 (3) 5 (3) 56 (3)
Cross tensor, $S$ [ $\text{\AA}^\circ \times 10^2$ ]	13 (6) 22 (4) -22 (4)	-10 (3) -2 (8) 1 (4)	17 (4) 8 (5) -11	2 (6) 8 (5) -5 (4)	-9 (4) -6 (8) -1 (5)	0 (4) 2 (5) 4

(2) R.m.s. differences  $(U_{ij})_{\text{obs}} - (U_{ij})_{\text{calc}}$  referred to axes  $a, b, c^*$ 

	0.003 $\text{\AA}^2$	(20°C)	0.003 $\text{\AA}^2$	(-150°C)
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(3) Principal axes of  $L$  and the angles which they make with the molecular axes of inertia ( $I_x, I_y, I_z$ , Fig. 2)

	20°C				-150°C			
		$I_x$	$I_y$	$I_z$		$I_x$	$I_y$	$I_z$
$L_1$	33.5 ( $^\circ$ ) <sup>2</sup>	90.5°	98.9°	8.9°	15.8 ( $^\circ$ ) <sup>2</sup>	90.6°	96.5°	6.5°
$L_2$	52.6 ( $^\circ$ ) <sup>2</sup>	8.9	91.0	81.1	33.1 ( $^\circ$ ) <sup>2</sup>	5.0	94.9	78.9
$L_3$	97.4 ( $^\circ$ ) <sup>2</sup>	89.1	1.2	89.4	63.3 ( $^\circ$ ) <sup>2</sup>	95.0	8.1	83.6

Table 4. *Best least-squares plane through the ring atoms*(1) The plane equations of the form  $Ax + By + Cz = D$ , referred to the crystallographic axes

	$A$	$B$	$C$	$D$ ( $\text{\AA}$ )
20°C	5.7144	-2.8027	0.4525	0.3679
-150°C	5.5648	-2.6931	0.4424	0.3637

(2) Atomic displacements from the plane for the ring atoms which form the plane

	20°C	-150°C
N(1)	-0.001 $\text{\AA}$	-0.003 $\text{\AA}$
C(2)	0.002	0.002
N(3)	-0.001	-0.001
C(4)	0.001	-0.001
C(5)	0.000	0.003

(3) Displacements of other atoms

	20°C	-150°C
H(1)	0.048 $\text{\AA}$	0.050 $\text{\AA}$
H(2)	0.015	0.019
H(4)	0.020	0.022
H(5)	0.014	0.036
N(3)*	0.311	0.299
H(4)†	-0.603	-0.533
H(5)†	-0.268	-0.169

\* N(3)' is hydrogen-bonded to N(1).

† These atoms form the shortest intermolecular H(4)···H(5) distances (Fig. 3).

occur in the C(2)–N bond lengths [1.337 (2), 1.316 (2)  $\text{\AA}$  in imidazole, and 1.324 (4)  $\text{\AA}$  in the imidazolium ion] and in the N(1)–C(2)–N(3) angle [112.0 (1)° in imidazole and 108.6 (1)° in the imidazolium ion; values uncorrected for thermal motion]. These comparisons suggest that proton transfer from N(1) to N(3) or proton addition at N(3) does not involve major changes in electronic structure, particularly when N(1) and N(3) are already engaged in strong hydrogen bonds such as those in the crystal structures of imidazole, imidazolium phosphate and imidazolium sulfate. In this respect, the imidazole moiety of histidine would appear to be well suited for mediating proton-transfer reactions in biological systems.

The hydrogen bond N(1)···N(3) distance (2.86  $\text{\AA}$ ) is the same for both neutron determinations and for the X-ray determination at -150°C (Martínez-Carrera, 1966). The neutron H(1)···N(3) distances are 1.83  $\text{\AA}$  at 20°C and 1.81  $\text{\AA}$  at -150°C and the N(1)–H(1)···N(3) angles are 173° at 20°C and 174° at -150°C. These parameters are not considered to be significantly different since they are subject to undetermined thermal motion corrections which are probably at least as great as the intramolecular distance and angle corrections.

The crystal structure of imidazole is shown by Martínez-Carrera (1966) in projections down the  $a$  and  $b$  axes. The projection normal to the plane of an

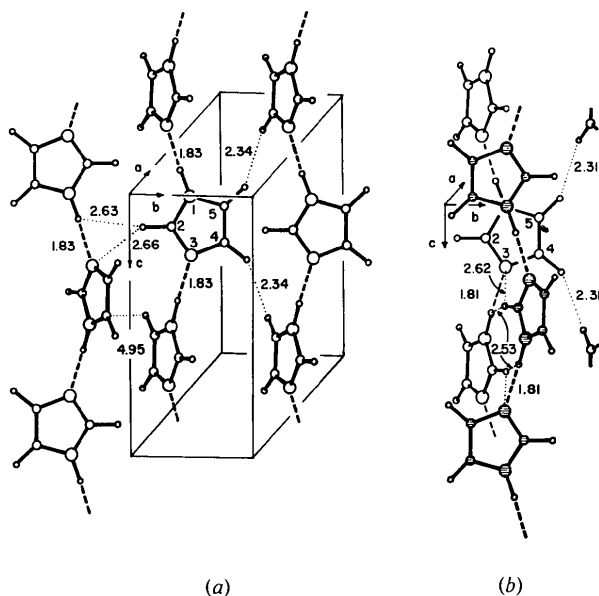


Fig. 3. The crystal structure of imidazole viewed normal to the plane of a molecule. (a) Distances (Å) for the structure at 20°C. (b) Distances (Å) for the structure at -150°C. The chain of molecules with shaded atoms is omitted from (a).

imidazole molecule (Fig. 3) shows additional features. The bond C(2)–H(2) points towards the hydrogen-bonding region between the H(1) and N(3) atoms of a neighboring ribbon. However, the H(2)···N(3) distance (2.66 Å at 20°C, 2.62 Å at -150°C) is too long to be an additional hydrogen-bonding interaction. The hydrogen-bonded ribbons are stacked so that each atom N(1) is superposed on another N(1) with N···N distances of 3.54 Å at 20°C, 3.42 Å at -150°C and each hydrogen-bonded proton H(1) is superposed on the center of a neighboring imidazole ring.

A comparison of the crystal structures at the two temperatures shows no significant change in the lattice parameter *c*. This is due to the similarity in the

parameters of the hydrogen bond which links the molecules in chains parallel to *c*. There is a small change in the dihedral angle between the planes of hydrogen-bonded molecules (60.2° at 20°C, 62.0° at -150°C) but the main difference is in the packing of the hydrogen-bonded chains. At 20°C, the center of mass for the molecule described in Table 2 has coordinates (0.95, 2.15, 1.77 Å) with respect to the axes *a*, *b*, *c*\* and the crystallographic origin. At -150°C, the center of mass is at (0.86, 2.13, 1.77 Å). Thus, the centers of this molecule and the centrosymmetrically related molecule in a neighboring chain are 0.19 Å closer at -150°C.

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