separated, the aqueous layer was extracted with additional ether, and the combined ethereal extracts were dried ($MgSO_4$) and concentrated. The crude product was crystallized from petroleum ether/methylene chloride to yield 4 mg (40%) of chuangxinmycin: mp 145-145.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (d, 3 H J = 7 Hz), 3.80 (d of q, 1 H, J = 7, 3.5 Hz), 4.30 (d, 1 H, J = 3.5 Hz), 6.9-7.3 (m, 4 H), 8.6 (br s, 1 H).

Exact mass calcd for $C_{12}H_{11}NO_2S$: 233.0511. Found: 233.0507.

Acknowledgment. We are indebted to the National Institutes of Health (Grant R01 HL 20579) for support of these investigations. We are grateful to Dr. Zhi-Ping Zhang of the Institute of Materia Medica for generous samples of chuangxinmycin. The technical assistance of Scott Gordon is also acknowledged.

Registry No. *cis*-(-)-**1**, 63339-68-4; **4**, 83561-15-3; **7**, 73363-65-2; **10**, 606-20-2; **11**, 73363-64-1; **13**, 83561-16-4; **15**, 78283-22-4; **15** diethyl acetal, 83561-17-5; **16**, 83561-18-6; **17**, 73363-63-0; **19**, 83602-19-1; **20**, 83602-20-4; $HSCH_2CO_2CH_3$, 2365-48-2; *N*,*N*-dimethylformamide dimethyl acetal, 4637-24-5; triethyl orthoformate, 122-51-0.

Supplementary Material Available: X-ray structure and listings of atomic coordinates, temperature parameters, bond distances, and bond angles (6 pages). Ordering information is given on any current masthead page.

Structure and Conformation of the Antiviral Nucleoside 2′-Fluoro-5-iodoarabinosylcytosine (FIAC). The Gauche Effect in Nucleosides[1]

George I. Birnbaum,*[2a] Miroslaw Cygler,[2a] Kyoichi A. Watanabe,[2b] and Jack J. Fox[2b]

Contribution from the Department of Biological Sciences, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6, and the Sloan-Kettering Institute for Cancer Research, New York, New York 10021. Received April 15, 1982

Abstract: The three-dimensional structure of 2′-fluoro-5-iodoarabinosylcytosine (FIAC), an inhibitor of herpes simplex and herpes zoster viruses, was determined by X-ray crystallography. The crystals belong to the monoclinic space group $P2_1$, and the cell dimensions are a = 4.747 (2), b = 14.017 (2), and c = 18.514 (3) Å, β = 90.28°. Intensity data were measured with a diffractometer, and the structure was solved by the heavy-atom method. Least-squares refinement, which included the coordinates of the hydrogen atoms, converged at R = 4.8%. In the asymmetric unit there are two crystallographically independent molecules of FIAC that are related by a pseudo-2-fold screw axis. The conformation about the glycosidic bond is anti, χ_{CN} having the rather low value of 19.1°. Contrary to expectations based on the substituent effect, the furanose ring adopts the C(3′) endo-C(2′) exo (type N) pucker. The influence of electronegative substituents on the ring conformation is being discussed in terms of the gauche effect. The $-CH_2OH$ side chain is disordered, giving rise to equal populations of the gauche$^+$ and trans rotamers.

The antiviral activities of some arabinonucleosides as well as of some 5-substituted 2′-deoxyribonucleosides have been known for several years.[3] Recently, Watanabe et al.[4] synthesized a new series of variously 5-substituted 2′-deoxy-2′-fluoroarabinofuranosylpyrimidines, several of which exhibited marked antiherpetic activity. One of these, 1-(2′-deoxy-2′-fluoro-β-D-arabinofuranosyl)-5-iodocytosine (also called 2′-fluoro-5-iodoarabinosylcytosine or FIAC) was found[4,5] to be especially capable of suppressing the replication of various strains of herpes simplex virus types 1 and 2, as well as of herpes zoster and cytomegalovirus. Continuing our structural studies of chemotherapeutic nucleosides,[6] we decided to carry out an X-ray analysis of FIAC. In particular, we wished to compare the conformation in the solid state with that determined in solution[7] and with the conformations of other arabinonucleosides. The effect of electronegative ring substituents on the conformation of the furanose ring in nucleosides has been the subject of some discussion in recent literature.[8-10] Since no fluoroarabinonucleoside has ever been subjected to an X-ray analysis, the crystal structure determination of FIAC was considered to be particularly valuable.

Experimental Section

2′-Fluoro-5-iodoarabinosylcytosine (FIAC), $C_9H_{11}N_3O_4FI$, was prepared as described by Watanabe et al.[4] and crystallized from methanol. Systematic absences and the symmetry of reflection intensities on precession photographs indicated the orthorhombic space group $P2_12_12_1$. All crystals in our possession were rather mosaic (0.8-0.9°); nevertheless we collected data with molybdenum radiation on a CAD-4 diffractometer. The cell dimensions were as follows: a = 4.742 (4), b = 14.012 (5), and c = 18.504 (6) Å. The angles α, β, and γ were 90°, within experimental error (±0.2°). The data were corrected for Lorentz and polarization factors and for absorption. The structure was determined by the heavy-atom method and refined by block-diagonal least squares with anisotropic temperature parameters for non-hydrogen atoms. The refinement converged at R = 0.069 (R' = 0.077) for 1464 observed re-

---

(1) Issued as NRCC No. 20495.

(2) (a) National Research Council. (b) Sloan-Kettering Institute for Cancer Research.

(3) For a recent review, see: De Clercq, E.; Descamps, J.; Verhelst, G.; Walker, R. T.; Jones, A. S.; Torrence, P. F.; Shugar, D. *J. Infect. Dis.* **1980**, *141*, 563-574.

(4) Watanabe, K. A.; Reichman, A.; Hirota, K.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1979**, *22*, 21-24.

(5) (a) Lopez, C.; Watanabe, K. A.; Fox, J. J. *Antimicrob. Agents Chemother.* **1980**, *17*, 803-806. (b) Fox, J. J.; Lopez, C.; Watanabe, K. A. In "Medicinal Chemistry Advances"; De las Heras, F. G.; Vega, S., Eds.; Pergamon Press: New York, 1981; pp 27-40.

(6) (a) Birnbaum, G. I.; Lin, T.-S.; Shiau, G. T.; Prusoff, W. H. *J. Am. Chem. Soc.* **1979**, *101*, 3353-3358. (b) Birnbaum, G. I.; Deslauriers, R.; Lin, T.-S.; Shiau, G. T.; Prusoff, W. H. *Ibid.* **1980**, *102*, 4236-4241. (c) Birnbaum, G. I.; Watanabe, K. A.; Fox, J. J. *Can. J. Chem.* **1980**, *58*, 1633-1638. (d) Birnbaum, G. I.; Cygler, M.; Kusmierek, J. T.; Shugar, D. *Biochem. Biophys. Res. Commun.* **1981**, *103*, 968-974.

(7) Lipnick, R. L.; Fissekis, J. D. *Biochim. Biophys. Acta* **1980**, *608*, 96-102.

(8) Uesugi, S.; Miki, H.; Ikehara, M.; Iwahashi, H.; Kyogoku, Y. *Tetrahedron Lett.* **1979**, 4073-4076.

(9) Klimke, G.; Cuno, I.; Lüdemann, H.-D.; Mengel, R.; Robins, M. J. *Z. Naturforsch., C: Biosci.* **1980**, *35C*, 853-864.

(10) (a) Guschlbauer, W.; Jankowski, K. *Nucleic Acids Res.* **1980**, *8*, 1421-1433. (b) Haertlé, T.; Wohlrab, F.; Guschlbauer, W. *Eur. J. Biochem.* **1979**, *102*, 223-230.

0002-7863/82/1504-7626$01.25/0

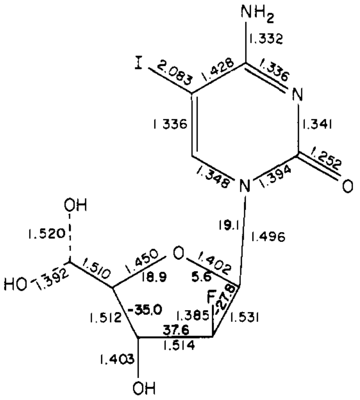


Figure 1. Average bond lengths and some torsion angles in FIAC. The disorder of O(5′) is indicated by dashed bonds.

flections. However, we were suspicious of the results because of unusually high discrepancies between observed and calculated structure factors for many reflections, both weak and strong. For instance, 1 1 11 ($|F_o|$ = 4.46, $|F_c|$ = 30.33), 0 1 14 (7.98, 27.36), 1 2 14 (4.90, 22.86), 0 1 15 (8.41, 26.00), 2 1 3 (89.56, 70.24). Consequently, we decided to recrystallize our sample of FIAC, and we managed to obtain crytstals that, although smaller, were much less mosaic (0.3°). One of these crystals, measuring 0.05 × 0.10 × 0.26 mm, was mounted on the CAD-4 diffractometer, and the dimensions of the unit cell were determined from a least-squares refinement of the angular settings of 22 reflections. These reflections, located in four different octants, had medium intensities and were in the mid range of the molybdenum sphere ($27 < 2\theta < 34°$). The new cell parameters showed that the space group is, in fact, monoclinic, $P2_1$. The following crystal data were obtained: a = 4.747 (2), b = 14.017 (2), and c = 18.514 (3) Å, β = 90.28 (2)°; V = 1229.5 Å^3, d_x = 2.01 g cm^{-3}, Z = 4, $F(000)$ = 720, μ (Mo Kα) = 26.6 cm^{-1}. The intensity data were measured ($\omega/2\theta$ scans) at room temperature (20 °C) with monochromatized Mo Kα radiation (λ = 0.71069 Å). Three reflections were monitored at intervals of 100 min; their intensities showed variations of ±2.5%. Of the 3848 reflections with $2\theta \leq 60°$, there were 2636 reflections with $I > 1.5\sigma(I)$. The intensities were corrected for Lorentz and polarization factors. An analytical absorption correction was also applied, varying in the range 1.14–1.30.

Refinement was resumed with the atomic parameters previously obtained, and the second molecule in the asymmetric unit was found on a weighted Fourier map. The two independent molecules are related to each other by a pseudo-2-fold screw axis, making the structure pseudoorthorhombic. In each molecule, the oxygen atom in the side chain was found in two equally populated positions. Consequently, O(5′) and O(5″) were refined with occupancy factors of 0.5. The refinement was by block-diagonal least squares. All scattering factors were taken from the "International Tables for X-ray Crystallography",[11] and the iodine curve was corrected for anomalous dispersion ($\Delta f'$ = −0.726, $\Delta f''$ = 1.812). The hydrogen atoms were located on difference Fourier maps, and their coordinates were also refined. Each hydrogen atom was assigned a temperature parameter corresponding to that of the heavy atom to which it is bonded. Throughout the refinement the function $\sum w(|F_o| - |F_c|)^2$ was minimized and a factor of 0.8 applied to all shifts. The following weighting scheme was used during the final stages: $w = |F_o|/27$ for $|F_o| \leq 27$, $w = 27/|F_o|$ for $|F_o| > 27$. This weighting scheme made the average values of $w(\Delta F^2)$ fairly independent of $|F_o|$ and $\sin^2 \theta$. After the final cycle, the average parameter shift equaled 0.1σ and the largest 0.5σ. The conventional residual index R is 0.048, and the weighted index R' is 0.049 for 2636 reflections. The observed and calculated structure factors of the previously mentioned reflections are as follows: 1 1 11 (30.68, 30.28) , 0 1 14 (27.61, 27.63), 1 2 14 (23.65, 23.50), 0 1 15 (24.78, 25.65), 2 1 3 (66.10, 64.49). There are many significant differences in the calculated structure factors of hkl and $hk\bar{l}$ pairs: e.g., 2 1 1 (51.91, 41.85), 4 2 1 (18.27, 11.42), 2 4 1 (27.70, 21.41), 2 8 1 (17.71, 9.08), 2 1 2 (48.12, 38.56). A final difference Fourier map showed no significant features. The final atomic coordinates of the non-hydrogen atoms and their equivalent isotropic B values are given in Table I.

Results and Discussion

The chemical structure of FIAC is illustrated in Figure 1, which also shows the averaged bond lengths and some torsion angles.

Table I. Final Atomic Parameters and Their Standard Deviations[a]

atom	x	y	z	B_{eqv}
N(1)	3189 (14)	4493 (4)	3825 (3)	1.8 (1)
	11743 (14)	5521 (5)	8829 (3)	2.0 (1)
C(2)	4007 (18)	3538 (6)	3737 (4)	2.3 (2)
	10977 (18)	6467 (6)	8739 (4)	2.3 (2)
O(2)	3001 (14)	2936 (4)	4160 (3)	3.1 (2)
	12001 (13)	7086 (4)	9154 (3)	2.7 (1)
N(3)	5731 (15)	3301 (5)	3194 (4)	2.4 (2)
	9233 (16)	6711 (5)	8198 (4)	2.4 (2)
C(4)	6755 (16)	3963 (6)	2758 (4)	2.1 (2)
	8160 (16)	6030 (6)	7762 (3)	2.2 (2)
N(4)	8638 (21)	3695 (6)	2269 (4)	3.7 (2)
	6271 (21)	6305 (6)	7269 (4)	4.0 (2)
C(5)	5915 (20)	4938 (6)	2820 (4)	2.5 (2)
	9039 (20)	5061 (6)	7840 (4)	2.6 (2)
I(5)	7324.6 (17)	6008.0 (5)	2133.6 (4)	4.37 (2)
	7587.5 (18)	4000.0	7140.9 (4)	4.52 (2)
C(6)	4162 (17)	5152 (5)	3367 (4)	2.0 (2)
	10815 (20)	4836 (6)	8368 (4)	2.5 (2)
C(1′)	1312 (18)	4733 (5)	4438 (4)	2.1 (2)
	13675 (17)	5286 (6)	9451 (4)	2.1 (2)
C(2′)	2981 (17)	4834 (6)	5138 (4)	2.0 (2)
	11993 (17)	5154 (6)	10153 (4)	2.3 (2)
F(2′)	5397 (11)	4286 (4)	5162 (3)	3.0 (1)
	9613 (11)	5730 (4)	10175 (3)	3.1 (1)
C(3′)	3671 (16)	5905 (5)	5150 (4)	1.9 (2)
	11290 (16)	4118 (6)	10158 (4)	2.1 (2)
O(3′)	4315 (15)	6196 (4)	5852 (3)	3.2 (2)
	10691 (15)	3821 (4)	10868 (3)	3.2 (2)
C(4′)	975 (17)	6309 (6)	4842 (4)	2.3 (2)
	13973 (15)	3701 (6)	9853 (5)	2.1 (2)
O(4′)	30 (12)	5612 (4)	4314 (3)	2.3 (1)
	14942 (12)	4391 (4)	9326 (3)	2.5 (1)
C(5′)	1239 (22)	7275 (7)	4493 (6)	3.4 (2)
	13666 (22)	2733 (7)	9499 (6)	3.5 (3)
O(5′)	332 (3)	7305 (10)	3865 (7)	3.0 (3)
	1161 (3)	2691 (8)	8876 (7)	2.6 (3)
O(5″)	−147 (3)	7694 (9)	4481 (6)	2.8 (3)
	1628 (3)	2317 (9)	9468 (7)	3.3 (3)

[a] The top and bottom values refer to molecules A and B, respectively. The x coordinates of O(5′) and O(5″) were multiplied by 10^3; all other coordinates by 10^4.

Table II. Bond Lengths (Å) in Molecules A and B[a]

	molecule	
	A	B
N(1)–C(2)	1.404	1.384
N(1)–C(6)	1.338	1.357
N(1)–C(1′)	1.486	1.506
C(2)–N(3)	1.341	1.341
C(2)–O(2)	1.249	1.254
N(3)–C(4)	1.324	1.348
C(4)–C(5)	1.428	1.428
C(4)–N(4)	1.329	1.334
C(5)–C(6)	1.348	1.325
C(5)–I(5)	2.079 (8)	2.087 (8)
C(1′)–C(2′)	1.522	1.540
C(1′)–O(4′)	1.393	1.410
C(2′)–C(3′)	1.537	1.490
C(2′)–F(2′)	1.381	1.389
C(3′)–C(4′)	1.510	1.513
C(3′)–O(3′)	1.395 (9)	1.410 (9)
C(4′)–O(4′)	1.451	1.450
C(4′)–C(5′)	1.505 (13)	1.514 (13)
C(5′)–O(5′)	1.529 (17)	1.510 (17)
C(5′)–O(5″)	1.414 (17)	1.371 (18)

[a] Estimated standard deviations are 0.010–0.012 Å unless otherwise indicated.

The bond lengths and bond angles of the independent molecules A and B are given in Tables II and III. Some selected torsion angles are listed in Table IV. The precision of the results is not as high as one attains with structures without heavy atoms, but quite respectable when one considers the presence of two iodine

---

(11) "International Tables for X-ray Crystallography", Ibers, J. A., Hamilton, W. C., Eds.; Kynoch Press: Birmingham, England, 1974; Vol. IV.

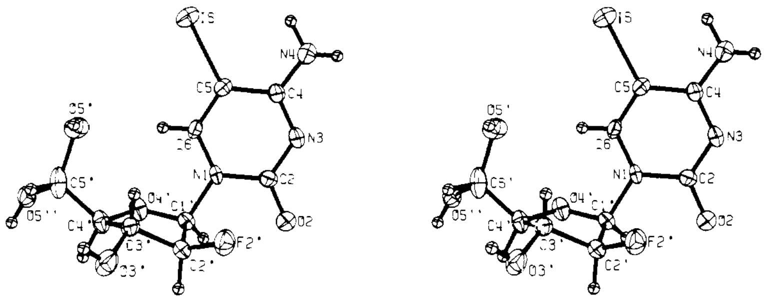


Figure 2. Stereoscopic view of FIAC; the thermal ellipsoids correspond to 50% probability.

Table III. Bond Angles (deg) in Molecules A and B[a]

	molecule A	molecule B
C(2)-N(1)-C(6)	119.3	121.2
C(2)-N(1)-C(1')	118.2	117.4
C(6)-N(1)-C(1')	122.6	121.4
N(1)-C(2)-N(3)	120.7	119.8
N(1)-C(2)-O(2)	117.7	119.2
N(3)-C(2)-O(2)	122.7	121.1
C(2)-N(3)-C(4)	120.7	119.8
N(3)-C(4)-C(5)	121.2	120.2
N(3)-C(4)-N(4)	117.9	117.2
C(5)-C(4)-N(4)	120.9	122.6
C(4)-C(5)-C(6)	116.6	119.0
C(4)-C(5)-I(5)	123.4	121.3
C(6)-C(5)-I(5)	120.0	119.7
C(5)-C(6)-N(1)	122.6	120.0
N(1)-C(1')-C(2')	111.1	110.8
N(1)-C(1')-O(4')	109.7	109.2
O(4')-C(1')-C(2')	106.5	104.8
C(1')-C(2')-C(3')	102.3	103.8
C(1')-C(2')-F(2')	113.9	112.3
C(3')-C(2')-F(2')	111.5	112.6
C(2')-C(3')-C(4')	100.4	100.7
C(2')-C(3')-O(3')	110.2	109.8
C(4')-C(3')-O(3')	115.2	114.1
C(3')-C(4')-O(4')	105.2	105.3
C(3')-C(4')-C(5')	115.3	115.4
O(4')-C(4')-C(5')	110.1	109.7
C(4')-O(4')-C(1')	110.6	110.2
C(4')-C(5')-O(5')	114.0 (9)	115.3 (9)
C(4')-C(5')-O(5'')	107.6 (9)	108.3 (9)
O(5')-C(5')-O(5'')	124 (1)	122 (1)

[a] Estimated standard deviations are 0.6-0.8° unless otherwise indicated.

Table IV. Selected Torsion Angles (deg)

		molecule A	molecule B
C(6)-N(1)-C(1')-C(2')		−97.4	−96.7
C(6)-N(1)-C(1')-O(4')	χ_{CN}	20.1	18.2
C(2)-N(1)-C(1')-C(2')		81.2	84.1
C(2)-N(1)-C(1')-O(4')		−161.3	−161.0
N(1)-C(1')-C(2')-C(3')		91.7	89.8
N(1)-C(1')-C(2')-F(2')		−28.7	−32.0
O(4')-C(1')-C(2')-C(3')	τ_1	−27.7	−27.8
O(4')-C(1')-C(2')-F(2')		−148.1	−149.6
C(1')-C(2')-C(3')-C(4')	τ_2	37.4	37.9
C(1')-C(2')-C(3')-O(3')		159.3	158.5
F(2')-C(2')-C(3')-C(4')		159.5	159.5
F(2')-C(2')-C(3')-O(3')		−78.7	−79.9
C(2')-C(3')-C(4')-O(4')	τ_3	−34.8	−35.2
C(2')-C(3')-C(4')-C(5')		−156.2	−156.3
O(3')-C(3')-C(4')-O(4')		−153.1	−152.7
O(3')-C(3')-C(4')-C(5')		85.5	86.2
C(3')-C(4')-O(4')-C(1')	τ_4	18.9	18.9
C(5')-C(4')-O(4')-C(1')		143.7	143.6
C(4')-O(4')-C(1')-N(1)		−114.4	−113.5
C(4')-O(4')-C(1')-C(2')	τ_0	5.9	5.3
C(3')-C(4')-C(5')-O(5')		59.1	58.6
O(4')-C(4')-C(5')-O(5')		−59.6	−60.1
O(4')-C(4')-C(5')-O(5'')		82.7	81.0
C(3')-C(4')-C(5')-O(5'')		−158.6	−160.4

Table V. Deviations of Atoms (Å) from Least-Squares Planes[a]

atom	molecule A	molecule B	atom	molecule A	molecule B
N(1)	−0.004	−0.015	C(6)	0.004	0.019
C(2)	−0.003	0.000	C(1')[b]	−0.046	−0.055
N(3)	0.014	0.019	O(2)[b]	0.025	0.040
C(4)	−0.020	−0.026	N(4)[b]	−0.114	−0.107
C(5)	0.011	0.008	I(5)[b]	0.024	0.040

[a] Estimated standard deviations are 0.001 Å for I and 0.006-0.009 Å for the other atoms. [b] Atoms not included in the calculation of the plane.

atoms in the asymmetric unit. The two independent molecules of FIAC being related by pseudosymmetry, it is not surprising that their geometries are identical within experimental error. We can therefore use average values of bond lengths (Figure 1), bond angles, and torsion angles for comparisons with related nucleosides.

Aglycone Moiety. The six atoms of the pyrimidine ring are almost but not exactly coplanar (Table V). Of the ring substituents, N(4) shows the largest deviation from the mean plane, probably because of the hydrogen bonds in which it takes part (see below). The deviations of the other substitutents are also statistically significant.

All bond lengths and bond angles are in very good agreement with the average values that were calculated from 11 N(1)-substituted, unprotonated cytosine rings.[12] This means that neither the bulk of the iodine atom nor its tendency to withdraw electrons is sufficient to cause appreciable changes of the ring geometry.

The overall conformation of the molecules can be seen in the stereoscopic plot (Figure 2). The orientation of the pyrimidine ring with respect to the arabinosyl moiety falls just outside the usual anti range. The values of the glycosyl torsion angles χ_{CN} [C(6)-N(1)-C(1')-O(4')] are 18.2° and 20.1° in molecules A and B, respectively. In the literature we found ten other crystal structures of β-arabinonucleosides with the anti conformation.[13] In nine of these, χ_{CN} was in the range 24.1-36.6°, and only in arabinosyladenine was χ_{CN} (57.8°) found to be substantially different.[13f] It is reasonable to assume that this narrow range is attributable to intramolecular interactions between the "up" substituents at C(2') (in most cases -OH) and either H(6) (in pyrimidines) or H(8) (in purines). As χ_{CN} increases, the O(2')···H contacts decrease and may become too short, especially in the case

---

(12) Wang, A. H.-J.; Barrio, J. R.; Paul, I. C. *J. Am. Chem. Soc.* **1976**, *98*, 7401-7408.

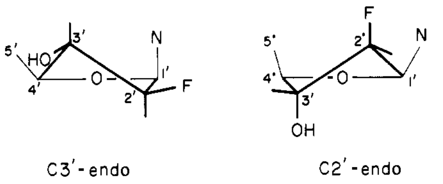
(13) (a) Tougard, P. *Biochim. Biophys. Acta* **1973**, *319*, 116-121. (b) Sherfinski, J. S.; Marsh, R. E. *Acta Crystallogr., Sect. B* **1973**, *29B*, 192-198. (c) Tollin, P.; Wilson, H. R.; Young, D. W. *Ibid.* **1973**, *29*, 1641-1647. (d) Tougard, P. *Ibid.* **1973**, *29*, 2227-2232. (e) Tougard, P.; Lefebvre-Soubeyran, O. *Ibid.* **1974**, *30*, 86-89. (f) Bunick, G.; Voet, D. *Ibid.* **1974**, *30*, 1651-1660. (g) Chwang, A. K.; Sundaralingam, M.; Hanessian, S. *Ibid.* **1974**, *30*, 2273-2277. (h) Sherfinski, J. S.; Marsh, R. E.; Chwang, A. K.; Sundaralingam, M. *Ibid.* **1979**, *35*, 2141-2144. (i) Saenger, W. *J. Am. Chem. Soc.* **1972**, *94*, 621-626. (j) Birnbaum, G. I.; Darzynkiewicz, E.; Shugar, D. *Ibid.* **1975**, *97*, 5904-5908.

of pyrimidine nucleosides. One would expect this effect to be particularly pronounced when the sugar ring is in the C(2′) endo conformation and the 2′-OH group is axially oriented. In fact, theoretical calculations by Yathindra and Sundaralingam[14] indicated a relationship between χ_{CN} and the phase angle of pseudorotation (P) which is inverse to that found in ribonucleosides, i.e., a higher range for χ_{CN} in C(3′) endo than in C(2′) endo arabinosides. The limited data available thus far do not appear to bear out this conclusion. It has also been pointed out[13f] that in β-arabinosides the distance between O(2′) and the glycosyl nitrogen atoms is shorter that the van der Waals contact of 2.9 Å. Previous crystal structures have shown this distance to be in the range 2.75–2.85 Å.[13] The van der Waals radius of fluorine being somewhat smaller than that of oxygen, it is not surprising that in FIAC the N(1)···F(2′) distance is only 2.704 Å.

Arabinose Moiety. All bond lengths in the sugar moiety, except one, have normal values. The exception is C(5′)–O(5′), which is about 0.1 Å longer than usual. This may be attributable to the previously mentioned disorder. As is often the case, C(4′)–O(4′) is significantly longer than C(1′)–O(4′). The C(2′)–F(2′) bond agrees in length with C–F bonds found in two 2′-deoxy-2′-fluororibonucleosides.[15,16] The endocyclic bond angles are essentially the same as those observed in other arabinonucleosides with a type-N conformation.[13f-i] Exocyclic angles are not comparable because they are strongly influenced by the hydrogen bonds in which OH groups participate. This must account for the significant difference between C(2′)–C(3′)–O(3′) and C(4′)–C(3′)–O(3′).

The most interesting aspect of this structure is the conformation of the sugar ring and the effect of the electronegative F substituent on it. The phase angle of pseudorotation (P) is 10.0°, and the maximum amplitude of puckering (τ_m) is 38.2°.[17] Thus, the ring has the C(3′) endo–C(2′) exo conformation (${}^3T_2$) and its pucker can also be described as type N. This conformation is in disagreement with recently made observations and predictions.[8,10] Uesugi et al.[8] studied the ^{1}H NMR spectra of a series of 2′-substituted 2′-deoxyadenosines and observed a linear relationship between the electronegativity of the substituent and the mole fraction of the N conformer. The largest electronegativity (for F) corresponded to the highest proportion (67%) of the N conformer. They concluded that it should be possible to predict the conformation of the sugar moiety on the basis of the electronegativity of the 2′-substituent, not only for adenosines but for other nucleosides as well. Since in FIAC the configuration of the F substitutent is “up” rather than “down”, thus reversing the direction of this polar bond, their conclusion would lead one to expect a low proportion of the N conformation.

A similar study was published more recently by Guschlbauer et al.,[10] who carried out NMR analyses of 2′-substituted uridines. They found that the mole fraction of the N conformer increases approximately linearly with increasing electronegativity of the 2′-substituent. These authors concluded that the polarity of the sugar substituents has a dominant influence on the conformation of the pentofuranose ring because the most electronegative substituent “pulls the pucker towards its side”.[10a] Therefore, they predicted[10b] “that the fluorinated arabinosyl analogue should be in an extreme S form”. Moreover, they suggested[10a] “that the difference in electronegativity of H and OH is the dominating force in the differences between DNA and RNA”. They considered it desirable to investigate the theoretical basis for their findings but did not themselves offer any explanations.



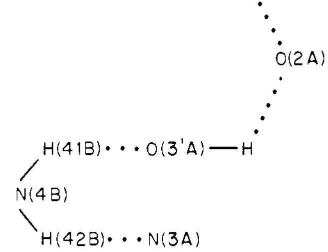
C3′-endo   C2′-endo

Figure 3. Arabinose rings of FIAC in C(3′) endo and C(2′) endo conformations.

The theoretical basis of what Uesugi et al.[8] and Guschlbauer et al.[10] have observed appears to be[18] the well-known “gauche effect”, which was described as “a tendency to adopt that structure which has the maximum number of gauche interactions between the adjacent electron pairs and/or polar bonds”.[20] In 2′-deoxy-2′-fluoro*ribo*nucleosides, the strongly polar C(2′)–F bond is gauche oriented with respect to C(1′)–O(4′) and C(3′)–O(3′) if the ring conformation is C(3′) endo (type N). However, if the conformation is C(2′) endo (type S), C(2′)–F has the less favorable trans orientation with respect to C(1′)–O(4′). This explains the observed preference for a type-N pucker, which, according to recent calculations by Olson,[19] amounts to 1.5 kcal mol^{-1}. In 2′-deoxy-2′-fluoro*arabino*nucleosides, there is no such definite preference. When the ring adopts the type-N conformation, C(2′)–F has the preferred gauche orientation to C(3′)–O(3′) but it is trans to C(1′)–O(4′). In the case of type-S pucker, the situation is reversed, but this conformer is slightly favored because C(3′)–O(3′) is gauche to C(4′)–O(4′) (Figure 3). However, the gauche effect is rather weak for C–O/C–O interactions (0.6 kcal mol^{-1})[21] and could be easily overcome by packing forces (e.g., intermolecular hydrogen bonds) in the solid state or by solvent and temperature effects in solution. It should be noted that Lipnick and Fissekis recently carried out a 270-MHz ^{1}H NMR analysis of FIAC and of several other arabinosylcytosines with F, Cl and OMe substituted at C(2′).[7] Their study showed that in all these cases, as well as in unsubstituted arabinosylcytosine, there is an ~50:50 mixture of type-N and type-S conformers. These observations contradict the semiempirical energy calculations of Yathindra and Sundaralingam,[14] according to which arabinonucleosides should have a preference for the type-N conformation.

As mentioned above, the $-CH_2OH$ side chain is disordered, giving rise to two equally populated positions for the oxygen atom. O(5′) corresponds to the g^+ conformation while O(5″) gives the t rotamer. These conformations are the most commonly observed ones in nucleosides, and Lipnick and Fissekis also observed an equal population (41%) of these two rotamers in aqueous solution (the remaining 18% were assigned to the g^- rotamer).[7] In the crystal structure of FIAC, these conformations are stabilized by hydrogen bonds (see below).

Hydrogen Bonding and Packing. All OH and NH protons participate in intermolecular hydrogen bonds. In addition, there are intramolecular C–H···O bonds present. The hydrogen-bond network can be represented schematically as follows:



The other half of the network can be obtained by interchanging molecules A and B in the above scheme. The geometrical details of all hydrogen bonds are given in Table VI. As commonly observed in X-ray analyses, the O–H, N–H, and C–H bonds

---

(14) Yathindra, N.; Sundaralingam, M. *Biochim. Biophys. Acta* **1979**, *564*, 301–310.

(15) Suck, D.; Saenger, W.; Main, P.; Germain, G.; Declercq, J.-P. *Biochim. Biophys. Acta* **1974**, *361*, 257–265.

(16) Hakoshima, T.; Omori, H.; Tomita, K.; Miki, H.; Ikehara, M. *Nucleic Acids Res.* **1981**, *9*, 711–729.

(17) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205–8212.

(18) The contribution of the gauche energy term to the conformations of ribose and 2′-deoxyribose sugars was recently discussed by Olson.[19]

(19) Olson, W. K. *J. Am. Chem. Soc.* **1982**, *104*, 278–286.

(20) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102–111.

(21) Zefirov, N. A.; Samoshin, V. V.; Subbotin, O. A.; Baranenkov, V. I.; Wolfe, S. *Tetrahedron* **1978**, *34*, 2953–2959.

Table VI. Distances and Angles for Hydrogen Bonds

D	A	A at	distances, Å			angles, deg	
			D···A	H···A	$\mathrm{H}\cdots\mathrm{A}_{\mathrm{corr}}$	D–H···A	H–D···A
C(6A)-H···	O(5′A)	x, y, z	3.182	2.35	2.16	159	15
O(5′A)-H···	O(5″A)	$1+x, y, z$	2.774	2.02	1.80	175	4
O(5″A)-H···	O(2A)	$\bar{x}, {}^1/_2+y, 1-z$	2.644	1.91	1.78	148	22
O(3′A)-H···	O(2A)	$1-x, {}^1/_2+y, 1-z$	2.751	2.02	1.79	175	4
N(4B)-H(41B)···	O(3′A)	x, y, z	2.782	2.16	2.01	133	35
N(4B)-H(42B)···	N(3A)	$1-x, {}^1/_2+y, 1-z$	3.075	2.36	2.06	169	8
C(6B)-H···	O(5′B)	x, y, z	3.173	2.21	2.15	156	16
O(5′B)-H···	O(5″B)	$-1+x, y, z$	2.811	1.86	1.84	177	2
O(5″B)-H···	O(2B)	$3-x, -{}^1/_2+y, 2-z$	2.696	2.12	1.86	149	24
O(3′B)-H···	O(2B)	$2-x, -{}^1/_2+y, 2-z$	2.748	1.91	1.79	169	8
N(4A)-H(41A)···	O(3′B)	$x, y, -1+z$	2.780	2.19	2.15	118	44
N(4A)-H(42A)···	N(3B)	$2-x, -{}^1/_2+y, 1-z$	3.085	2.31	2.08	162	13

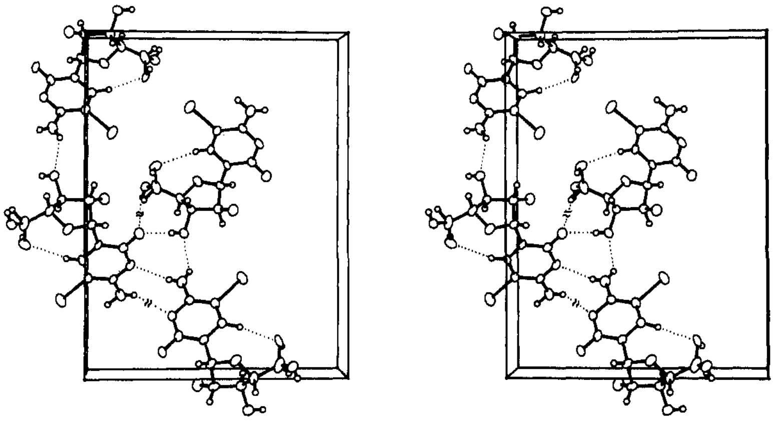


Figure 4. Stereoscopic view along x of the molecular packing in the crystal. The directions of the axes are $y \leftarrow$ and $z \downarrow$. Dotted lines indicate hydrogen bonds.

appear shorter than their real values of 0.97, 1.04, and 1.08 Å, respectively. By extending the covalent bond lengths in the direction of the bond to their real values, one obtains corrected H···A distances that reflect more accurately the strengths of these hydrogen bonds. It can be seen that all corrected H···A distances are appreciably shorter than van der Waals contacts. The participation of H(6) in hydrogen bonds has been noted in a number of crystal structures. Usually, O(5′) acts as the acceptor,[22] but O(4′) has also been found in that role.[6b,23] In the former case, it is reasonable to assume that the C–H···O bond stabilizes the g^+ conformation of the $-CH_2OH$ side chain. The disorder of the side chain in FIAC can be explained by the fairly strong hydrogen bonds in which O(5′) and O(5″) participate, both as donors and as acceptors.

In addition to its participation in hydrogen bonds, O(5′) is in intermolecular contact with I(5), which is very much shorter (3.050 Å) than 3.55 Å, the sum of van der Waals radii. Short I···O distances in the range 2.92–3.25 Å have also been found in 5-iododeoxyuridine[24] and in several drug-dinucleoside complexes.[25] Camerman and Trotter[24] ascribed them to charge-transfer bonds in DNA involving donation of oxygen lone-pair electrons to vacant 5d orbitals on the iodine. If such bonds were formed between the two strands of viral DNA, they would hinder strand separation and thus impair the reproduction of the virus. This mechanism could account for the antiviral properties of 5-iododeoxyuridine and of FIAC.

There are no other short intermolecular distances. The packing of the molecules in the crystal is shown in Figure 4. It can be seen that the pyrimidine bases are hydrogen bonded to each other but there is no base stacking.

Acknowledgments. All crystallographic computations were carried out with programs written by Ahmed et al.[26] Figures 2 and 4 were drawn with the ORTEP program of Johnson.[27] M.C. thanks the National Research Council of Canada for a Research Associateship during 1979–1981.

Supplementary Material Available: Anisotropic temperature parameters of the non-hydrogen atoms, coordinates and isotropic temperature parameters of hydrogen atoms, observed and calculated structure amplitudes (19 pages). Ordering information is given on any current masthead page.

---

(22) (a) Srikrishnan, T.; Parthasarathy, R. *Acta Crystallogr., Sect. B* **1978**, *34*, 1363–1366. (b) Hillen, W.; Egert, E.; Lindner, H.; Gassen, H. G. *Biochemistry* **1978**, *17*, 5314–5320.

(23) Furberg, S. *Acta Chem. Scand., Ser. B* **1978**, *32*, 478–482.

(24) Camerman, A.; Trotter, J. *Acta Crystallogr.* **1965**, *18*, 203–211.

(25) (a) Jain, S. C.; Tsai, C.; Sobell, H. M. *J. Mol. Biol.* **1977**, *114*, 317–331. (b) Reddy, B. S.; Seshadri, T. P.; Sakore, T. D.; Sobell, H. M. *Ibid.* **1979**, *135*, 787–812. (c) Jain, S. C.; Bhandary, K. K.; Sobell, H. M. *Ibid.* **1979**, *135*, 813–840.

(26) Ahmed, F. R.; Hall, S. R.; Pippy, M. E.; Huber, C. P. *J. Appl. Crystallogr.* **1973**, *6*, 309–346.

(27) Johnson, C. K. ORTEP Report ORNL-3794 (2nd revision); Oak Ridge National Laboratory: Oak Ridge, TN, 1970.