

The Crystal and Molecular Structure of 5-Chlorouridine

By STUART W. HAWKINSON* AND CHARLES L. COULTER†

Department of Anatomy, University of Chicago, Chicago, Ill. 60637, U.S.A.

(Received 2 February 1970)

5-Chlorouridine forms monoclinic crystals of space group $P2_1$ from aqueous solution, with $a=7.536$, $b=5.790$, $c=13.219$ Å, $\beta=99.89^\circ$, and two molecules per cell. Three-dimensional diffractometer data were collected with Cu $K\alpha$ radiation. The structure was determined using Patterson and Fourier synthesis methods and refined by full-matrix least-squares. The final R value was 3.15% for the 1061 observed data and 4.1% for all 1241 data. The molecular structure and conformation agree with other studies of pyrimidine nucleosides and bases. The sugar conformation is $C(2')$ -endo and the $C(5')$ -O(5') bond is *gauche* to both O(1') and C(3'). The glycosidic bond is at an angle of 8.4° to the base plane, with C(1') 0.21 Å out of that plane. The base-sugar torsion angle is -51.4° , and analysis of the thermal parameters suggests that the base is librating about the glycosidic bond. Angle N(3)-C(4)-C(5) seems to be sensitive to the C(5) substituent, and is about 2° smaller here than in unsubstituted or methyl substituted pyrimidines. The nucleoside molecules in the crystal structure are arranged into base-linked, parallel stranded ribbons along b , held together by hydrogen bonds. This type of base association has been found or inferred from X-ray diffraction patterns for crystals of 5-bromouridine and 5-chlorouridine from several different solvents, and may be present in solution as well as in crystals. Implications of this type of polymer with respect to polynucleotide structures are discussed, and coordinates for a proposed model of polyuridylic acid are given.

Introduction

This investigation of the crystal structure of 5-chlorouridine was begun to clarify some aspects of the dimensions of the uracil base in uridine derivatives (Coulter, 1969). The nucleoside was found to crystallize from water as a base-linked ribbon of a type not previously considered for nucleic acids. A preliminary report on the work and on the chemical and biological implications of this type of polynucleotide structure has been published (Coulter & Hawkinson, 1969).

The crystal structure reported here is isomorphous with the 5-bromouridine crystal structure determined by Iball, Morgan & Wilson (1967). Both 5-bromouridine and its complex with dimethyl sulfoxide (Iball, Morgan & Wilson, 1968) crystallize as base-linked parallel stranded ribbons such as found here, but this feature of these structures was not discussed by Iball *et al.* (1967, 1968). A description of a polynucleotide model compatible with the 5-chlorouridine crystal structure is included here, along with approximate coordinates for the model.

Experimental

5-Chlorouridine was purchased from the Calbiochem Corporation (Lot no. 680104, A Grade). An unusually fine crystal was found in the material as supplied and was used for the collection of the diffraction data. Recrystallization of the compound from water gave crystals with cell dimensions and intensities indistinguish-

able from those observed for the original crystals. 5-Chlorouridine crystallizes from water in the form of colorless monoclinic prisms. Preliminary precession photographs showed the crystals to be monoclinic, and systematic extinctions ($0k0$, $k=2n+1$) suggested space group $P2_1$ for this optically active molecule. A crystal of approximate dimensions $0.08 \times 0.27 \times 0.10$ mm was aligned with the b axis of the crystal parallel to the φ axis of a General Electric goniostat. Nickel-filtered copper radiation was used in the measurement of 6 pairs of resolved α_1 , α_2 doublets (Cu $K\alpha_1$: $\lambda=1.5405$ Å; Cu $K\alpha_2$: $\lambda=1.5443$ Å) and 19 unresolved reflections (Cu $K\alpha$: $\lambda=1.5418$ Å). A least-squares fit to these 31 measured 2θ values gave as cell dimensions: $a=7.536 \pm 0.001$, $b=5.790 \pm 0.001$, $c=13.219 \pm 0.002$, $\beta=99.89 \pm 0.01^\circ$. The flotation density measured in a carbon tetrachloride-methyl iodide mixture, was 1.63 g.cm $^{-3}$; the calculated density for 2 molecules of 5-chlorouridine in the cell is 1.627 g.cm $^{-3}$.

The intensity data were measured using Cu $K\alpha$ radiation with a General Electric XRD-5 diffractometer equipped with a scintillation counter and pulse height analyzer. The stationary crystal-stationary counter method, with a 4° take-off angle, was used for reflections with $2\theta < 90^\circ$ and a θ - 2θ scan method for reflections for which $90^\circ < 2\theta \leq 145^\circ$. For the low angle data, peaks and backgrounds were counted for 10 seconds. The high angle reflections were scanned at the rate of 2° .min $^{-1}$ over 2θ ranges of ± 1.5 to $\pm 2.5^\circ$; the range was selected to insure that counting losses due to spectral dispersion were less than 4% with an average of 2.5% (Alexander & Smith, 1962). Ten- or twenty second backgrounds were collected before and after each scan. Integrated intensities were also measured for 50

* Postdoctoral trainee under NIH-GM-94.

† To whom correspondence should be addressed.

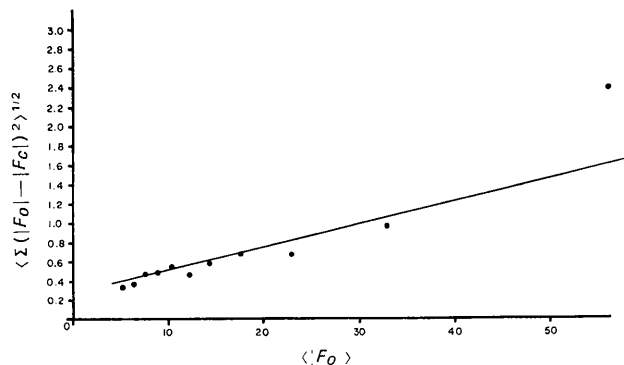


Fig. 1. A graph of σ vs. $|F_o|$ for the 5-chlorouridine data; omission of 2 of the 41 reflections in the last point lowers that σ to 2.1.

peaks with $20^\circ < 2\theta < 90^\circ$ and the low-angle data were approximately converted to integrated intensities using the mean ratios of integrated to peak intensities as a function of 2θ (Alexander & Smith, 1962). The error in this conversion, as estimated from fit of the data to the intensity ratio curve, was less than 4%. Three peaks were monitored at 4 hour intervals throughout the data collection. Systematic fluctuations in these reference intensities were observed half way through the data collection; the cause was a defective tube in the amplifier circuit. After replacing the tube, the monitor intensities became stabilized and remained constant $\pm 4\%$ for the remainder of the data collection. Intensities measured before the tube replacement were divided into four ranges and rescaled to the common final scale on the basis of the reference intensities and remeasurement of some reflections. The maximum correction was 13%. Time considerations ruled out the possibility of duplicate collection of the affected data. The final observational data consisted of 1061 non-zero intensities and

180 reflections which were too weak to measure (less than twice background).

The linear absorption coefficient for Cu $K\alpha$ radiation is 32.5 cm^{-1} for 5-chlorouridine. Absorption corrections were calculated with a program supplied by L. H. Dahl, University of Wisconsin, which uses the method described by Busing & Levy (1957). The largest corrections in intensity were 25% for reflections with high k indices. The resultant intensities were corrected for Lorentz and polarization effects, and placed on an approximate absolute scale using Wilson's (1942) method.

All calculations were carried out with the aid of the IBM 7094/7040 system at the University of Chicago. The Fourier synthesis program used was *ERFR2* (Sly, Shoemaker & van den Hende, 1962); Busing, Martin & Levy's *Least-Squares* (1962) and *Function and Error* (1964) programs, Johnson's (1965) *ORTEP* program, and Schomaker & Trueblood's (1968) program for thermal motion analysis were all used in the refinement and elucidation of the structure. The atomic scattering factors for chlorine, oxygen, nitrogen and carbon were taken from *International Tables for X-ray Crystallography* (1962), and the hydrogen scattering factors were from Stewart, Davidson & Simpson (1965). The anomalous dispersion corrections for chlorine were those calculated by Cromer (1965).

Solution and refinement

A trial structure was derived from a sharpened Patterson function, calculated using $(|E|^2 - 1)$ coefficients. The chlorine-chlorine Harker peak was easily identified, and a search for inter- and intramolecular chlorine to light atom vectors suggested positions for 15 of the 18 non-hydrogen atoms in the molecule. A Fourier synthesis, phased on the basis of these 15 atomic positions, revealed the 3 missing atoms from the ribose. Isotropic least-squares refinement using unit weights reduced R

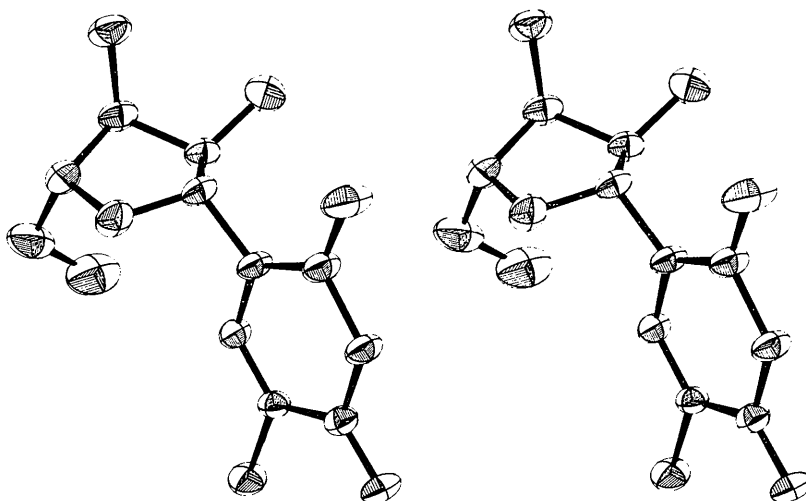


Fig. 2. A stereoscopic view of the 5-chlorouridine molecule showing the thermal ellipsoids.

nucleotides (Sundaralingam, 1965), although intramolecular strain can alter this as, for example, in cyclic uridine-3',5'-phosphate where C(4')-endo was the observed conformation (Coulter, 1969). The torsion angles for the ribose and the dihedral angles defining the conformation of C(5')-O(5') relative to the sugar are given in Table 7; these values agree with those found for similar structures as summarized by Sundaralingam (1965, 1969) and Shefter & Trueblood (1965). The torsion angle of the sugar with the base, φ_{CN} , is -51.4° which is in the *anti* range (Donohue & Trueblood, 1960). Model considerations suggest that a purine or pyrimidine base would show maximum libration about the glycosidic bond. We have evaluated this hypothesis using Schomaker & Trueblood's (1968) thermal analysis program for 5-chlorouridine (Table 8). The most satisfactory results were indeed obtained by treating the 9 atoms of the base as a rigid group. The root-mean-square difference between the observed and calculated U_{ij} ,* corrected for the degrees of freedom, was 0.0014

$$* \text{ Temperature factor} = \exp [-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^{*}b^{*} + 2U_{13}hla^{*}c^{*} + 2U_{23}klb^{*}c^{*})].$$

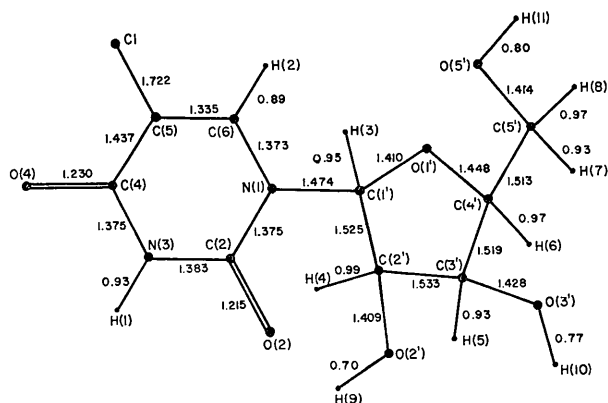


Fig. 3. Bond distances. The estimated standard deviations for bonds not involving H, C(5') or O(5') are 0.004 Å.

Å² which indicates that the assumption of rigidity was a reasonable one. For a rigid sugar, the r.m.s. deviation was 0.0039 Å². The translational components of the rigid body motion are nearly isotropic, in contrast with

Table 3. *Thermal parameters* ($\times 10^5$) *and their estimated standard deviations**

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl	1752 (15)	2701 (29)	404 (4)	-333 (19)	44 (6)	444 (10)
N(1)	1158 (44)	1696 (81)	232 (13)	-247 (50)	-93 (18)	14 (26)
C(2)	1272 (52)	1764 (98)	247 (15)	-281 (64)	-49 (21)	6 (34)
N(3)	1242 (42)	1812 (84)	250 (13)	-393 (53)	-98 (18)	-14 (28)
C(4)	988 (46)	1676 (93)	266 (15)	180 (58)	9 (21)	12 (31)
C(5)	1083 (48)	1741 (90)	252 (14)	146 (59)	57 (21)	91 (33)
C(6)	1054 (46)	1641 (89)	292 (15)	-213 (60)	-3 (21)	69 (33)
O(2)	2214 (52)	2411 (78)	313 (12)	-913 (60)	-208 (20)	242 (29)
O(4)	1363 (41)	2313 (73)	261 (11)	35 (46)	-164 (17)	34 (25)
C(1')	1111 (51)	1799 (100)	249 (15)	-114 (59)	-91 (22)	-57 (31)
C(2')	1344 (56)	1579 (92)	265 (15)	-182 (57)	20 (22)	-54 (32)
C(3')	1565 (62)	1999 (105)	267 (15)	-285 (64)	-91 (24)	-92 (34)
C(4')	1123 (53)	3790 (141)	319 (16)	-412 (83)	-73 (24)	-71 (45)
C(5')	2290 (89)	5916 (229)	431 (21)	-2054 (145)	156 (35)	-38 (69)
O(1')	1238 (42)	2750 (92)	350 (13)	-58 (51)	-40 (18)	-340 (28)
O(2')	1779 (47)	2635 (84)	399 (13)	41 (58)	243 (20)	-76 (30)
O(3')	1741 (48)	3108 (90)	245 (11)	202 (56)	-55 (18)	-32 (29)
O(5')	3361 (88)	3714 (126)	722 (23)	-1621 (95)	-55 (35)	494 (48)

$$* \text{ Temperature factor} = \exp [-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + 2B_{12}hk + 2B_{13}hl + 2B_{23}kl)].$$

Table 4. *Hydrogen atom positional and thermal parameters with estimated standard deviations*

	x/a	y/b	z/c	B	$\Delta\rho_0$
H(1)	0.427 (5)	0.641 (9)	-0.103 (3)	5.1 (1.0) Å	0.32 e.Å ⁻³
H(2)	0.007 (4)	0.087 (5)	-0.170 (2)	1.7 (0.6)	0.35
H(3)	-0.020 (4)	0.497 (7)	-0.355 (2)	1.8 (0.5)	0.41
H(4)	-0.002 (4)	0.005 (7)	-0.347 (2)	2.3 (0.6)	0.42
H(5)	-0.275 (4)	-0.016 (8)	-0.459 (2)	3.2 (0.7)	0.37
H(6)	-0.437 (5)	0.316 (8)	-0.376 (3)	3.9 (0.8)	0.31
H(7)	-0.489 (6)	-0.050 (10)	-0.328 (4)	6.3 (1.2)	0.29
H(8)	-0.439 (5)	0.120 (8)	-0.237 (3)	4.1 (0.9)	0.33
H(9)	0.130 (6)	0.084 (11)	-0.458 (4)	6.9 (1.3)	0.25
H(10)	-0.249 (6)	0.197 (11)	-0.562 (4)	6.2 (1.2)	0.25
H(11)	-0.285 (9)	-0.249 (16)	-0.247 (6)	13.0 (2.1)	0.10*

* The standard deviation of the electron density is about 0.1 e.Å⁻³; thus the position of H(11) is uncertain.

Table 5. Distances and angles involving hydrogen atoms

Bond	Distance	At atom	Subtended by	Angle
H(1)—N(3)	0.93 Å	N(3)	H(1), C(2)	119°
		N(3)	H(1), C(4)	114
H(2)—C(6)	0.89	C(6)	H(2), C(5)	124
		C(6)	H(2), N(1)	114
H(3)—C(1')	0.95	C(1')	H(3), O(1')	112
		C(1')	H(3), N(1)	106
		C(1')	H(3), C(2')	111
H(4)—C(2')	0.99	C(2')	H(4), O(2')	109
		C(2')	H(4), C(1')	113
		C(2')	H(4), C(3')	109
H(5)—C(3')	0.93	C(3')	H(5), O(3')	106
		C(3')	H(5), C(2')	115
		C(3')	H(5), C(4')	112
H(6)—C(4')	0.97	C(4')	H(6), C(5')	110
		C(4')	H(6), O(1')	103
		C(4')	H(6), C(3')	113
H(7)—C(5')	0.93	C(5')	H(7), H(8)	110
		C(5')	H(7), O(5')	115
		C(5')	H(7), C(4')	106
H(8)—C(5')	0.97	C(5')	H(8), O(5')	117
		C(5')	H(8), C(4')	98
H(9)—O(2')	0.70	O(2')	H(9), C(2')	107
H(10)—O(3')	0.77	O(3')	H(10), C(3')	97
H(11)—O(5')	0.80	O(5')	H(11), C(5')	107
H(1)—O(4)	1.97			
H(9)—O(3')	2.12			
H(10)—O(2)	2.19			

Table 6. Least-squares planes for the ribose

Plane	Distance out of plane in Å				
	I	II	III	IV	V
N(1)	-0.877	-0.902	-0.568	-0.724	-0.282
C(1')	-0.016*	0.094*	0.190*	0.128*	0.392
C(2')	-0.540	-0.054*	-0.176*	-0.202*	-0.086*
O(2')	-0.070	0.675	0.611	0.522	0.665
C(3')	0.014*	0.486	0.107*	0.204*	0.138*
O(3')	1.368	1.912	1.494	1.608	1.494
C(4')	-0.024*	0.058*	-0.258	-0.130*	-0.145*
O(1')	0.025*	-0.098*	-0.122*	-0.094	0.093*
C(5')	-1.260	-1.239	-1.663	-1.487	-1.557
O(5')	-2.406	-2.235	-2.572	-2.467	-2.466

* These atoms were used to define the planes.

Equations of the planes (x, y, z in fractional cell coordinates):

$$\begin{array}{l}
 \text{I} \quad -1.517x + 4.647y - 6.857z = 3.9343 \text{ \AA} \\
 \text{II} \quad -0.678x + 3.765y - 9.620z = 4.3546 \\
 \text{III} \quad 0.263x + 4.428y - 8.458z = 4.0899 \\
 \text{IV} \quad -0.303x + 4.301y - 8.611z = 4.1778 \\
 \text{V} \quad 0.340x + 4.706y - 7.668z = 3.7331
 \end{array}$$

the anisotropic librational components. The principal axis of libration of the base lies 21.5° from the glycosidic bond direction and 2° from the base plane, thus approximately agreeing with a libration about the C(1')—N(1) bond. The libration-corrected lengths and bond angles differed from the original set by at most 0.005 \AA and 0.2° ; this corresponds to less than 2σ , and the corrections were considered negligible in this case.

Table 7. Some torsion angles for 5-chlorouridine

O(1') → C(1')	-17.8°
C(1') → C(2')	32.3
C(2') → C(3')	-33.8
C(3') → C(4')	24.6
C(4') → O(1')	-4.5
φ_{CN}	-51.4
$ \varphi_{\text{OO}} $	66.3
$ \varphi_{\text{OC}} $	52.3

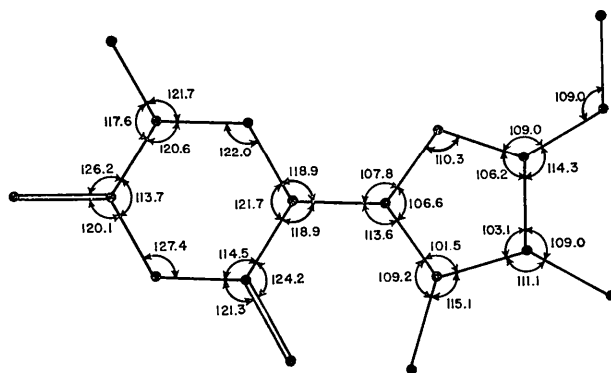
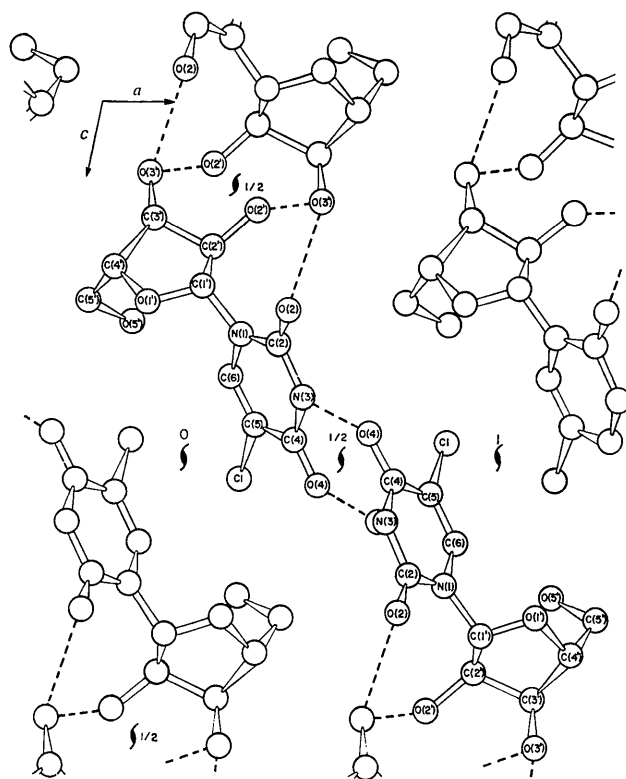


Fig. 4. Bond angles. The estimated standard deviations are 0.3°.

Fig. 5. The crystal structure viewed down *b*; hydrogen bonds are dashed.

The pyrimidine ring distances and angles agree well with the averaged distances and angles given by Donohue (1968*a*) for thymine and uracil, and with the more recent values from cyclic uridine-3',5'-phosphate (Coulter, 1969) and thymidine (Young, Tollin & Wilson, 1969). The only significant differences between the present structure and the earlier studies are in the carbonyl bond lengths, which are longer when the carbonyl oxygen atom is hydrogen bonded, as here, than when it is not, as in the cyclic UMP study (1.23 Å *vs.* 1.20 Å), and in the N(3)-C(4)-C(5) angle which is less here (113.7°) than in uracil (Stewart & Jensen, 1967) thymidine or

Table 8. Eigenvalues and eigenvectors† for the tensors **T** and **ω** for 5-chlorouridine

	Rigid base	Rigid sugar	Rigid molecule
T	0.17 Å	0.21 Å	0.19 Å
	-0.762	0.894	0.970
	-0.594	-0.354	-0.199
	-0.257	0.212	0.136
		0.395	0.201
			0.259
ω	5.5°	5.8°	5.2°
	-0.307	-0.047	0.378
	-0.476	-0.991	0.850
	-0.824	-0.126	0.365
			0.918
			0.926
			-0.346
			-0.154
	0.0014 Å ²	0.0039 Å ²	0.0052 Å ²

† With respect to *a*, *b*, *c** axes.

$$[\Sigma(AU_{ij})^2/(n-s)]^{1/2}$$

1-methylthymine (Hoogsteen, 1963), where the angles were 115.5, 115.8 and 116.1° respectively. Sundaralingam & Jensen (1965) noted that this angle was sensitive to protonation of N(3) in cytosine; it may also be sensitive to the C(5) substituent. The angle was 112.6° in 5-fluoro-2'-deoxy- β -uridine (Harris & MacIntyre, 1964). The carbonyl oxygen atom O(4) is bent towards N(3) as it was in the earlier studies, and the external angles about C(4)–O(4) are not affected by the C(5) substituent (Coulter, 1969). The least-squares plane data for the base are given in Table 9. The base is planar ± 0.02 Å, and atoms O(4) and C(1') are significantly out of this plane; for C(1') this corresponds to an 8.4° bend of the β -glycosidic bond from the base plane. This feature is evident in Fig. 2. C(1') is often 0.1 to 0.2 Å from the plane (Davies, 1967), and it is apparent that bending about the glycosidic bond is a favored way to remove intramolecular (Coulter, Hawkinson & Friedmann, 1969) or crystal packing strain in these molecules.

The arrangement of the molecules in the cell is shown in Fig. 5. The hydrogen bonds between O(3') and O(2) (2.82 Å) and O(3') and O(2') (2.81 Å) hold the base-linked ribbons together. The only other close contact (3.05 Å) is between O(5') and O(1') of the adjacent ribose along *b*. The C(5')–O(5')–O(1') angle is 128.0°, which suggests that this contact is a weak hydrogen bond. The arrangement of the bases is illustrated in

Table 9. *Least-squares plane through the uracil ring*

	Distance out of plane
C(1')	0.215 Å
N(1)*	0.006
C(2)*	–0.001
O(2)	0.006
N(3)*	–0.012
C(4)*	0.018
O(4)	0.074
C(5)*	–0.014
Cl	0.045
C(6)*	0.002

* These atoms were used to define the plane. Equation of the plane (*x, y, z*, in fractional cell coordinates):

$$-5.612x + 3.250y + 6.392z = -0.8599 \text{ \AA}.$$

Fig. 6.* The hydrogen bonding involves the same atoms as Donohue's bonding scheme 18, for thymine, among the possible nucleic acid pairs (Donohue, 1956; Donohue & Trueblood, 1960). The Figure illustrates the interleaving of the bases which are linked *via* N(3)–O(4) hydrogen bonds across the 2₁ axis at *a*/2. The base planes are 34.2° from being parallel to the *b* axis. The factors controlling the degree of tilt appear to be the chlorine–ring contact for adjacent bases along *b* and

* Similar base linkage arrangements have been observed in crystal structures of uridine 2',3'-cyclophosphorothioate (Saenger & Eckstein, 1970) and of 2-thiouridine (Hawkinson, unpublished).

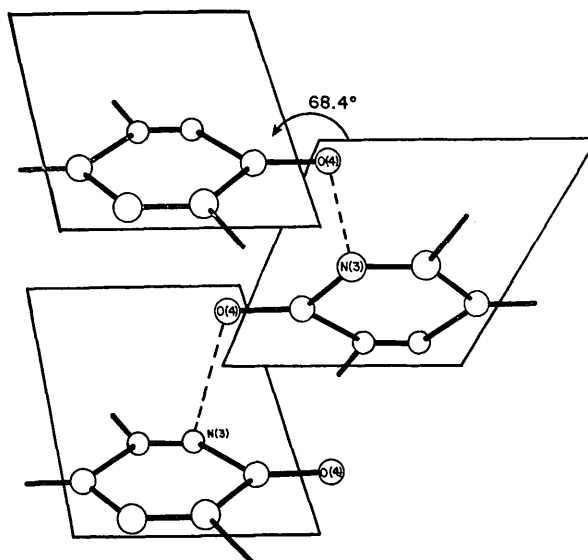


Fig. 6. The planes of the hydrogen-bonded bases.

the hydrogen bonding arrangement of the bases. The Cl–O(4) contact between hydrogen-bonded bases is 3.300 Å, slightly more than the sum of the van der Waals radii (Pauling, 1960). The distances and angles involving the inter-base hydrogen bonds are shown in Fig. 7. Atom O(4*A*) is at $(1-x, \frac{1}{2}+y, -z)$ relative to the coordinates in Table 2, and atom N(3*B*) is at $(1-x, -\frac{1}{2}+y, -z)$. These atoms are 0.33 and 2.03 Å out of the plane of the bases shown, on opposite sides. Donohue (1968*b*) has discussed similar cases of non-planarity in hydrogen-bonded carbonyl systems. The C(1')–C(1') distance across a base pair is 11.04 Å, a value close to that predicted for DNA base pairs.

Ts'o & Chan (1964) reported that purine and pyrimidine nucleosides including 5-bromouridine tend to aggregate in aqueous solutions. For purines and purine-pyrimidine mixtures the association was shown to involve base stacking (Chan, Schweizer, Ts'o & Helmkamp, 1964; Schweizer, Chan & Ts'o, 1965) but the experiments on pyrimidine solutions were not as clear. Two equilibrium constants were required to adequately explain the osmotic coefficient data for 5-bromouridine, and it seems likely that the association in this case is, at least in part, the same as that found in the crystal structure (Iball *et al.*, 1967) and that 5-chlorouridine would associate in the same way. The stability of these base-paired ribbons is reflected by the finding of the same polymer structure in the 5-bromouridine–dimethylsulfoxide complex (Iball *et al.*, 1968), and the same crystal form and probably the same structure for 5-chlorouridine crystallized from ethanol and acetone. Adenosine and 5-bromouridine crystallize from water as a base-stacked 1:1 complex (Haschemeyer & Sobell, 1965) in agreement with the magnetic resonance studies (Schweizer *et al.*, 1965). Further studies are in progress to establish, if possible, the solution conformation of

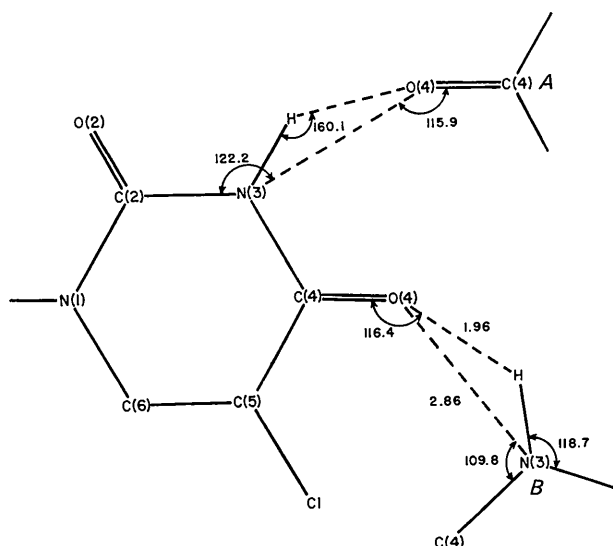


Fig. 7. Hydrogen-bond distances and angles between bases.

the 5-chlorouridine aggregates. Presumably the amount of this structure present in dilute aqueous solution would be small, since water would compete for the exposed hydrogen bonding sites. The relevance of this type of polymer assembly to the nucleic acid and polynucleotide structure is also being examined, and we have suggested that poly U may have this structure (Coulter & Hawkinson, 1969). Such a polymer would not be appreciably stabilized by hydrophobic stacking of the bases (Ts'o, 1969). Approximate coordinates for one such model are given in Table 10. M. Sundaralingam has pointed out that the phosphate ester conformations in this model, especially about O(3'), are not the preferred ones (Sundaralingam, 1969); this is reflected in the close contact (2.0 Å) between the hydrogen atom on C(4') and O(6) of the phosphate group. More acceptable models are possible (Sundaralingam, unpublished) if the angle of the base tip and the helix repeat are adjusted, but within the restrictions of the crystal structure ($b=5.79$ Å and a 2_1 helix) this was our best effort. It is clear that a polynucleotide with this type of base linkage is plausible, and detailed adjustments in the model would best be done in fitting experimental data.

Table 10. Cylindrical polar coordinates for the polymer

The Z repeat is 5.79 Å, the helix rotation 180°, and translation 2.9 Å. φ is given relative to $\varphi_p=0.0$.

	r	φ	Z
Cl	2.50 Å	59.8°	0 Å
N(1)	3.86	0	2.07
C(2)	3.18	-9.9	3.11
O(2)	3.82	-19.3	3.96
N(3)	1.80	-6.8	3.10
H(N3)	1.40	-27.6	3.74
C(4)	1.29	28.2	2.21

Table 10 (cont.)

	r	φ	Z
O(4)	0.87	93.7	2.38
C(5)	2.26	29.1	1.15
C(6)	3.37	13.8	1.12
H(C6)	4.01	16.7	0.47
C(1')	5.33	-1.4	2.09
H(C1')	5.61	-0.9	3.05
O(1')	5.94	9.7	1.41
C(2')	6.00	-13.6	1.45
H(C2')	5.52	-18.2	0.65
O(2')	6.35	-22.5	2.43
H(O2')	6.47	-29.5	2.04
C(3')	7.25	-7.2	1.00
H(C3')	7.60	-10.9	0.10
O(3')	8.38	-6.9	1.90
C(4')	7.02	4.9	0.61
H(C4')	7.94	8.4	0.82
C(5')	6.84	6.8	-0.90
Ha(C5')	5.79	8.0	-1.14
Hb(C5')	7.42	13.7	-1.20
O(5')	7.47	-2.2	-1.59
P	8.53	0	3.10
O(6)	8.60	9.3	2.66
O(7)	9.89	-1.7	3.61

We thank Mrs Marsha Greaves for the Figures and her assistance, and Dr George Holzwarth for helpful discussions. This research was supported by NSF Grant GB-8103.

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Structure Cristalline de Dérivés de la Phénothiazine. I. Diéthazine

PAR PIERRE MARSAU

Laboratoire de Cristallographie et Minéralogie (associé au C.N.R.S.), Faculté des Sciences, 351, Cours de la Libération, 33 Talence, France

(Reçu le 16 mars 1970)

The structure of diethazine has been determined from 2942 diffractometer data by the symbolic addition method. The hydrogen atoms were located by analysis of the three-dimensional density function ($R=0.054$). The structure takes the same 'roof' configuration as phenothiazine but is more open. The crystal appears to be held together by the chlorine atom which forms a strong hydrogen bond (N-H-Cl) with the nitrogen atom of one molecule and makes close contact with four other neighbouring molecules.

Introduction

Les dérivés de la phénothiazine présentent un grand intérêt en pharmacologie. Leurs propriétés, assez diverses, sont essentiellement liées à la nature de la chaîne amino-aliphatique fixée au noyau phénothiazinique. Ainsi prométhazine (Phénergan) et thiazinanium (Miltorgan) sont connus pour leurs propriétés antihistaminiques. Diéthazine (Diparcol) et isothazine (Parsidol) sont des antiparkinsoniens. Chlorpromazine (Largactil) et methopromazine (Mopazine) sont des neuroleptiques.

Le nombre de dérivés ainsi utilisés dans la pratique médicale est très grand, chaque produit présentant souvent plusieurs activités à des degrés divers.

A ce jour, dans cette série de composés, les structures de la phénothiazine (Wood, McCale & Williams, 1941; Bell, Blount, Briscoe & Freeman, 1968) et de la chlorpromazine base (McDowell, 1969) ont été déterminées.

Données expérimentales

La diéthazine, ou (diéthyl-amino-2-éthyl)-10 phénothiazine, cristallise aisément à partir d'une solution

dans un mélange chloroforme-xylène. On obtient des prismes, souvent volumineux, transparents, de symétrie monoclinique [faces naturelles (011)] allongés suivant la direction *a*. Point de fusion $F=177^{\circ}\text{C}$.

Données cristallographiques

Paramètres de la maille:

$$\begin{aligned} a &= 7,34 \pm 0,005 \text{ \AA} \\ b &= 16,41 \pm 0,01 \\ c &= 15,22 \pm 0,01 \\ \beta &= 98^{\circ} 15' \pm 15' \\ V &= 1816 \text{ \AA}^3 \end{aligned}$$

Densité calculée $1,229 \text{ g.cm}^{-3}$ pour $Z=4$
mesurée $1,266 \text{ g.cm}^{-3}$.

Les extinctions systématiques sont celles du groupe d'espace $P2_1/c$.

La structure a été résolue à partir de 2942 taches de diffraction mesurées au diffractomètre automatique. Les corrections géométriques et de polarisation ont été appliquées de la façon habituelle. Il n'a pas été tenu compte de l'absorption, les cristaux utilisés ayant une section à peu près carrée n'excédant pas $0,04 \text{ mm}^2$.