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The Crystal Structure of Cytosine Hydrochloride*

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Crystals of cytosine hydrochloride, $C_4H_6N_3O^+ \cdot Cl^-$, are monoclinic, space group $P2_1/n$, with $a = 8.316$ (3), $b = 6.831$ (2), $c = 11.043$ (4) Å, and $\beta = 96.67$ (2)°; $Z = 4$; $D_m = 1.55$, $D_c = 1.57$ g cm⁻³. Data were collected on an automated diffractometer; the structural parameters were refined to an R index of 0.049 for 1413 reflections. Features of the structure include layers of molecules joined by N–H···O hydrogen bonds across centers of symmetry, and N–H···Cl contacts between these dimers. In contrast to other protonated pyrimidines, the cytosine rings show parallel stacking, with a separation of 3.3 Å.

Introduction

This crystal structure analysis was undertaken to aid in the interpretation of ESR experiments on X-ray irradiated single crystals of cytosine hydrochloride (Westhof, Flossman & Müller, 1975). Crystals were grown by slow evaporation from concentrated hydrochloric acid. The crystal used for both preliminary photographic analysis and data collection was a trapezohedron with dimensions 0.92 × 0.50 × 0.33 mm. Precession and Weissenberg photographs indicated space group $P2_1/n$ with $Z = 4$. Lattice parameters obtained from a least-squares fit to diffractometer 2θ values are: $a = 8.316$ (3), $b = 6.831$ (2), $c = 11.043$ (4) Å, and $\beta = 96.67$ (2)°.

1413 intensity data were collected at ambient temperature by a θ – 2θ scan technique to a maximum $2\theta = 150^\circ$ on a Datex-automated General Electric diffrac-

tometer equipped with Ni-filtered Cu $K\alpha$ radiation.† Three check reflections, which were monitored every 50 reflections, showed a total intensity fluctuation of $\pm 2\%$. The data were corrected for absorption ($\mu = 47.34$ cm⁻¹); the transmission coefficients ranged from 0.118 to 0.378.

Preliminary Cl coordinates were obtained from a Patterson calculation, and subsequent electron density maps yielded the coordinates of all the non-hydrogen atoms of the cytosine moiety. After several cycles of isotropic full-matrix refinement, a difference map indicated all six H atoms. Further full-matrix least-squares calculations including positional and anisotropic temperature parameters for the nine heavy atoms, positional and isotropic temperature parameters for the six H atoms and a scale factor, led to a final R index of 0.049, and a goodness-of-fit

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† The structure factor table has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32179 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. *Final positional and thermal parameters with variances in parentheses*Heavy-atom positional parameters are $\times 10^5$ and the H positional parameters and U_{ij} 's $\times 10^4$.

	<i>x</i>	<i>y</i>	<i>z</i>	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	5972 (7)	12532 (8)	16536 (5)	530 (4)	386 (3)	367 (3)	103 (2)	-6 (2)	86 (2)
N(1)	15019 (22)	-31272 (26)	55525 (15)	362 (9)	299 (8)	316 (8)	-78 (7)	-70 (6)	48 (6)
C(2)	8838 (23)	-24734 (28)	44349 (17)	303 (9)	303 (9)	326 (9)	-34 (7)	-38 (7)	28 (7)
O(2)	-1273 (21)	-33776 (23)	37561 (14)	458 (9)	392 (8)	389 (8)	-163 (7)	-151 (6)	80 (6)
N(3)	14187 (20)	-6672 (25)	41147 (15)	322 (8)	293 (8)	305 (8)	-40 (6)	-30 (6)	49 (6)
C(4)	25486 (23)	3999 (28)	48076 (17)	277 (9)	286 (9)	375 (10)	-30 (7)	35 (7)	-33 (7)
N(4)	29893 (26)	20875 (30)	43849 (20)	445 (11)	339 (9)	487 (11)	-112 (8)	25 (8)	54 (8)
C(5)	31803 (24)	-3613 (31)	59551 (19)	325 (10)	352 (10)	369 (10)	-61 (8)	-48 (8)	-38 (8)
C(6)	26415 (26)	-21163 (31)	62857 (18)	358 (10)	374 (10)	317 (10)	-43 (8)	-72 (7)	5 (8)

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>		<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
H(1)	1090 (35)	-4210 (46)	5738 (28)	3.91 (0.59)	H(4)'	3746 (40)	2713 (58)	4679 (30)	5.70 (0.86)
H(3)	1050 (31)	-177 (42)	3302 (26)	3.36 (0.51)	H(5)	3944 (37)	300 (56)	6517 (32)	5.31 (0.71)
H(4)	2549 (35)	2402 (45)	3624 (26)	3.66 (0.57)	H(6)	2988 (32)	-2772 (44)	7100 (25)	3.80 (0.58)

$\{\omega = [\sum \omega(|F_o|^2 - |F_c|^2)^2 / (M - S)]^{1/2}$ for $M = 1413$ observations, $S = 106$ parameters, and $\omega = 1/\sigma^2(F_o)^2\}$ of 4.54. Scattering factors were those in *International Tables for X-ray Crystallography* (1962), except for H (Stewart, Davidson & Simpson, 1965). Final positional and thermal parameters for all the atoms are given in Table 1.

Discussion

Distances and angles for the cytosine cation are shown in Fig. 1. Standard deviations in these values are about 0.003 Å and 0.2° for the heavy atoms and 0.03 Å and

Table 2. *Bond distances and angles in the cytosine ring for the present structure, cytosine (C), hemiprotonated cytosine (C½H⁺), and fully protonated cytosine (CH⁺)*

	This work	C	C½H⁺	CH⁺
N(1)-C(2)	1.356 Å	1.376 Å	1.351 Å	1.381 Å
C(2)-N(3)	1.372	1.357	1.366	1.385
N(3)-C(4)	1.354	1.339	1.353	1.352
C(4)-C(5)	1.413	1.418	1.427	1.411
C(5)-C(6)	1.345	1.337	1.363	1.346
C(6)-N(1)	1.361	1.353	1.365	1.364
C(2)-O(2)	1.226	1.246	1.250	1.214
C(4)-N(4)	1.312	1.334	1.323	1.313
C(6)-N(1)-C(2)	122.6°	121.7°	122.0°	121.4°
N(1)-C(2)-N(3)	115.6	118.9	117.6	114.8
C(2)-N(2)-C(4)	124.3	119.3	121.9	125.7
N(3)-C(4)-C(5)	118.0	122.2	120.7	117.1
C(4)-C(5)-C(6)	118.1	117.3	115.6	118.8
C(5)-C(6)-N(1)	121.4	120.7	122.1	122.4
N(1)-C(2)-O(2)	123.4	119.0	121.3	123.4
N(3)-C(2)-O(2)	121.0	122.1	121.1	121.9
N(3)-C(4)-N(4)	118.5	117.6	117.3	119.8
C(5)-C(4)-N(4)	123.5	120.2	121.9	123.2

2.0° for the H atoms. Bond distances and angles for cytosine and some of its derivatives are given in Table 2. The values quoted for cytosine, C, were averaged from cytosine and its monohydrate (McClure & Craven, 1973). Those for the hemiprotonated species, C½H⁺, were taken from cytosine-5-acetic acid (Marsh, Bierstedt & Eichhorn, 1962), where half a proton is resident on N(3) and the other half is resident on the acetic acid carboxyl group. The values quoted for the cation, CH⁺, were averaged from 2'-deoxycytidine hydrochloride (Subramanian & Hunt, 1970), the two independent cations in 1-methylcytosine hydrochloride (Trus & Marsh, 1972) and 1-(β-D-arabino-furanosyl)cytosine hydrochloride (Sherfinski & Marsh, 1973). The protonated CH⁺ species are all N(1) substituted in contrast to the present, hemiprotonated, and cytosine structures where N(1) contains a proton.

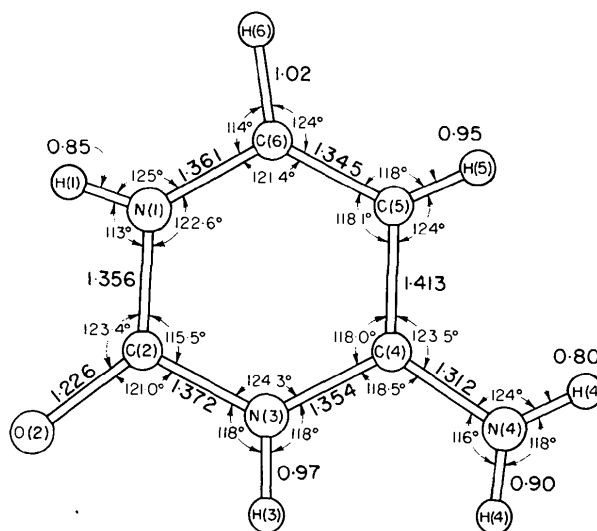


Fig. 1. Distances and angles for the cytosine molecule.

The effect of protonation of N(3) can clearly be seen on the geometry about N(3). The C(2)—N(3)—C(4) angle increases by about 5° and both the N(1)—C(2)—N(3) and N(3)—C(4)—C(5) angles decrease correspondingly by 3 to 4°. Also, both the C(2)—N(3) and the N(3)—C(4) distances increase by about 0.02 Å. Other differences in the distances and angles in the cited structures can be attributed to different hydrogen-bonding configurations. In the CH⁺ compounds O(2) failed to form any strong hydrogen bonds and was only involved in short C—H···O contacts. In both cytosine structures O(2) forms two very weak N—H···O hydrogen bonds. The presence of strong N—H···O hydrogen bonds in both the present and the C¹/₂H⁺ structures is evidenced by a decrease in both the N(1)—C(2) and C(2)—N(3) bonds, coupled with an increase in the C(2)—O(2) bond length. This effect on the bond distances is a consequence of the stabilization of the partial negative charge at the O atom, thus increasing the double-bond character of the N(1)—C(2) and C(2)—N(3) bonds while increasing the single-bond character of the C(2)—O(2) bond. The C(2)—N(3) bond distances in Table 2 are influenced by the competition between protonation at N(3) (bond-length extension) and the strength of the hydrogen bonding at O(2) (bond-length contraction). In addition, the C(4)—N(4) distance decreases as the strength of the hydrogen bond, N(4)—H(4)···A, increases. In the cytosine and hemiprotonated structures, O atoms serve as hydrogen-bond acceptors and as the C(4)—N(4) distances indicate, the N—H···O hydrogen bonds are much stronger in the hemiprotonated structures. Cl⁻ ions serve as the hydrogen-bond acceptors in both the present and the other fully protonated species, resulting in the short C(4)—N(4) bonds in these structures.

Details of the hydrogen-bond scheme for cytosine hydrochloride are given in Fig. 2. Except for the centro-

symmetric set of N(1)—H(1)···O(2) hydrogen bonds, the hydrogen-bonding scheme is essentially identical with that found in 1-methylcytosine hydrochloride (Trus & Marsh, 1972). Besides this additional set of hydrogen bonds, each cytosine cation forms hydrogen bonds with three Cl⁻ ions (Fig. 3) and, in particular, a short contact at the site of protonation, N(3).

Extensive base stacking in nonprotonated-pyrimidine structures and the lack of stacking in protonated pyrimidines has been well documented (Bugg, Thomas,

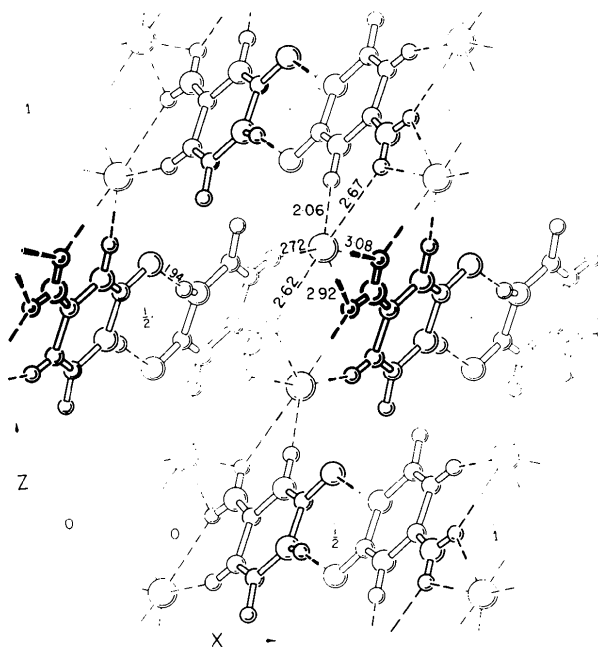


Fig. 3. A view up [010].

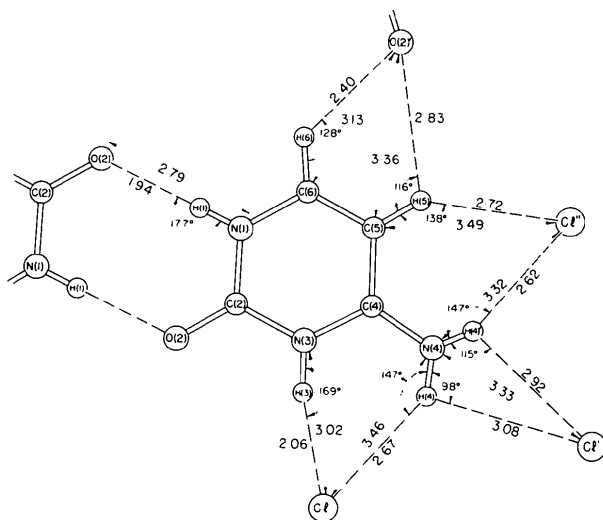


Fig. 2. Details of the hydrogen-bonding scheme.

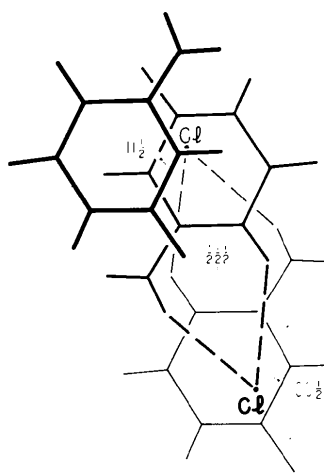


Fig. 4. A view perpendicular to the cytosine plane, indicating the base stacking not commonly found in protonated pyrimidines.

Table 3. Deviations (\AA) of the atoms in the cytosine molecule from the least-squares plane

The C, N, and O atoms were given equal weight in the calculation. The code for the atoms involved in intermolecular contacts is: (unit-cell translation along a, b, c , and the equivalent position number, where numbers 1 to 4 are $x, y, z; \frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z; \bar{x}, \bar{y}, \bar{z}; \frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z$ respectively).

N(1)	-0.014	H(1)	-0.053
C(2)	0.009	H(3)	-0.046
O(2)	0.009	H(4)	0.048
N(3)	-0.019	H(4)'	0.141
C(4)	0.001	H(5)	-0.019
N(4)	0.005	H(6)	-0.022
C(5)	0.003		
C(6)	0.006	Cl(000, 2)	-0.079
		Cl(000, 1)	0.236
		Cl(000, 4)	0.227
		O(2)(0 $\bar{1}$ 0, 2)	-0.078
		O(2)(0 $\bar{1}$ 1, 3)	-0.222

Rao & Sundaralingam, 1971). As shown in Fig. 4, the pyrimidine rings in cytosine hydrochloride stack about centers of symmetry $00\frac{1}{2}, 11\frac{1}{2}$, etc., but not about the center $\frac{1}{2}\frac{1}{2}\frac{1}{2}$. The very strong N(3)—H(3) \cdots Cl hydrogen bond helps delocalize the positive charge of N(3), allowing the rings to stack with N(3) above the C(5)—C(6) bond (Fig. 4). The distance between stacked rings is 3.31 \AA and between unstacked rings, 3.23 \AA . As pointed out above, the hydrogen-bonding scheme in 1-methylcytosine hydrochloride is very similar to that in the present structure, but the partial positive charge on the N(1) methyl group does not allow for stacking.

The deviations from planarity of all the atoms in the pyrimidine ring and the atoms hydrogen-bonded to the ring are given in Table 3. The cytosine molecules are inclined approximately 63° to the ac plane.

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