

The Crystal and Molecular Structure of 1-(3-Chloro-2-hydroxypropyl)-2-methyl-5-nitroimidazole (Ornidazole), $C_7H_{10}ClN_3O_3$

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Ornidazole, $C_7H_{10}ClN_3O_3$, crystallizes in the triclinic, space group $P\bar{1}$, with $a=13.605(2)$, $b=14.054(1)$, $c=8.913(5)$ Å, $\alpha=71.59(2)$, $\beta=78.73(2)$, $\gamma=64.86(1)^\circ$, $\mu=3.26$ cm $^{-1}$, $D_c=1.499$ g/cm 3 , $D_m=1.497$ g/cm 3 , $F(000)=684$, and $z=6$. Intensities for 2693 unique reflections were measured on a CAD4 diffractometer with graphite-monochromated Mo-K α radiation. The structure was solved by direct method and refined by block-diagonal least squares to a final R of 0.081 ($R_w=0.047$) for 1952 reflections with $F_o > 3\sigma(F_o)$. The asymmetric unit contains three independent molecules of the title compound. The bond lengths and bond angles are comparable with the values found in the other nitro-substituted compounds. The nitro groups are rotated (6.9° , 6.6° , 2.6° for the three independent molecule, respectively) about the C-N axes from the imidazole planes. The crystal structures are linked by two intermolecular hydrogen bonds of O-H—N type and one intermolecular hydrogen bond of O-H—O type.

Introduction

Nitroimidazoles are very often associated with antimicrobial activity, whereas imidazolines are often present in drugs acting as the adrenergic agents. These suggest, as a working hypothesis, that these particular imidazole derivatives are essential parts of the respective pharmacophores. The crystal structures of 5-nitro-substituted imidazole derivatives which are biologically active against both anaerobic protozoa and bacteria have been reported to obtain a better understanding of the structure-activity relationship.¹⁻⁵ The crystal structure of ornidazole has been determined to establish its solid state conformation and to compare the geometric properties with the other nitroimidazole derivatives.

Experimental

Pale-yellow, transparent crystals were grown at room temperature by slow evaporation from benzene-toluene (1:1) solution. The crystal density was measured in carbon tetrachloride and benzene by the flotation method. A crystal of approximate dimensions of $0.03 \times 0.13 \times 0.49$ mm was used for data collection with graphite-monochromated Mo-K α radiation on a CAD4 automated diffractometer. The cell constants and their estimated standard deviations were refined by least-squares methods from the setting angles of 25 reflections with $18^\circ < 2\theta < 23^\circ$. Total 3138 reflections were collected by the ω - 2θ scan mode with $\Delta\omega = (0.8 + 0.34 \tan\theta)^\circ$ in indices range of $-13 \leq h \leq 14$, $0 \leq k \leq 15$, $-9 \leq l \leq 9$ ($2\theta_{max} > 46^\circ$). Of these, 2693 reflections were considered as observed ($I_o \geq 1.2\sigma(I_o)$). Three standard reflections ($-2\ 6\ -1$), ($5\ 0\ 1$), ($4\ 1\ 1$) checked after every 200 reflections showed 0.3% intensity change during data collection. The intensity data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by the direct method (shelxs-86)⁶ and refined by block-diagonal least squares methods (shelx-76).⁷ The E map computed with the best set of phase showed all non-hydrogen atoms. Most hydrogen atoms were located from difference Fourier synthesis, but

the hydrogen atoms of methyl groups were calculated assuming an idealized geometry (1.08 Å). The structure was refined with anisotropic thermal parameters for non-hydrogen atoms and with isotropic thermal parameters for the hydrogen atoms. The refinement converged at the final $R=0.081$ and $R_w=0.047$. The final weighting scheme used was $\omega = k / [\sigma^2(F_o) + dF_o]^2$, where k and d were 1.929 and 0.00009. In the final cycle of refinement the maximum parameter shift $(\Delta/\sigma)_{max}$ was 0.07. The maximum and minimum residual density in the final difference map were 0.31 and -0.29 eÅ $^{-3}$, respectively. Atomic scattering factors for non-hydrogen atoms were taken from *International Tables for X-ray Crystallography*, those for H atoms from Stewart, Davidson & Simpson.⁸⁻⁹

Results and Discussion

The final atomic coordinates and equivalent isotropic thermal parameters are listed in Table 1. The bond lengths and angles are given in Table 2 and 3. The molecular structures with atomic numbering scheme are shown in Figure 1. The bond lengths in the imidazole ring are comparable with the values found by neutron diffraction for pure imidazole.¹⁰ The bond lengths of C(5)-N(12) vary from 1.409(11) to 1.434(14) Å for the independent molecules (II) and (III) in the unit cell. The mean bond length of 1.419(14) Å is slightly longer than those in the other nitroimidazole compounds. The two N-O bond lengths (from 1.208(12) to 1.229(11) Å) of the nitro groups agree very well with those observed in the other nitro-substituted compounds such as carnidazole, sulnidazole, metronidazole, tinidazole, misonidazole¹⁻⁵ and niridazole.¹¹ The imidazol rings in the three independent molecules are planar. The maximum deviations from the least square planes are 0.01 for C(4), 0.01 for C(4*) and 0.009 Å for C(4'), respectively. The nitro groups are rotated (6.9° , 6.6° , 2.6°) about the C-N axes from the imidazole planes. The N(1)-C(5)-C(4) angles vary from 106.9(8)° to 108.3(8)° for the independent molecules (II) and (III), respectively. These values are larger than those of imidazole. This pattern is probably

Table 1. The final atomic coordinates and equivalent isotropic thermal parameters of non-hydrogen atoms

atoms	x	y	z	Ueq	atoms	x	y	z	Ueq
molecule (I)					molecule (II)				
N(1)	8844(6)	4607(6)	2969(9)	0.032	N(1*)	1064(6)	9523(6)	1766(8)	0.033
C(2)	9719(8)	4184(7)	3803(11)	0.034	C(2*)	641(8)	10368(7)	2420(10)	0.036
N(3)	10426(6)	4649(7)	3187(10)	0.045	N(3*)	-406(6)	10623(6)	2866(8)	0.039
C(4)	9998(9)	5428(9)	1866(13)	0.048	C(4*)	-665(8)	9899(9)	2519(12)	0.044
C(5)	9013(9)	5432(8)	1708(13)	0.045	C(5*)	196(8)	9231(8)	1821(10)	0.035
C(6)	7883(8)	4325(9)	3408(14)	0.039	C(6*)	2194(8)	9040(8)	1136(12)	0.035
C(7)	7927(8)	3425(8)	2836(12)	0.037	C(7*)	2881(7)	8051(7)	2391(11)	0.030
O(8)	8489(4)	2428(5)	3903(7)	0.037	O(8*)	2864(5)	8364(5)	3769(8)	0.042
C(9)	6789(8)	3572(9)	2666(14)	0.041	C(9*)	4040(9)	7647(1)	1710(15)	0.054
CL(10)	6763(2)	2455(2)	2187(3)	0.048	CL(10*)	4849(2)	6398(2)	3033(3)	0.071
C(11)	9908(14)	3291(12)	529(17)	0.059	C(11*)	1282(13)	10949(12)	2607(25)	0.064
N(12)	8307(8)	6077(7)	474(11)	0.056	N(12*)	273(7)	8393(6)	1202(9)	0.042
O(13)	8529(7)	6795(6)	-493(9)	0.090	O(13*)	-583(6)	8299(5)	1202(7)	0.058
O(14)	7525(6)	5885(6)	412(9)	0.083	O(14*)	1138(5)	7780(5)	729(8)	0.062
molecule(III)					O(8')				
N(1')	3781(5)	11501(6)	-5121(9)	0.037	O(8')	2381(6)	13835(7)	-5333(10)	0.053
C(2')	3394(7)	11128(9)	-3623(13)	0.043	C(9')	3750(9)	14302(10)	-7194(16)	0.073
N(3')	3192(6)	10255(7)	-3478(10)	0.052	CL(10')	2804(2)	15548(2)	-8229(3)	0.075
C(4')	3458(8)	10053(8)	-4919(14)	0.048	C(11')	3197(13)	11608(15)	-2249(17)	0.063
C(5')	3802(7)	10816(7)	-5935(11)	0.031	N(12')	4149(6)	10918(8)	-7584(12)	0.057
C(6')	4092(9)	12444(9)	-5632(14)	0.041	O(13')	4414(6)	11677(6)	-8352(8)	0.074
C(7')	3213(8)	13483(8)	-6475(13)	0.043	O(14')	4130(6)	10234(6)	-8149(9)	0.084

Table 2. The bond lengths (Å) of ornidazole

	molecule (I)	molecule (II)	molecule (III)
N(1)-C(2)	1.34(1)	1.34(1)	1.36(1)
N(1)-C(5)	1.40(1)	1.39(1)	1.37(1)
N(1)-C(6)	1.47(1)	1.47(1)	1.47(1)
C(2)-N(3)	1.33(1)	1.32(1)	1.33(1)
C(2)-C(11)	1.49(2)	1.48(2)	1.51(2)
N(3)-C(4)	1.36(1)	1.34(1)	1.35(1)
C(4)-C(5)	1.37(2)	1.34(1)	1.36(1)
C(5)-N(12)	1.41(1)	1.41(1)	1.43(1)
C(6)-C(7)	1.48(1)	1.54(1)	1.52(2)
C(7)-O(8)	1.41(1)	1.42(1)	1.40(1)
C(7)-C(9)	1.50(1)	1.50(2)	1.53(2)
C(9)-CL(10)	1.77(1)	1.80(8)	1.76(1)
N(12)-O(13)	1.21(1)	1.23(1)	1.23(1)
N(12)-O(14)	1.22(1)	1.22(1)	1.23(1)

due to the electron withdrawing properties of the nitro-group and is also observed in the other nitroimidazoles.¹²⁻¹⁴ The lone-pair-induced alternations of the bond angles at N(1) and N(3) are also observed. In imidazole and 2-nitroimidazole the C(2)-N(1)-C(5) angles are significantly larger than the C(2)-N(3)-C(4) angle. The same results have been found in 2-methyl-4-nitroimidazole,¹⁴ carnidazole and sulnidazole. But in ornidazole, the C(2)-N(3)-C(4) angles are larger than C(2)-N(1)-C(5) angles for the three independent molecules in asymmetric unit, and the same pattern has been found in

Table 3. The bond angles (°) of ornidazole

	molecule (I)	molecule(II)	molecule(III)
N(3)-C(2)-N(1)	113.4(8)	112.4(8)	111.8(9)
C(4)-N(3)-C(2)	106.0(8)	105.4(7)	105.9(8)
C(4)-C(5)-N(1)	107.2(9)	106.9(8)	108.3(8)
C(5)-N(1)-C(2)	104.5(7)	104.6(7)	104.8(7)
C(5)-C(4)-N(3)	108.9(9)	110.6(8)	109.2(8)
C(6)-N(1)-C(2)	126.4(8)	126.5(8)	124.2(8)
C(6)-N(1)-C(5)	128.9(8)	128.9(7)	131.0(8)
C(7)-C(6)-N(1)	116.1(8)	111.1(8)	113.2(8)
O(8)-C(7)-C(6)	108.7(8)	110.4(7)	107.5(9)
C(9)-C(7)-C(6)	109.4(8)	108.3(8)	105.8(8)
C(9)-C(7)-O(8)	112.5(8)	107.8(7)	110.6(8)
CL(10)-C(9)-C(7)	112.1(7)	110.2(8)	110.0(7)
C(11)-C(2)-N(1)	125.1(10)	123.4(9)	126.4(10)
C(11)-C(2)-N(3)	121.5(10)	124.1(9)	121.8(10)
N(12)-C(5)-N(1)	124.4(9)	123.6(8)	123.8(8)
N(12)-C(5)-C(4)	128.3(10)	129.5(9)	127.9(9)
O(13)-N(12)-C(5)	117.1(9)	116.0(7)	119.7(8)
O(14)-N(12)-C(5)	119.8(9)	122.3(8)	116.3(8)
O(14)-N(12)-O(13)	123.2(9)	121.7(7)	124.0(10)

1,3-bis(carboxymethyl)-imidazole¹⁵ and metronidazole. A common feature of the imidazole ring is that C(2)-N(3) bond is the shortest in most cases, indicating a more or less localized double bond between these atoms. In the ornidazole the C(2)-N(3) bond lengths vary from 1.323 to 1.330 Å with

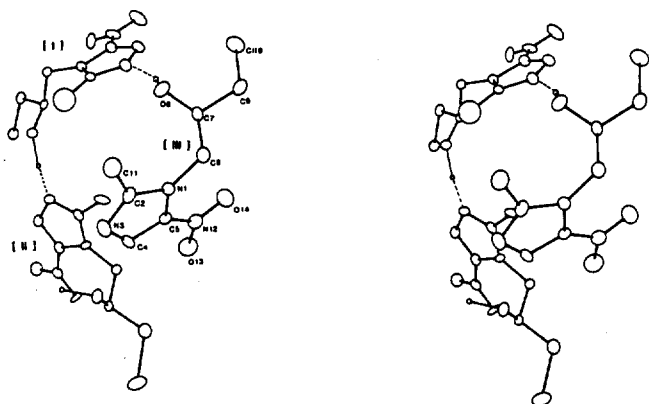


Figure 1. Stereoscopic drawing of the molecular structure with numbering scheme Dotted lines indicated intermolecular hydrogen bonding.

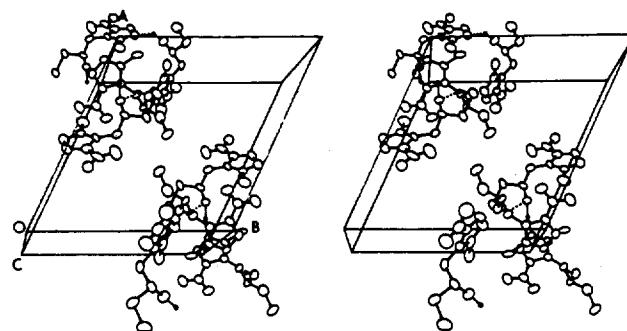


Figure 2. Stereoscopic drawing of the crystal packing Dotted lines indicated intermolecular hydrogen bonding.

Table 4. comparison of bond lengths (Å) and angles (°) in imidazole ring of ornidazole

	ORN 1	ORN 2	ORN 3	MEAN	SUL	CAR	MET	TIN	IMI	MIS
N1-C2	1.337(11)	1.334(11)	1.361(14)	1.344(14)	1.349(4)	1.341(4)	1.351(2)	1.357(4)	1.342(5)	1.359(3)
C2-N3	1.325(12)	1.323(12)	1.342(12)	1.330(12)	1.315(4)	1.343(5)	1.334(2)	1.335(4)	1.332(5)	1.308(3)
N3-C4	1.355(14)	1.342(12)	1.350(14)	1.349(14)	1.367(4)	1.357(5)	1.359(2)	1.354(5)	1.367(5)	1.366(3)
C4-C5	1.372(15)	1.338(14)	1.335(14)	1.348(15)	1.335(4)	1.355(5)	1.356(5)	1.362(4)	1.359(6)	1.356(3)
C5-N1	1.401(13)	1.393(12)	1.365(10)	1.386(13)	1.356(4)	1.401(5)	1.383(2)	1.388(4)	1.362(4)	1.362(3)
N1-C6	1.470(12)	1.468(13)	1.471(13)	1.470(13)	1.471(5)	1.475(4)	1.475(2)	—	—	1.466(3)
C2-C11	1.486(17)	1.484(16)	1.506(18)	1.492(18)	1.479(6)	1.481(6)	1.479(3)	—	—	—
C5-N12	1.413(12)	1.409(11)	1.434(14)	1.419(14)	1.411(4)	1.401(5)	1.414(2)	1.412(4)	—	—
C5-N1-C2	104.5(7)	104.6(7)	104.8(7)	104.6(7)	106.5(3)	105.5(3)	105.5(1)	—	106.7(3)	104.5(2)
N1-C2-N3	113.4(8)	112.4(8)	111.8(9)	112.5(9)	111.1(3)	112.1(3)	111.5(1)	—	112.0(3)	113.8(2)
C2-N3-C4	106.0(8)	105.4(7)	105.9(8)	105.8(8)	106.3(3)	105.4(3)	106.2(1)	—	105.0(3)	104.2(2)
N3-C4-C5	108.9(9)	110.6(8)	109.2(8)	109.6(9)	108.5(3)	109.9(3)	109.1(1)	—	109.9(3)	110.0(2)
C4-C5-N1	107.2(9)	106.9(8)	108.3(8)	107.5(9)	107.5(3)	107.1(3)	107.6(1)	—	106.4(3)	107.6(2)

*ORN: 1-(3-Chloro-2-hydroxypropyl)-2-methyl-5-nitroimidazole(Ornidazole). *SUL: O-Methyl[2-(2-ethyl-5-nitroimidazol-1-yl)ethyl]thiocarbamate(Sulnidazole). *CAR: O-Methyl[2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl]thiocarbamate(Carnidazole) H₂O. *MET: 2-(2-Methyl-5-nitro-1-imidazolyl)ethanol(Metronidazole). *TIN: 1-[2-(Ethylsulfonyl)ethyl]-2-methyl-5-nitro-1H-imidazole(Tinidazole). *IMI: Imidazole. *MIS: α -(Methoxymethyl)-2-nitro-1H-imidazole-1-ethanol(Misonidazole).

a mean value of 1.326 Å, which are in good agreement with the value of the other imidazole derivatives. The three N(3)-C(4) bond lengths [mean value 1.346(14) Å] are intermediate between a double bond (1.265 Å) and a single bond (1.470 Å). A comparison of the major bond lengths and angles in the imidazole derivatives is summarized in Table 5. The propyl groups are twisted with respect to the imidazole rings as indicated by the torsion angles θ , χ and τ , where $\theta = [C2-N1-C6-C7]$, $\chi = [N1-C6-C7-C9]$ and $\tau = [C5-N1-C6-N7]$. These conformations are also observed in other nitroimidazoles.¹²⁻¹⁴ The torsion angles $\theta_1(89(1)^\circ)$, $\chi_1(153(1)^\circ)$ and $\tau_1(-97(1)^\circ)$ for the molecule (I) are very different from those values [$\theta_2(-95(1)^\circ)$, $\chi_2(176(1)^\circ)$, $\tau_2(85(1)^\circ)$, $\theta_3(98(1)^\circ)$, $\chi_3(170(1)^\circ)$ and $\tau_3(-82(1)^\circ)$] for the independent molecules (II) and (III). This is probably due to the strong intermolecular hydrogen bonds of hydroxyl group O(8)-H. The packing diagram is shown in Figure 2. The crystal structures are linked by two intermolecular hydrogen bonds of O-H...N type [O(8)-H...N(3*); 2.692(9) Å, 171.9(7)° and O(8')-H...N(3); 2.821

(10) Å, 162.5(7)°] and one intermolecular hydrogen bond of O-H...O(8)[1-x, 1-y, 1-z] type[2.779(9) Å, 158(6)°].

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Determination of Net Atomic Charges Using a Modified Partial Equalization of Orbital Electronegativity Method

V. Application to Silicon-Containing Organic Molecules and Zeolites

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The parameters for an empirical net atomic charge calculation method, Modified Partial Equalization of Orbital Electronegativity (MPEOE), were determined for the atoms in organosilicon compounds and zeolites. For the organosilicon family, the empirical parameters were determined by introducing both experimental and *ab initio* observables as constraints, these are the experimental and *ab initio* dipole moments, and the *ab initio* electrostatic potential of the organosilicon molecules. The Mulliken population was also introduced though it is not a quantum mechanical observable. For the parameter optimization of the atoms in the aluminosilicates, the dipole moments and the electrostatic potentials which calculated from the 6-31G** *ab initio* wave function were used as constraints. The empirically calculated atomic charges of the organosilicons could reproduce both the experimental and the *ab initio* dipole moments well. The empirical atomic charges of the aluminosilicates could reproduce the *ab initio* electrostatic potentials well also.

Introduction

Several empirical net atomic charge calculation methods have been developed for both saturated^{1,2} and unsaturated molecules.³⁻⁵ However, the parameters for each empirical method were developed mainly for typical organic molecules. The empirical methods are not suitable for the net atomic charge calculation of inorganic molecules, for example, zeolites. Since silicon shows similar chemical behavior with carbon, silicon is an important component of not only many inorganic compounds like zeolites but also organosilicon compounds.

Since *net atomic charge* is not a quantum mechanical *observable* in spite of the fact that it is one of the most important physical quantities in chemistry, many models have been proposed for calculating the net atomic charge. Two main roles of the magnitude of the net atomic charge are (i) to describe the deficiency or sufficiency of the electron population of the atom in a molecule and (ii) to reproduce the electrostatic potential around a given molecule.

The electrostatic interaction energy is an important component in the description of the intermolecular interaction energy of polar molecules. Therefore there are lots of efforts

to describe the electrostatic potential accurately. One of the most popular quantum mechanical approaches for point charge calculation is Mulliken population analysis method.⁶ Though the charges are calculated from the electron density of a molecule, the Mulliken charge poorly describes the electrical moments and the electrostatic potential which are calculated from quantum mechanical wave functions.

Momany⁷ and Cox and Williams⁸ calculated the point charges located on every atomic centers in a molecule using the electrostatic potentials as constraints, namely Potential Derived (PD) method. In the method, it was assumed that the point charges which can reproduce the electrostatic potential well can be a good representation for the electrostatic interaction. The dipole moments of molecules which calculated with the PD point charges usually agreed well with the experimental dipole moments when a large basis set is used for the *ab initio* electrostatic potential calculation. Though the PD charge set is a good representation for the electrostatic potential, the point charges are not transferable between the molecules which have similar chemical environments.

For the calculation of the point charges of large molecules, for example, proteins and nucleic acids, several empirical methods were proposed on *electronegativity equalization* concept introduced by Sanderson (Electronegativity Equalization

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