
**THE CRYSTAL AND ELECTRON STRUCTURE
OF N-(2,2,2-TRICHLORO-1-MORPHOLINO-ETHYL) FORMAMIDE**

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The crystal structure was solved by direct methods and refined by the least squares method in a 9×9 block diagonal approximation using the anisotropic temperature parameters. The *R*-factor was decreased to a final value of 5.6% for 970 observed reflexions. The crystals are monoclinic with a space group of $P2_1/c$ and lattice parameters of $a = 1.1056(11)$, $b = 0.8913(11)$, $c = 1.2023(16)$ nm, $\beta = 96.32^\circ$, and $Z = 4$. The crystal structure consists of discrete molecules between which hydrogen interactions of the N—H \cdots O and C—H \cdots O type were observed. The lengths of the N1—C3 (0.1432 nm) and C3—O1 (0.1203 nm) bonds and valence angles, C3—N1—C1 (119.9°), N1—C3—O1 (126.5°), indicate considerable delocalization of the π -electrons and participation of the lone electron pair on N1 nitrogen in the conjugation in the N1—C3—O1 molecular fragment. The CNDO/2 quantum chemical method was used to calculate the electron structure. Calculation for partial optimization of the dihedral angles, φ and ω , indicated that the most stable form is obtained for the values $\varphi = 0^\circ$, $\psi = 120-150^\circ$, $240-270^\circ$ and $\omega = 150-210^\circ$, $330-30^\circ$.

N-(2,2,2-trichloro-1-morpholino-ethyl) formamide, termed trimorphamide, is a new grain mould fungicide developed in the laboratories of the Research Institute for Chemical Technology, Bratislava. It is the active substance in the products Fademorf EC 20 and Fademorf DP 50 against pathogens of the *Erysiphacaea* species and is absorbed by both the roots and the part of the plant above the ground.

As the trimorphamide molecule contains one optically active carbon, there are two optically active forms of the molecule one of which is biologically active.

This work was carried out in order to solve the crystal molecular and electron structure of trimorphamide in order to find the relationship between the absolute configuration of the optically active molecule and its biological activity.

EXPERIMENTAL**Preparation of the Substance and its Basic Crystallographic Parameters**

N-(2,2,2-Trichloro-1-morpholino-ethyl)formamide was prepared in three stages.

N-(2,2,2-Trichloro-1-hydroxyethyl) Formamide

An amount of 181.8 g (1.2 mol) of chloral was added to 54 g (1.2 mol) formamide in 500 ml toluene with stirring at the reflux temperature. The mixture was stirred at this temperature for 30 min. and then cooled to 5°C. The precipitated product was separated by filtration and washed with toluene. In this way, 205.8 g of chloralformamide with a m.p. of 123–124°C was obtained, corresponding to a yield of 89%.

N-(1,2,2,2-Tetrachloroethyl) Formamide

An amount of 71.4 g of thionyl chloride (0.6 mol) was added to 96.2 g N-(2,2,2-trichloro-1-hydroxy-ethyl) formamide (0.5 mol) in 300 ml toluene with stirring at 70°C. The mixture was refluxed and stirred for 3 h. After cooling to 10°C, the precipitated product was separated by filtration and washed with toluene. An amount of 94.6 grams of product with a m.p. of 98–100°C was obtained, corresponding to 89% yield.

N-(2,2,2-Trichloro-1-morpholino-ethyl) Formamide¹

A solution of 42.6 g N-(2,2,2-tetrachloroethyl) formamide (99%) (0.2 mol) in 150 ml of toluene was added to a mixture of 18.8 g (0.21 mol) morpholine (97%), 8 g (0.2 mol) NaOH and 45 ml water with rapid stirring and cooling. The temperature was maintained at 20–25°C by cooling. After completion of the addition, this temperature was maintained in the stirred mixture for a further 15 min. The mixture was then heated to 65°C and then transferred to a separating funnel and the lower layer was separated from the toluene solution of the product. The toluene was distilled off at reduced pressure to dryness. An amount of 52.6 g of the product was thus obtained, corresponding to a yield of 89%. Recrystallization of this product yielded two types of crystals with different shape, melting point and colour. The substance was dissolved in toluene and heated to a temperature above 70°C; on cooling, colourless to pale pink rod-like crystals with sharp edges precipitated. The m.p. of these crystals was 112–115°C. The purity of this substance was confirmed by elemental analysis for C, H, N on a Carlo Erba Model 1102 instrument. For C₇H₁₁N₂O₂Cl₃ (261.5) calculated 32.14% C, 4.24% H, 10.71% N; found 32.04% C, 4.28% H, 10.72% N. A crystal density of 1.45(2) · 10³ kg m⁻³ was measured by the flotation method in a saturated ZnSO₄ solution. The calculated density for four formula units per unit cell is 1.47 · 10³ kg · m⁻³.

A crystal in the form of a rhombic prism with dimensions of 0.2 · 0.2 · 0.3 mm was selected for obtaining the basic crystallographic data and for intensity measurements.

Systematic absence of reflections of the $h0l$ type for $l = 2n + 1$ and $0k0$ type for $k = 2n + 1$ unambiguously indicated² the presence of a centrosymmetric space group with $P2_1/c$ symmetry². The dimensions of the unit cell found from oscillation and Weissenberg patterns were refined by the least squares method using 8 centred reflections. The integral intensity was measured using a four-ring computer-controlled Syntex P2 diffractometer equipped with a scintillation counter and pulse height analyzer. Nickel monochromated CuK α radiation was used with generator working parameter of 46 kV/20 mA and scanning technique $\Theta : 2\Theta$. The crystal was recentered

after each 500 intensity measurements. The intensity was recorded in the range $0^\circ < 2\theta \leq 100^\circ$. Of the total of 1 605 symmetric, independent reflections, 970 were classified as "observed" and used in the final structure solution. All the intensities were corrected for the Lorentz and polarization factors and converted to an absolute scale. Correction for absorption was neglected. Table I lists the basic crystallographic data for trimorphamide.

Solution and Refinement of the Structure

The structure was solved by direct methods. The positions of the three chlorine atoms was found from the *E*-map calculated from *E*-values greater than 1.4. The positions of the remaining atoms in the trimorphamide molecule (O, N and C) were found by step-wise application of Fourier synthesis of the electron density. After determining the positions of all the non-hydrogen atoms, the structure was refined in three cycles by the least squares method, isotropic thermal parameters and unit weighing schemes. In the next 5 cycles of the refinement, the anisotropic thermal vibrations of all the atoms were assumed and were refined together with the positional parameters by the least squares method using minimization function $\sum w(|F_0| - |F_c|)^2$; in the 9×9 block-diagonal approximation the *R*-factor, defined as $\sum ||F_0| - |F_c|| / \sum |F_0|$, decreased to a value of 0.06.

Introduction of hydrogen atoms into the trimorphamide structure, with positions determined from the differential Fourier map and further isotropically refined, decreased the *R*-factor after 4 refinement cycles to a final value of $R = 0.056$ ($R_w = 0.055$). In the last structure refinement cycle, the shifts in the positional parameters of all the non-hydrogen atoms were less than 0.2σ . The differential Fourier synthesis of the residual electron density did not exhibit significant fluctuations. The highest electron maximum $0.45 \cdot 10^3 \text{ e nm}^{-3}$ appeared at positions corresponding to the chlorine atoms. The scattering factors for the neutral atoms and the atomic absorption coefficients were taken from the tables³. The refined fractional atomic coordinates and their thermal parameters are given in Tables II and III. The interatomic bonding distances and valence angles are listed in Tables IV and V. Fig. 1 depicts projection of the structure onto the (010) plane.

All the calculations were carried out on the XTL module Syntex P2₁ instrument using a Siemens 4004/150 computer.

Calculation of the Electron Structure

The quantum chemical CNDO/2 method was used to calculate the electron structure, explicitly considering all the valence electrons⁴. As the trimorphamide molecule has a large number of variable geometric parameters, the calculation was limited to partial optimization of the three dihedral angles φ , ψ and ω (Fig. 2). The optimization step was 30° . The angle φ defines the deviation from planarity of the formamide part, *i.e.* the rotation of the N1, H1, Cl plane and H3, C3, O1 semi-plane around the C3—N1 bond. The angle ψ is the dihedral angle in the order C3—N1—C1—C2, representing rotation of the formamide part around the C1—C2 axis at the asymmetric centre. The angle ω is the dihedral angle C5—N2—C1—C2 and represents rotation of the morpholine cycle around the C1—C2 axis.

The remaining geometry was considered fixed with the following general parameters⁵: C3—O1 0.120 nm, C—H 0.106 nm, C3—N1 0.134 nm, N1—C1, C1—N2, N2—C5 and N2—C7 0.144 nm, C4—O2 and C6—O2 0.140 nm, all the C—C bonds 0.152 nm and C—Cl bonds 0.175 nm.

The bonding angles were considered, depending on the hybridization, — sp^2 -centres to equal 120° and sp^3 -centres to equal 109.5° . sp^2 hybridization was considered to be present for the C3, N1 and O1 atoms; for the others, sp^3 hybridization was considered.

TABLE I
Basic crystallographic data for trimorphamide

Empirical formula	$C_7H_{11}N_2O_2Cl_3$	Unit cell volume	$V = 1.1775(24) \text{ nm}^3$
Relative molecular mass	261.5	Number of formula units per unit cell	$Z = 4$
Crystallographic system	monoclinic	Number of electrons per unit cell	$F(000) = 536$
Space group	$P2_1/c$	Experimental crystal density	$D_0 = 1.45(2) \cdot 10^3 \text{ kg m}^{-3}$
Unit cell dimensions and the corresponding standard deviations	$a = 1.1056(11) \text{ nm}$ $b = 0.8913(11)$ $c = 1.2023(16)$ $\beta = 96.32(10)^\circ$	Calculated density	$D_c = 1.47 \cdot 10^3 \text{ kg m}^{-3}$
		Linear absorption coefficient	$\mu(\text{CuK}\alpha) = 6.9 \text{ mm}^{-1}$
		Melting point	112–115°C

RESULTS AND DISCUSSION

Fig. 1 depicts the distribution of the molecular units of trimorphamide in the unit cell projected onto the (010) plane. All the atoms of the molecule are localized in general positions. The crystal structure consists of discrete trimorphamide molecules that are noncentrosymmetric and between which hydrogen interactions of the N—H...O and C—H...O types were found. Both the H...O distances in the N1—H...O1 (0.1567 nm) and C1—H...O2 (0.2455 nm) interactions are less than the sum of the van der Waals radii (0.26 nm). The H...O1 interaction is interesting in that it forms an angle of 110.5° with the O1—C3 bond and the HN1 hydrogen atom lies at such a distance from the O1 oxygen that it is possible to assume stronger

TABLE II

Positional parameters ($\cdot 10^4$) of the atoms in the crystal structure of trimorphamide (standard deviations given in brackets)

Atom	x/a	y/b	z/c
C11	2 035(2)	2 447(2)	1 887(2)
C12	512(2)	4 679(2)	2 749(2)
C13	2 551(2)	3 512(2)	4 141(2)
O1	4 762(4)	7 232(6)	3 015(6)
O2	1 845(5)	7 238(5)	— 811(4)
N1	4 057(5)	4 906(7)	2 510(5)
N2	2 332(4)	5 798(5)	1 270(4)
C1	2 802(6)	5 339(7)	2 384(5)
C2	2 023(6)	4 054 (7)	2 762(5)
C3	4 921(8)	5 926(10)	2 825(8)
C4	2 294(9)	5 768(10)	— 742(7)
C5	3 070(8)	5 501(9)	344(7)
C6	1 146(9)	7 543(12)	83(7)
C7	1 900(8)	7 341(9)	1 185(7)
HN1	4 391(95)	3 515(123)	2 338(87)
HC1	3 065(40)	6 239(54)	3 028(39)
HC3	5 729(69)	5 417(81)	3 135(60)
H1C4	1 536(50)	5 155(61)	— 729(49)
H2C4	3 000(58)	5 782(72)	—1 326(58)
H1C5	3 790(51)	6 138(63)	435(45)
H2C5	3 330(52)	4 559(63)	441(47)
H1C6	746(51)	8 483(63)	— 56(46)
H2C6	433(71)	6 878(84)	15(66)
H1C7	1 345(52)	7 453(64)	1 794(51)
H2C7	2 682(52)	8 025(61)	1 276(49)

TABLE III

Anisotropic temperature coefficients ($\cdot 10^4$) of the nonhydrogen atoms in the crystal structure of trimorphamide

Atom	U11	U22	U33	U23	U13	U12
Cl1	1 027(13)	613(9)	977(14)	— 88(10)	215(11)	— 132(10)
Cl2	820(12)	1 018(14)	1 080(16)	— 41(12)	446(11)	— 131(10)
Cl3	1 700(20)	985(15)	722(12)	300(12)	42(12)	— 167(14)
O1	869(39)	602(34)	2 641(78)	— 126(43)	395(44)	— 154(30)
O2	1 424(44)	844(35)	733(34)	241(28)	404(32)	249(33)
N1	739(40)	639(36)	1 012(47)	15(33)	18(33)	— 16(35)
N2	731(33)	570(32)	639(34)	73(27)	231(27)	53(27)
C1	573(39)	638(40)	634(44)	180(37)	40(32)	— 37(35)
C2	906(47)	578(39)	660(43)	25(34)	32(36)	— 137(38)
C3	834(60)	720(57)	1 534(86)	69(59)	— 10(57)	— 87(58)
C4	1 219(74)	963(66)	772(61)	224(52)	328(58)	182(61)
C5	982(65)	636(52)	933(68)	73(48)	417(53)	191(50)
C6	1 074(70)	1 050(68)	872(68)	329(59)	296(59)	367(69)
C7	949(59)	760(53)	764(58)	98(45)	329(51)	184(48)

TABLE IV

Interatomic bonding distances (10^{-10} m) in the trimorphamide molecule with standard deviations given in brackets

Bond	Bond length	Bond	Bond length
Cl1—C2	1·778(6)	C7—N2	1·456(9)
Cl2—C2	1·760(7)	H—N1	1·317(109)
Cl3—C2	1·764(6)	H—Cl	1·130(47)
C2—Cl	1·531(9)	H—C3	1·035(74)
N1—C1	1·432(9)	H1—C4	1·002(56)
N2—C1	1·441(8)	H2—C4	1·107(71)
O1—C3	1·203(11)	H1—C5	0·974(57)
N1—C3	1·342(11)	H2—C5	0·891(57)
N2—C5	1·475(10)	H1—C6	0·954(57)
C4—C5	1·501(12)	H2—C6	0·982(77)
C4—O2	1·401(10)	H1—C7	1·010(63)
C6—O2	1·417(11)	H2—C7	1·054(57)
C6—C7	1·496(12)		

interaction than mere van der Waals. The HN1 hydrogen is located in a position such that the N1—HN1 and O1...HN1 distances (0.1317 and 0.1567 nm) lie in an interval between the Pauling covalent bonding distances^{6,7} (0.098 and 0.094 nm) and the lengths of van der Waals bonds. The approach of the hydrogen to the O1 atom results in a lengthening of the N1—N bond.

The length of the N1—C3 (0.1342 nm), C3—O1 (0.1203 nm) bonds and values of the C3—N1—C1 (119.9°), H—N1—C1 (121.5°), H—N1—C3 (118.6°), N1—C3—O1 (126.5°) and HC3—C3—O1 (119.6°) valence angles indicate considerable delocalization of the π -electrons and inclusion of the lone electron pair on the N1 nitrogen in the conjugation of the N1—C3—O1 molecular fragment. This is because the six-atom system C1—N1—H—C3—O1—H is sufficiently planar to permit approach of the same end of a second molecule (formamide end) to a distance <0.28 nm) sufficient for interaction. The formation of intermolecular interactions through the O1 oxygen atoms leads to formation of an eight-membered ring consisting

TABLE V
Bonding Angles (°) in the trimorphamide molecule with standard deviations given in brackets

Atoms	Angle	Atoms	Angle
O1—C3—N1	126.5(0.8)	H—C1—N2	118.3(2.4)
C3—N1—C1	119.9(0.6)	H—C1—C2	116.0(2.5)
N1—C1—N2	114.5(0.5)	H1—C5—C4	112.8(3.3)
N1—C1—C2	109.7(0.6)	H1—C5—N2	108.9(3.4)
N2—C1—C2	109.3(0.5)	H1—C5—H2	106.7(5.0)
C11—C2—C12	108.6(0.3)	H2—C5—C4	114.1(3.6)
C11—C2—C13	110.2(0.4)	H2—C5—N2	105.5(3.9)
C12—C2—C13	108.1(0.4)	H1—C4—O2	102.7(3.2)
C1—C2—C11	112.7(0.4)	H1—C4—C5	107.4(3.3)
C1—C2—C13	110.2(0.4)	H1—C4—H2	131.8(4.8)
C1—N2—C5	118.6(0.5)	H2—C4—O2	102.8(3.4)
C5—N2—C7	108.7(0.6)		
N2—C5—C4	108.5(0.7)	H1—C6—O2	108.4(3.6)
N2—C7—C6	108.8(0.7)	H1—C6—C7	117.6(3.4)
C5—C4—O2	111.4(0.7)	H1—C6—H2	99.2(5.6)
C4—O2—C6	110.7(0.7)	H2—C6—O2	108.7(4.8)
O2—C6—C7	110.6(0.7)	H2—C6—C7	111.4(4.6)
H—C3—O1	119.6(4.0)	H1—C7—C6	107.8(3.3)
H—C3—N1	111.4(4.1)	H1—C7—N2	105.2(3.3)
H—N1—C3	118.6(4.5)	H1—C7—H2	115.1(4.6)
H—N1—C1	121.5(4.5)	H2—C7—C6	113.2(3.2)
H—C1—N1	86.8(2.3)	H2—C7—N2	106.3(3.1)

of the atoms of the formamide moiety of the molecule, HN1—C3—O1, and atoms related by a symmetry element (2_1 axes). It seems that the HN1 and HC1 interactions with the oxygen atoms of the neighbouring molecule are decisive for the conformation of the trimorphamide molecule and its position in the crystal.

The six-membered heterocyclic morpholine ring is in the chair conformation and the O2 oxygen atom is twisted towards the HC1 hydrogen atom with which it forms a hydrogen bond. The C—Cl distances and distances between the atoms in the morpholine ring correspond to single bonds. The average valence angle value on the carbon atoms in this part of the molecule corresponds to sp^3 tetrahedral angles.

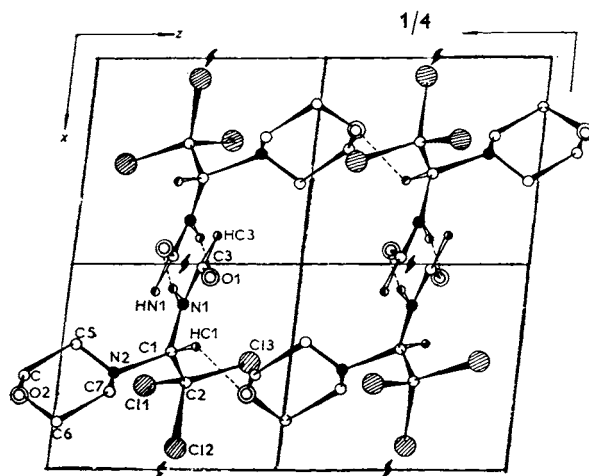


FIG. 1

Projection of the structure of trimorphamide onto the (010) plane

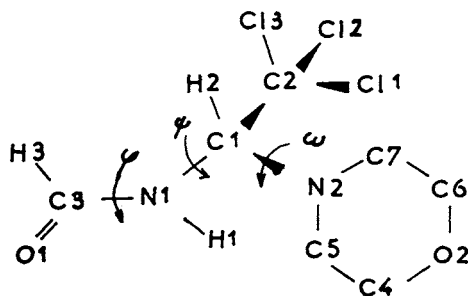


FIG. 2

Numbering of atoms and designation of optimized dihedral angles in the trimorphamide molecule

It follows from the X-ray structural results for the trimorpholine molecule that in the solid state this molecule exists as the racemate as it crystallizes in a centrosymmetric group.

It was found by the quantum chemical calculations that the most stable conformation is found for the values $\varphi = 0^\circ$, $\psi = 120-150^\circ$, $240-270^\circ$, $\omega = 150-210^\circ$, $330-30^\circ$. It should be pointed out that only partial optimization was carried out in which the values were not all optimized simultaneously and a number of geometric parameters were considered fixed. It follows from the value $\varphi = 0^\circ$ that the formamide group (*i.e.* the O1, C3, H3, N1, H1 and C2 atoms) is planar. However, this plane can be oriented in at least two possible conformations with respect to the N1—C1—C2 plane (the ψ value). This morpholine ring is in a stable conformation with respect to the C1—C2 plane when lying at angles defined by the ω value.

These calculations indicate that the studied molecule can have a number of stable forms, in both the R and S conformations. Clearly, the calculations refer to an isolated trimorphamide molecule and the crystal field would have to be taken into consideration for comparison with the structure in the solid phase. In spite of this effect, there is no great difference between the values calculated and those found for the solid phase.

Calculation of the electron structure also provided a number of indices characterizing the electron structure and providing information on the electron distribution in the molecule and the strengths of the individual bonds. Table VI lists the values

TABLE VI
Charge values on the individual atoms and Wiberg bonding indices

Atom	charge, q	bond	I_w
O1	-0.28	O1—C3	1.90
C3	+0.33	C3—N1	1.14
H3	+0.01	C3—H3	0.94
N1	-0.28	N1—C1	1.04
H1	+0.17	C1—C2	0.89
C1	+0.31	C1—N2	0.98
H2	+0.05	N2—C5	0.97
N2	-0.218	N2—C7	0.99
Cl, 1, 2, 3	-0.10	C7—C6	1.02
C2	+0.16	C2—C11	1.03
C5	+0.13	C5—C4	1.01
C4	+0.11	C4—O2	0.98
O2	-0.11	C6—O.2	0.97

of charge q for the individual atoms and the Wiberg index I for conformations $\varphi = 0^\circ$, $\psi = 120^\circ$ and $\omega = 150^\circ$. The charge values indicate considerable polarization of the formamide part of the molecule as well as of the C1—N2 and O2—C4 (or C6) bonds. This charge distribution and the spatial arrangement (geometry) of the molecule determine its biological activity.

The determined polarization is also important in stabilization of the crystal. It was found by the experimental determination of the structure in the solid phase in this work that the intermolecular interactions are most important in the formamide part of the molecule, primarily between the O1 oxygen and the H1 hydrogen. It follows from the calculations that the O1 oxygen has a quite large negative charge (-0.28) and the H1 hydrogen has a positive charge ($+0.17$). This charge separation increases the coulombic interactions important for the overall stabilization of the crystal.

It follows from the Wiberg index values that the C3=O1 bond is double but that π -electrons are also delocalized in the region of the C3—N1 bond. The other bonds have the character of single bonds.

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