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Structure of 5′-Chloro-3′,5′-dideoxyformycin A Monohydrate. The Effects of Protonation on Formycin Structure and Conformation

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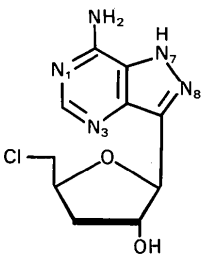
Abstract. $C_{10}H_{12}ClN_5O_2.H_2O$, $M_r = 287{\cdot}71$, monoclinic, $C2$, $a = 22{\cdot}935\ (2)$, $b = 4{\cdot}832\ (1)$, $c = 13{\cdot}772\ (1)$ Å, $\beta = 125{\cdot}19\ (1)°$, $V = 1247{\cdot}3$ Å^3, $Z = 4$, $D_x = 1{\cdot}532$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54184 Å, $\mu = 28{\cdot}825$ cm^{-1}, $F(000) = 300$, $T = 298$ K, final $R = 0{\cdot}037$ for 1685 observed reflections. Small changes in geometry around ring purine atoms C(2) and N(3) have been found relative to protonated analogues. The sugar rings adopt a C(2′)-*endo* pucker and the glycosidic angle is *anti*.

Introduction. The *C*-nucleoside formycin A {(*S*)-1-*C*-(7-amino-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl)-1,4-anhydro-D-ribitol} is a substrate for the enzyme adenosine deaminase, and inhibits the deamination reaction that it catalyses (Suhadolnik, 1979). Formycin has anti-tumour properties, although its ease of deamination has hindered use in humans.



The present study forms part of a programme exploring the structure–activity relationships of formycin and its derivatives. The crystal structures of 3′-deoxyformycin A (McKenna, Neidle & Serafinowski, 1987) and 2′,3′-dideoxyformycin A (Neidle, Urpi, Serafinowski & Whitby, 1989) have been determined, with both in the form of hydrochloride salts. Several crystallographic analyses on formycin itself have been previously reported (Prusiner, Brennan & Sundaralingam, 1973; Koyama, Umezawa & Iitaka, 1974). This study, on 5′-chloro-3′,5′-dideoxyformycin A (Serafinowski, 1987), examines the effects of (i) base neutrality and (ii) replacement of the standard 5′ hydroxyl group on structural features.

Experimental. Irregularly shaped colourless crystals of the title compound were grown with difficulty from a 1:1 ethanol:water solution. One of approximate dimensions 0·2 × 0·1 × 0·05 mm was used for all the crystallographic work. Preliminary oscillation and Weissenberg photographs showed triclinic symmetry. Accurate cell dimensions were obtained by least-squares refinement of 25 θ values ($10 \le \theta \le 21°$) measured on an Enraf–Nonius CAD-4 diffractometer. Intensity data were collected with an ω–2θ scan technique, with a maximum scan time of 100 s per reflection, using graphite-monochromated Cu $K\alpha$ radiation. Data collection was performed on a primitive triclinic cell of dimensions $a = 4{\cdot}832\ (1)$, $b = 11{\cdot}720\ (1)$, $c = 12{\cdot}047\ (1)$ Å, $\alpha = 70{\cdot}82\ (1)$, $\beta = 78{\cdot}29\ (1)$ and $\gamma = 78{\cdot}08\ (1)°$, with two independent molecules in the asymmetric unit.

2664 unique reflections were measured for $1{\cdot}5 \le \theta \le 65°$ and $0 \le h \le 5$, $-13 \le k \le 12$, $-14 \le l \le 14$, in the triclinic cell. It was subsequently found that the data could be satisfactorily indexed in a *C*-centred monoclinic space group; the data were accordingly merged to this symmetry, resulting in 2129 unique reflections with a merging agreement index (on F) of 0·019. 1685 reflections had $I \ge 1{\cdot}5\sigma(I)$ and were used in the subsequent refinement.

The structure was solved by direct methods using the *SHELX*84 program (Sheldrick, 1984). The space-group assignment of $C2$ is unambiguous since the 5′-chloro-3′,5′-dideoxyformycin used is a single stereoisomer. The most consistent E map revealed

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the positions of the Cl atom and most of the base and sugar atoms. Remaining non-H atoms were found in difference Fourier syntheses. Anisotropic least-squares refinement resulted in an R factor of 0·070. The positions of all H atoms were determined from difference Fourier maps, including those for the water molecule. Their positional and isotropic temperature factors were included in the refinement which resulted in a final R value of 0·037 and wR of 0·045. The weighting scheme used was of the form $w = [\sigma^2(F) + (0{\cdot}04|F_o|)^2]^{-1}$. An empirical absorption correction (Walker & Stuart, 1983) was applied to the data ($T_{min} = 0{\cdot}96$, $T_{max} = 1{\cdot}11$). Scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV).

Calculations were performed on a VAX 11/750 computer using the *SDP* system (Frenz, 1980). The maximum Δ/σ for the final least-squares cycle was 0·01, and the range of $\Delta\rho$ in the final difference Fourier map was $\pm 0{\cdot}18$ e Å^{-3}.

Discussion. The molecular structure of 5′-chloro-3′,5′-dideoxyformycin A is shown in Fig. 1, and atomic coordinates, bond distances and angles are given in Tables 1 and 2.*

Bond lengths and angles do not differ significantly from those in the crystal structure of 3′-deoxyformycin A hydrochloride (McKenna, Neidle & Serafinowski, 1987), apart from those in the vicinity of the purine ring atoms N(1) and N(3). The latter is protonated in 3′-deoxyformycin hydrochloride but not in the present structure. This difference is manifested in an increase in length of 0·05 Å for N(1)—C(2) and 0·024 Å for C(2)—N(3) in the present structure. Bond angles at C(2) and N(3) change by 3–4° between the protonated and neutral structures. These changes are broadly in accord with the limited number of N(3)-protonated structures surveyed by Taylor & Kennard (1982).

The sugar pucker in the molecule of 5′-chloro-3′,5′-dideoxyformycin A is in the pure C(2′)-*endo* range, with a pseudorotational phase angle P of 163·9 (6)° and a maximum degree of pucker τ_m of 37·8 (7)° (Altona & Sundaralingam, 1972).

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53514 (21 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

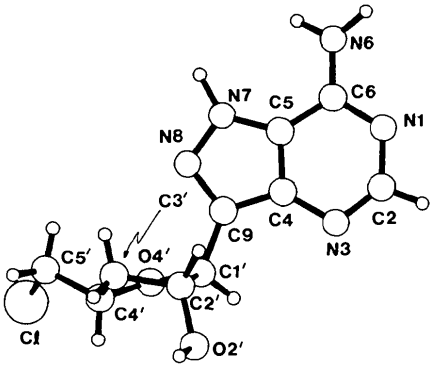

Fig. 1. Computer-drawn plot of 5′-chloro-3′,5′-dideoxyformycin A. The view is approximately normal to the mean plane of the deoxyribose group.

Table 1. *Positional parameters and equivalent isotropic thermal parameters with e.s.d.'s in parentheses*

$$B_{eq} = (4/3)[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)].$$

	x	y	z	B_{eq} (Å^2)
Cl	0·09108 (4)	0·169	0·72320 (7)	5·26 (2)
O*W*	0·0360 (1)	0·2812 (8)	0·9216 (2)	6·25 (8)
O(2′)	−0·20506 (9)	0·0837 (5)	0·4366 (1)	3·39 (5)
O(4′)	−0·05985 (7)	0·1376 (5)	0·6811 (1)	2·60 (4)
N(1)	−0·2429 (1)	−0·0361 (6)	0·8907 (2)	3·13 (5)
N(3)	−0·2287 (1)	0·1749 (6)	0·7467 (2)	2·70 (5)
N(6)	−0·1711 (1)	−0·3926 (6)	1·0160 (2)	3·45 (6)
N(7)	−0·09595 (9)	−0·3366 (6)	0·8917 (2)	2·84 (5)
N(8)	−0·0813 (1)	−0·2499 (5)	0·8138 (2)	2·74 (5)
C(1′)	−0·1314 (1)	0·0838 (6)	0·6477 (2)	2·34 (6)
C(2′)	−0·1672 (1)	−0·0965 (7)	0·5362 (2)	2·57 (6)
C(2)	−0·2587 (1)	0·1433 (8)	0·8035 (2)	3·30 (6)
C(3′)	−0·1041 (1)	−0·2306 (7)	0·5468 (2)	3·00 (7)
C(4)	−0·1737 (1)	−0·0071 (6)	0·7848 (2)	2·26 (6)
C(4′)	−0·0488 (1)	−0·0028 (7)	0·6004 (2)	2·60 (6)
C(5)	−0·1520 (1)	−0·1934 (6)	0·8754 (2)	2·31 (6)
C(5′)	0·0261 (2)	−0·1096 (8)	0·6695 (3)	3·79 (8)
C(6)	−0·1886 (1)	−0·2104 (7)	0·9299 (2)	2·59 (6)
C(9)	−0·1280 (1)	−0·0516 (6)	0·7489 (2)	2·24 (5)

Table 2. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

Cl—C(5′)	1·819 (3)	N(7)—C(5)	1·360 (4)
O(2′)—C(2′)	1·422 (3)	N(8)—C(9)	1·327 (3)
O(4′)—C(1′)	1·449 (3)	C(1′)—C(2′)	1·529 (4)
O(4′)—C(4′)	1·443 (4)	C(1′)—C(9)	1·501 (4)
N(1)—C(2)	1·350 (4)	C(2′)—C(3′)	1·513 (5)
N(1)—C(6)	1·333 (4)	C(3′)—C(4′)	1·512 (4)
N(3)—C(2)	1·315 (4)	C(4)—C(5)	1·378 (4)
N(3)—C(4)	1·370 (4)	C(4)—C(9)	1·410 (5)
N(6)—C(6)	1·340 (4)	C(4′)—C(5′)	1·497 (4)
N(7)—N(8)	1·361 (4)	C(5)—C(6)	1·413 (5)

C(1′)—O(4′)—C(4′)	109·8 (2)	C(5)—C(4)—C(9)	105·3 (2)
C(2)—N(1)—C(6)	118·4 (3)	O(4′)—C(4′)—C(3′)	104·4 (3)
C(2)—N(3)—C(4)	112·3 (3)	O(4′)—C(4′)—C(5′)	108·6 (2)
N(8)—N(7)—C(5)	110·7 (2)	C(3′)—C(4′)—C(5′)	113·1 (3)
N(7)—N(8)—C(9)	106·4 (3)	N(7)—C(5)—C(4)	107·2 (3)
O(4′)—C(1′)—C(2′)	106·0 (3)	N(7)—C(5)—C(6)	132·6 (3)
O(4′)—C(1′)—C(9)	109·8 (2)	C(4)—C(5)—C(6)	120·2 (3)
C(2′)—C(1′)—C(9)	113·2 (2)	Cl—C(5′)—C(4′)	112·0 (2)
O(2′)—C(2′)—C(1′)	107·2 (2)	N(1)—C(6)—N(6)	120·4 (3)
O(2′)—C(2′)—C(3′)	112·0 (3)	N(1)—C(6)—C(5)	116·8 (3)
C(1′)—C(2′)—C(3′)	102·5 (2)	N(6)—C(6)—C(5)	122·8 (3)
N(1)—C(2)—N(3)	129·7 (3)	N(8)—C(9)—C(1′)	122·0 (3)
C(2′)—C(3′)—C(4′)	102·8 (3)	N(8)—C(9)—C(4)	110·4 (3)
N(3)—C(4)—C(5)	122·6 (3)	C(1′)—C(9)—C(4)	127·5 (2)
N(3)—C(4)—C(9)	132·1 (3)		

The glycosidic angle is in the *anti* domain, with a value of 142·1 (4)°. This is in contrast with the *syn* conformation typical of formycin salts (McKenna, Neidle & Serafinowski, 1987; Koyama, Umezawa & Iitaka, 1974), with an intramolecular hydrogen bond between O(5′) and N(3) stabilizing the arrangement, which has been found in 3′-deoxyformycin A (McKenna, Neidle & Serafinowski, 1987) and 2′,3′-dideoxyformycin A (Neidle, Urpi, Serafinowski & Whitby, 1989) when they are hydrochloride salts. In the former case a proton was located attached to the N(3) atom; the analysis of 2′,3′-dideoxyformycin hydrochloride was of insufficient accuracy for it to be found. Formycin A 5′-monophosphate is similarly protonated at N(3) (Giranda, Berman & Schramm, 1988). The replacement of O(5′) by a Cl atom in the present structure renders such an interaction unlikely in the absence of protonation at N(3).

Conversely, the protonated form of 5′-chloro-3′,5′-dideoxyformycin A is likely to have a *syn* conformation in view of the high electronegativity of the Cl atom.

The conformation about the C(4′)—C(5′) bond is *trans* with a Cl—C(5′)—C(4′)—C(3′) torsion angle of 175·6 (3)°. It is possible that the increased size of the Cl atom, compared with a hydroxyl O atom in a normal nucleoside, is responsible for this *trans* arrangement.

The water molecule is, unusually, at close hydrogen-bonding distance to the deoxyribose sugar ring O atom [O*W*···O(4′) 2·809 (3) Å].

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5-Methylbenz[*a*]anthracene: a Mildly Carcinogenic Planar Polycyclic Hydrocarbon

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Abstract. $C_{19}H_{14}$, $M_r = 242·3$, monoclinic, $P2_1/c$, $a = 5·994$ (1), $b = 23·482$ (6), $c = 18·367$ (2) Å, $\beta = 90·57$ (1)°, $V = 2585·0$ (2) Å^3, $Z = 8$, $D_m = 1·23$ (1) (NaI flotation), $D_x = 1·25$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 5·6$ cm^{-1}, $F(000) = 1024$, $T = 298$ K, final $R = 0·053$ for 2618 observed reflections. The two independent molecules have different orientations within the cell and are nearly planar (r.m.s. deviations of C atoms 0·055 and 0·041 Å), but the dihedral angles of 3·4 and 6·2° between the outermost *A* and *D* rings are larger than in most benz[*a*]anthracenes unsubstituted in the bay position. The shortest mean C—C bonds are C5—C6 = 1·324 (4) (*K* region), C10—C11 = 1·357 (4), C8—C9 = 1·355 (4) and C2—C3 = 1·360 (4) Å. In the bay region, the beach bond is 1·471 (4) Å with beach angles C12—C18—C13 = 122·2 (4) and C18—C13—C1 = 121·4 (4)°.

Introduction. Isomeric monomethylbenz[*a*]anthracenes (MBA's) encompass a wide range of carcinogenic activities (Wislocki, Fiorentini, Fu, Yang & Lu, 1982). They, and the dimethylbenz[*a*]anthracenes (DMBA's), vary in shape from the appreciably distorted or type II (Briant, Jones & Shaw, 1985) when either or each of the bay sites 1 and 12 carries a

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