Nucleosides. XLIV. Long-Range Proton–Fluorine Spin–Spin Coupling in 5-Fluoropyrimidine Nucleosides[1]

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Abstract: A long-range spin–spin coupling has been observed between the anomeric proton (H-1′) and fluorine in 15 5-fluoropyrimidine nucleosides which is not present in their unfluorinated analogs. The long-range coupling has been confirmed in two cases by ^{19}F spectroscopy. The magnitude of $J_{H-1',F}$ is shown to be dependent upon the anomeric configuration of the nucleoside ($J_{H-1',F}$ for β compounds being >1.5 Hz; $J_{H-1',F}$ for α compounds being <1.5 Hz). The mechanism of the long-range coupling is concluded to be through the bonds and *not* through space. Possible through-bond mechanisms are discussed for the long-range proton–fluorine couplings observed.

In recent years, some 5-fluoropyrimidines and their nucleosides have been utilized extensively both as tools in the study of biological and biochemical processes and as chemotherapeutic agents of a relatively high order of activity. In previous papers[2-6] from this laboratory, syntheses of a number of 5-fluoropyrimidine nucleosides have been described. A study of the nmr spectra of these 5-fluoronucleosides has revealed a long-range spin–spin coupling, the nature of which is the subject of this report.

In 15 5-fluoropyrimidine nucleosides listed in Figure 1 (compounds **3–9** and **12–19**) a long-range coupling has been observed between the fluorine atom at C-5 and the anomeric proton, H-1′. The pertinent nmr data for the fluorinated compounds are given in Table I. Columns 7 and 8 of the table list the spin–spin coupling constants $J_{H-1',H-2'}$ and $J_{H-1',F}$, respectively.

The nmr spectra were determined on a Varian A-60 spectrometer using a sweep width of 500 Hz and a sweep time of 500 sec. The coupling constants listed for the anomeric signal are an average of 6–10 scans and are reproducible to ± 0.1 Hz.

In the case of 2′-deoxy compounds, where H-1′ is coupled to two C-2′ protons, the splitting of the triplet is given as the H-1′,H-2′ coupling constant when the magnitude of the coupling constants is the same. When the magnitude of the coupling constants is different, the larger coupling is listed first and the smaller coupling given in parentheses. The splitting patterns for the anomeric protons are described in column 9 of the table.

Table II lists, with few exceptions, the unfluorinated analogs (**22–27** and **30–34**) of those compounds in Table I which exhibited the long-range coupling. They are listed in the same order as those in Table I for easy reference. Examination of Table II shows that, in every case, the extra splitting found in the H-1′ signal is absent in the case of the unfluorinated compound. The unfluorinated analogs of **3** and **6** (Table IA) and of the α-D-fluoro compounds **15**, **17**, and **19** (Table IB) were not available for inclusion in Table II. Also, in two cases of fluorinated nucleoside–nucleoside pairs **7**, **25** and **8**, **26** the compound listed for comparison in Table II was the available isomer which most closely resembled the fluoro compound in Table I with respect to structure and configuration. As well, 1-(β-D-arabinofuranosyl)-5-chlorouracil (**24**) is also included in Table II and its H-1′ signal does not show the extra splitting.

The extra splitting in the anomeric (H-1′) signal is illustrated in Figure 2A–D for two pairs of compounds: 1-(2′-deoxy-β-D-*erythro*-pentofuranosyl)uracil (**42**) and its 5-fluoro analog, 1-(2′-deoxy-β-D-*erythro*-pentofuranosyl)-5-fluorouracil (**14**), and 1-β-D-arabinofuranosyluracil (**34**) and its 5-fluoro analog **18**. The coupled system contains five bonds. Starting at the fluorine atom the coupled system contains a single bond, a double bond, a single bond, a hetero atom, and two single bonds (dark lines, Figure 2B and 2D). The H-1′ signal for **32**, Figure 2A, is a triplet with a spacing of 6.9 Hz due to coupling with the two C-2′ protons. On the other hand the anomeric signal for its 5-fluoro analog **14**, Figure 2B, is a triplet of doublets, the extra spacing of 1.7 Hz being due to long-range coupling with the C-5 fluorine. Similarly **34**, Figure 2C, shows its H-1′ signal at δ 6.20 as a doublet ($J = 5.0$ Hz) due to coupling with H-2′. Its 5-fluoro analog **18** shows a doublet of doublets (δ 6.20) with an added splitting of 1.7 Hz due to coupling with the fluorine.

It is important to note that the type of substitution at the anomeric carbon (*i.e.*, having the two electronegative groups, the glycosyl nitrogen and the ring oxygen) seems to be essential for the long-range coupling to occur, since the methyl peak in 1-methyl-5-fluorouracil (**2**) is a sharp singlet at δ 3.38 showing no extra splitting due to the 5-fluoro substituent. The half-band width of the methyl peak in the spectrum of **2** (1.1 Hz) is found to be identical with that of its unfluorinated analog 1-methyluracil (**21**) (1.2 Hz) in D_2O solution. The half-band width of the DSS signal was 1.0 Hz in both cases. Because of the averaging due to free rotation of the methyl group the magnitude of a

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(1) (a) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08748). (b) After submission of this manuscript, a note appeared by F. Keller, J. E. Bunker, and A. R. Tyrrill in the New Compounds section of *J. Med. Chem.*, **10**, 979 (1967), which refers to an apparent long-range coupling between H-1′ and F in three 5-fluoropyrimidine nucleosides.
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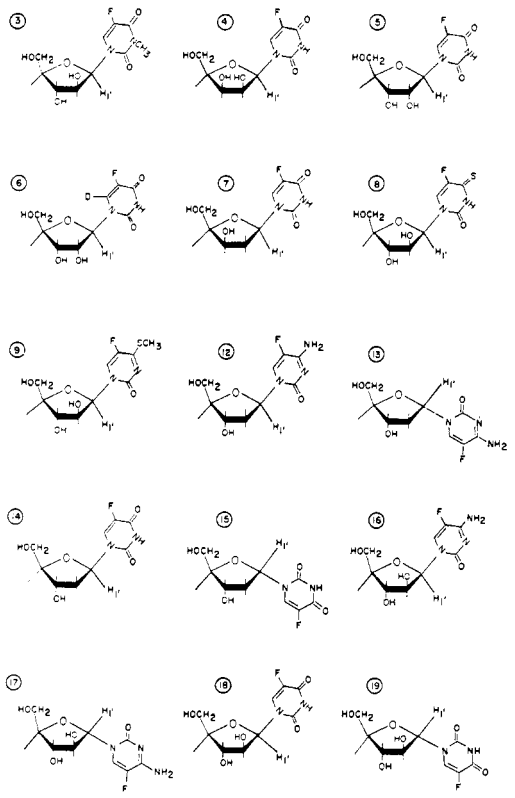


Figure 1.

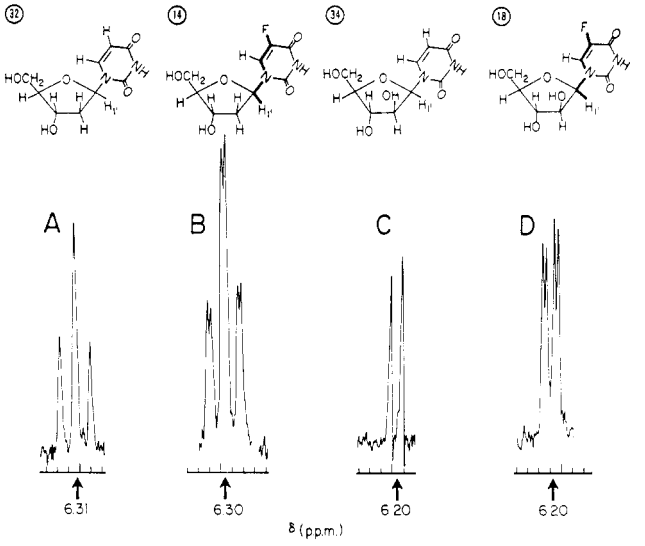


Figure 2. Comparison of anomeric proton (H-1′) signals of nucleosides and their 5-fluorinated analogs determined in D_2O (DSS internal standard).

long-range coupling F to CH_3 should be smaller than that observed in the fluoro nucleosides. However, such a long-range spin–spin interaction should still be observed, if it exists, at least in a substantial broadening of the methyl signal.

The long-range couplings to fluorine have been confirmed for the case of **5** and **14** by ^{19}F spectroscopy. In addition to the coupling with the C-6 proton, the ^{19}F spectrum showed a further smaller coupling of 1.65 Hz and 1.85 Hz for **5** and **14**, respectively, due to long-range coupling to H-1′. The secondary small H–F coupling observed in the ^{19}F spectra could also have

Table I. Nmr Spectral Data of Fluorinated Nucleosides and Pyrimidines in D_2O[a]

Compd	1-(D-Pentofuranosyl) sugar	Aglycon	δ_{H_6}, ppm	$\delta_{H_1'}$, ppm	J_{H_6-F}, Hz	$J_{H_1'-H_2'}$, Hz	$J_{H_1'-F}$, Hz	$H_{1'}$, signal	Ref
			A						
1[b]	...	5-Fluorouracil	7.67	...	5.4	...	...	...	*j*
2[c]	...	5-Fluoro-1-methyluracil	7.53	...	6.0	...	...	...	*k*
3[d]	β-Arabino	5-Fluoro-3-methyluracil	8.28	6.41	6.3	4.9	1.8	D–D[e]	*l*
4	β-Lyxo	5-Fluorouracil	8.14	6.20	6.9	6.0	1.7–1.8	D–D	4
5	β-Ribo	5-Fluorouracil	8.15	5.95	6.4 [6.90][f]	3.8	1.5 [1.65]	Q	4
5[g]	β-Ribo	5-Fluorouracil	7.85	5.96	6.3	4.0	1.7	Q	4
6	β-Ribo	6-Deuterio-5-fluorouracil	...	6.02	...	3.9	1.5	Q	*m*
7	β-Deoxylyxo	5-Fluorouracil	8.20	6.18	7.0	7.6 (2.5)	1.7	D–Q	5
8	β-Arabino	5-Fluoro-4-thiouracil	8.00	6.14	4.9	4.9	1.5	D–D	*k*
9[h,i]	β-Arabino	5-Fluoro-S-methyl-4-thiouracil	8.10	6.09	5.3	4.5	1.6	D–D	6
10	β-Deoxyribo	5-Trifluoromethyluracil	...	6.27	...	~6.0	~0	T	*n*
11	2,2′-Anhydro-β-arabino	5-Fluorouracil	8.14	6.59	4.0	5.9	0	D	4
			B						
12	β-Deoxyribo	5-Fluorocytosine	8.06	5.27	6.5	~6.4	1.6	T–D	2
13	α-Deoxyribo	5-Fluorocytosine	8.03	6.14	6.8	7.0 (2.7)	1.3	D–Q	*k*
14	β-Deoxyribo	5-Fluorouracil	8.11	6.30	6.5 [6.55][f]	~6.8	1.7 [1.85]	T–D	3, *o*
15	α-Deoxyribo	5-Fluorouracil	8.16	6.20	6.6	7.0 (2.8)	1.4	D–Q	3
16	β-Arabino	5-Fluorocytosine	7.98	6.17	6.6	4.7	1.8	D–D	6
17	α-Arabino	5-Fluorocytosine	7.84	5.89	6.4	3.6	1.3	Q	*p*
18	β-Arabino	5-Fluorouracil	8.08	6.20	6.7	5.0	1.7	D–D	4
19	α-Arabino	5-Fluorouracil	8.17	6.04	6.7	4.0	1.0	D–D	*k*

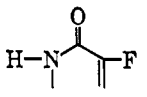
[a] Approximately 10% solution; sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) internal standard. [b] Three drops of NaOD added to dissolve sample. [c] δ_{CH_3} = 3.38 ppm (singlet). [d] δ_{CH_3} = 3.54 ppm (singlet). [e] D = doublet; T = triplet; Q = quartet; D–D = doublet of doublets, etc. [f] Numbers in brackets are ^{19}F values. [g] Several drops of NaOD added. [h] δ_{CH_3} = 2.55 ppm (singlet). [i] Solvent contained ~33% DMSO-d_6. [j] R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Amer. Chem. Soc.*, **79**, 4559 (1957). [k] See Experimental Section. [l] J. J. Fox, N. C. Miller, and R. J. Cushley, *Tetrahedron Letters*, 4927 (1966). [m] J. J. Fox, N. C. Miller, and R. J. Cushley, unpublished results. [n] C. Heidelberger, D. G. Parson, and D. C. Remy, *J. Med. Chem.*, **7**, 1 (1964). [o] I. Wempen and J. J. Fox, "Methods in Enzymology—Nucleic Acids," Vol. 12A, Academic Press Inc., New York, N. Y., 1967, p 64. [p] M. Hoffer, unpublished results.

Table II. Nmr Spectral Data of Nucleosides and Pyrimidines in D_2O[a]

Compd	1-(D-Pentofuranosyl) sugar	Aglycon	δ_{H_5}, ppm	δ_{H_6}, ppm	$\delta_{H_{1'}}$, ppm	$J_{H_5-H_6}$, Hz	$J_{H_{1'}-H_{2'}}$, Hz	$H_{1'}$ signal	Ref
20	...	Uracil	5.84	7.58	...	7.6	...	...	...
21[b]	...	1-Methyluracil	5.87	7.68	...	7.9	...	...	*h*
22	β-Lyxo	Uracil	6.33	8.28	6.64	8.1	4.9	D	*i*
23	β-Ribo	Uracil	5.93	7.91	5.94	8.2	4.0	D	...
24	β-Ribo	5-Bromouracil	...	8.41	5.90	...	3.2	D	*j*
25[c]	β-Deoxylyxo	Thymine	...	7.88	6.18	...	8.0 (3.0)	D–D	*k*
26[d]	β-Lyxo[e]	4-Thiouracil	6.44	7.78	6.06	7.6	6.1	D	*l*
27[f]	β-Arabino	S-Methyl-4-thiouracil	6.61	7.96	6.17	7.2	4.5	D	*m*
28[g]	β-Deoxyribo	Thymine	...	7.72	6.33	...	6.7	T	...
29	2,2′-Anhydro-β-arabino	Uracil	6.22	7.94	6.57	7.4	6.0	D	*n*, *o*
30	β-Deoxyribo	Cytosine	6.11	7.89	6.32	7.2	6.1	T	*p*
31	α-Deoxyribo	Cytosine	6.06	7.91	6.18	7.7	7.0 (3.0)	D–D	*p*
32	β-Deoxyribo	Uracil	5.93	7.90	6.31	8.3	6.9	T	*q*
33	β-Arabino	Cytosine	6.06	7.83	6.23	7.8	4.8	D	*r*
34	β-Arabino	Uracil	5.89	7.88	6.20	8.1	5.0	D	*o*

[a] Approximately 10% solution; DSS internal standard. [b] δ_{CH_3} = 3.42 ppm (singlet). [c] δ_{CH_3} = 1.91 ppm (singlet); $J_{CH_3-H_5}$ = 1.1 Hz. [d] Solvent contained 50% DMSO-d_6. [e] The compound with arabino configuration was not available. [f] δ_{CH_3} = 2.53 ppm (singlet). [g] δ_{CH_3} = 1.91 ppm (singlet); $J_{CH_3-H_6}$ = 1.1 Hz. [h] G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 2001 (1930). [i] R. Fecher, J. F. Codington, and J. J. Fox, *ibid.*, **83**, 1889 (1961). [j] P. A. Levene and F. B. LaForge, *Chem. Ber.*, **45**, 608 (1912). [k] J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963). [l] N. C. Yung and J. J. Fox, *ibid.*, **27**, 1477 (1962). [m] I. Wempen, N. Miller, E. Falco, and J. J. Fox, *J. Med. Chem.*, in press. [n] J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964). [o] D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956). [p] J. J. Fox, N. C. Yung, I. Wempen, and M. Hoffer, *J. Amer. Chem. Soc.*, **83**, 4066 (1961). [q] D. M. Brown, D. P. Parihar, C. B. Reese, and A. R. Todd, *J. Chem. Soc.*, 3035 (1958). [r] E. R. Walwick, W. K. Roberts, and C. A. Dekker *Proc. Chem. Soc.*, 84 (1959).

arisen from long-range coupling through the system



since Gronowitz, *et al.*,[7] have reported long-range interactions between H-5 and one of the N-H's in uracil. We have observed long-range coupling to the H-5 proton in 1-methyluracil (**21**) and in a number of pyrimidine nucleosides and have shown the long-range coupling in the H-5 signal to be due to H-3.[8] Very recently, a similar long-range coupling between H-3 and H-5 in 2′,5′-di-*O*-trityl-3′-ketouridine has been reported.[9] In order to exclude this coupling between F and H-3 all spectra were determined in D_2O to replace N–H by N–D. The situation similarly rules out coupling between H-1′ and H-3 as a cause of the observed extra splitting in the H-1′ signal. Similarly, the long-range splittings are not due to coupling between H-1′ and H-6 since: (a) the H-6 proton is unsplit by the amount shown by H-1′; (b) the spectrum of 1-(β-D-ribofuranosyl)-5-fluoro-6-deuteriouracil (**6**) still shows the extra splitting in H-1′. No extra splitting of magnitude similar to that found in H-1′ is discernible in the ring protons of the sugars when the 5-fluoro compounds in Table I are compared with their nonfluorinated analogs in Table II although in many cases the ring protons are not discernible. However, to our knowledge, no long-range effects between H-1′ and other furanosyl sugar protons have been reported in the 5-fluoropyrimidine nucleoside series at 60 MHz.

An important finding is the fact that of the four α and β pairs of 5-fluoropyrimidine nucleosides studied (compounds **12** to **19**, Table IB) the magnitude of the long-range coupling constant is *dependent on the anomeric configuration of the compound.* For the four β anomers, 1-(2′-deoxy-β-D-*erythro*-pentofuranosyl)-5-fluorocytosine (**12**), 1-(2′-deoxy-β-D-*erythro*-pentofuranosyl)-5-fluorouracil (**14**), 1-(β-D-arabinofuranosyl)-5-fluorocytosine (**16**), and 1-(β-D-arabinofuranosyl)-5-fluorouracil (**18**), the magnitude of $J_{H-1',F}$ given in Table IB is from 1.6 to 1.8 Hz (av = 1.7 Hz). For the four α anomers corresponding to the above, **13**, **15**, **17**, and **19**, the magnitude of $J_{H-1',F}$ given in Table IB is from 1.0 to 1.4 Hz (av = 1.25 Hz).

One can therefore conclude that, in D_2O solution, 1-D-aldopentofuranosyl-5-fluoropyrimidines of the α series possess a long-range H-1′,F coupling constant of <1.5 Hz while compounds of the β series possess a long-range H-1′,F coupling constant >1.5 Hz.

Indeed, the determination of the magnitude of the long-range coupling might be a useful method for the determination of the anomeric configuration of 5-fluoropyrimidine nucleosides of unknown structure.

Discussion

The phenomenon of long-range proton–proton spin–spin coupling has been the object of extensive reviews[10,11] and theoretical treatments.[12–15] However no such extensive theoretical treatment has been given to explain the mechanism of proton–fluorine long-range couplings. In 1961, Davis, *et al.*,[16] proposed a through-space mechanism to explain the stereospecific long-range H–F coupling in the saturated system 1,1-difluoro-1,2-dibromo-2-phenylethane. Extensive studies by Cross and Landis[17] on fluoro steroids

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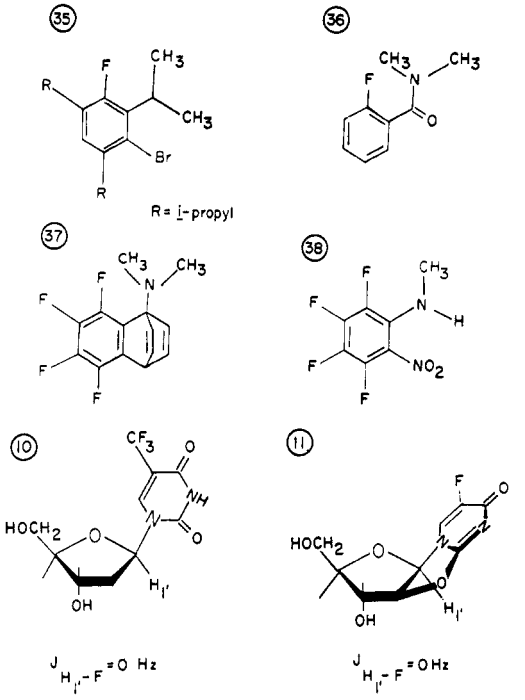

Figure 3.

tended to lend credence to the through-space mechanism. The mechanism is most attractive since the through-bond couplings in saturated systems should be small over four or more bonds and since the larger atomic radii of fluorine atoms allow through-space interactions over reasonable distances between atoms. Petrakis and Sederholm[18] proposed a similar through-space mechanism for long-range F–F couplings and have stated that the maximum distance over which such couplings can be observed is 2.73 Å, the sum of the van der Waals radii of two fluorine atoms. Recent work[19] however has suggested that probably a through-bond mechanism is also operative in long-range F–F coupling.

When one is dealing with systems with intervening π systems or atoms with free electrons the contribution through bonds (π and σ) cannot be discarded as easily. Wittstruck and coworkers[20] have found that spin–spin coupling of allylic fluorine with vinyl hydrogen exhibits steric dependence identical with allylic proton–proton spin–spin coupling. Allylic proton–proton coupling is known to arise from σ–π exchange terms[14] and the steric requirements have been well documented.[21–23]

More recently, long-range spin–spin coupling has been observed between aromatic fluorine and side-chain protons in a number of aromatic fluoro compounds. Myhre, *et al.*,[24] have reported long-range couplings between hydrogen on the β-carbons of alkyl substituents and fluorine in a number of 2,4,6-trialkylfluorobenzenes. For example the methyl region of the nmr spectrum of 3-bromo-2,4,6-triisopropylfluorobenzene (**35**) consisted of a set of doublets each for the methyl protons of the 4- and 6-isopropyl groups. The methyl protons due to the sterically crowded 2-isopropyl group of **35** consisted of a doublet of doublets, the smaller coupling (J = 1.8 Hz) being due to long-range H–F coupling. Lewin[25] has reported a long-range coupling between aromatic fluorine and *one* of the methyl groups of *o*-fluoro-N,N-dimethylbenzamide (**36**) ($J_{H,F}$ = 1.2 Hz). Brewer and coworkers[26] have reported a long-range F–CH_3 coupling of ~3.8 Hz in the tetrafluoro compound **37** formed by reaction of tetrafluorobenzyne and dimethylaminobenzene. Coupling between ring fluorine and side-chain protons in a large number of aromatic polyfluoro compounds with the side chains –XCH_3 (X = O, N, S, SO_2, C=O, or Sn) has been reported by Burdon.[27] In one example, N-methyl-2,3,4,5-tetrafluoro-6-nitroaniline (**38**) (X = N), long-range coupling of 5.4 Hz has been reported between the methyl group and F-2 (see Figure 3).

A through-space mechanism has been proposed to explain the long-range spin–spin couplings in compounds **36**, **37**, and **38**, while Myhre, *et al.*,[24] have stated that although a through-space mechanism is not proven in the case of **35** the coupling is "sensitive to internuclear distance."

Compounds **36**, **37**, and **38** possess a skeletal network for coupling almost identical with ours. In spite of this we suggest that, in the case of 5-fluoropyrimidine nucleosides, the long-range coupling is *through the bonds rather than through space.*

From a study of models, the most likely conformation of the fluoro nucleosides, as shown in Figure 2B and 2D, is one in which the 5,6 double bond is *endo* to the sugar moiety. Ulbricht and coworkers[28] have stated that, to explain the signs of the ORD curves of furanosyl nucleosides, the most likely conformation is one in which the 5,6 double bond "sits over" the furanose ring. This is referred to as the *anti* conformation. Cushley, *et al.*,[29] have recently published data on the effect of anisotropy of the 5,6 double bond on pmr acetoxy resonance signals in acetylated pyrimidine nucleosides. They found that if the C-1′,C-2′ substituents are *cis* there is a large paramagnetic shift in the C-2′ acetoxy signal upon hydrogenation of the 5,6 double bond and a small diamagnetic shift in the C-2′ acetoxy signal when the C-1′,C-2′ substituents are *trans*. These findings are best explained by the fact that the *major population* of conformers is that in which the 5,6 double bond is *endo* to the sugar ring. It must be emphasized that pure conformers are not required but simply a substantial population in a preferred conformation. In the case of the 5-fluoro nucleosides, such a conformation places the F and H-1′

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Table III. Nmr Spectral Data of Fluorinated Nucleosides in Other Solvents

Compd	1-(D-Pentofuranosyl) sugar	Aglycon	δ_{H_6}, ppm	$\delta_{H_{1'}}$, ppm	J_{H_6-F}, Hz	$J_{H_{1'}-H_{2'}}$, Hz	$J_{H_{1'}-F}$, Hz	Solvent[a]	$J_{H_{1'}-F}$,[b] Hz
14	β-Deoxyribo	5-Fluorouracil	8.27	6.20	7.2	6.7	1.8	DMSO-d_6	1.7
15	α-Deoxyribo	5-Fluorouracil	8.10	6.10	7.2	7.6 (4.0)	~2	DMSO-d_6	1.4
16	β-Arabino	5-Fluorocytosine	7.86	6.07	7.1	3.5	2	DMSO-d_6	1.8
18	β-Arabino	5-Fluorouracil	8.03	6.04	7.5	4	1.8	DMSO-d_6	1.7
39	Tribenzoyl-β-arabino	5-Fluorouracil	Hidden	6.66	...	~4.9	~1.3	DMSO-d_6	...
39	Tribenzoyl-β-arabino	5-Fluorouracil	Hidden	6.18	...	4.1	2.0	Pyridine-d_5	...

[a] Approximately 10% solution; tetramethylsilane (TMS) internal standard. [b] Value from Table I, solvent used was D_2O.

in the zig-zag or "W" (*trans–trans*) configuration which has been shown to be most suited for long-range couplings to occur in saturated systems. It also means that the coupled nuclei are farthest apart.

Calculations of the internuclear distance between H-1′ and F for 1-(2′-deoxy-β-D-ribofuranosyl)-5-fluorouracil (**14**) have been made for the more likely *endo* configuration and also for the *exo* configuration. Using the X-ray data of Harris and MacIntyre[30] we found for the *endo* case, where the *trans–trans* configuration obtains, a value of 5.28 Å for the distance between F and H-1′. For the *exo* case, where the proton and fluorine will now both be on the same side (*i.e.*, in a *cis–trans* arrangement), a value of 4.61 Å is found. *Both* of these values are greater than the sum of the van der Waals radii of proton and fluorine (~2.55 Å). There seems little likelihood therefore that there is any appreciable long-range coupling by through-space interactions of the proton and fluorine electrons. It must be emphasized that there will be no difference in the calculated internuclear distances by changing the anomeric configuration from β to α.

We have mentioned previously that for α-D compounds the magnitude of $J_{H,F}$ is smaller than for β-D compounds. In this case a slight distortion from the true *trans–trans* configuration is possible. More likely, however, the α compounds exist with a population of conformers wherein the 5,6 double bond *exo* to the sugar moiety is increased over that found for the β compounds. The four α compounds considered previously, **13**, **15**, **17**, and **19**, do not have bulky substituents in the 2′ or 4′ position which are *cis* to the aglycon. Hence the bulkier C-2 oxygen can more easily be accommodated "over" the sugar ring. A compound which might shed light on this postulate would be 1-(α-D-ribofuranosyl)-5-fluorouracil which would have a bulky *cis* substituent at C-2′. However, from studying the β series of compounds (Table I) the presence of the bulky hydroxymethyl group at C-4′ seems to be responsible for the conformational weighting. For instance, the H–F coupling constants for 1-(2′-deoxy-β-D-ribofuranosyl)-5-fluorouracil (**14**), which has only the C-4′ hydroxymethyl group "up," and 1-(β-D-lyxofuranosyl)-5-fluorouracil (**4**), which has groups "up" at 2′, 3′, and 4′, are equal in magnitude. If the α-D compounds have a greater population of conformers with the bulkier C-2 oxygen group *endo* to the furanose ring, a through-space mechanism is again ruled out. The *endo* configuration places the H-1′ and F atoms in a *cis–trans* arrangement, hence one would expect the magnitude of the long-range coupling constant to be greater for the α than the β compounds. However the results from Table I show that $J_{H-1',F}$ is greater for the β than the α compounds; hence the through-space mechanism seems unlikely.

A further argument for a change in the conformational weighting is seen from the solvent effects on the $J_{H,F}$ coupling constant shown in Table III. Comparison of columns 8 and 10 shows a discernible solvent effect on the long-range coupling constants for compounds **15** and **16** on changing solvents from D_2O to DMSO-d_6. Values in column 10 are those shown in the earlier table (Table I) and were run in D_2O. More striking perhaps is the solvent effect on the long-range coupling constant for 2′,3′,5′-tri-*O*-benzoyl-β-D-arabinofuranosyl-5-fluorouracil (**39**) in DMSO-d_6 ($J_{H-1',F} \cong 1.3$ Hz) and pyridine-d_5 ($J_{H-1',F} \cong 2.0$ Hz). Changes in the magnitude of long-range proton–proton spin–spin couplings have been noted previously by Whipple[31] and were explained by a change in rotational isomers due to solvent effect.

An explanation as to the type of through-bond coupling is less easy to discern. If a $\sigma-\pi$ mechanism is operative: (1) replacement of the vinyl fluorine by the trifluoromethyl group should change the sign but not the magnitude of the long-range coupling constant by analogy with that shown for long-range proton–proton couplings;[11] (2) the maximal value for J should be found when the angle made by the planar π–p system, made up of the 5,6 double bond and N-1, is 90° with respect to the C-1′,H-1′ σ bond. Such an orientation allows maximal overlap of the $\sigma-\pi$ system.

The following pieces of evidence rule out a $\sigma-\pi$ mechanism. First, there is no discernible long-range coupling between H-1′ and fluorine in 5-trifluoromethyl-β-D-*erythro*-pentofuranosyluracil (**10**) (Figure 3). Second, the angle between the pyrimidine ring and H-1′ in either preferred conformation (*i.e.*, 5,6 double bond *endo* or *exo* to the sugar ring) is close to zero. A study of 2,2′-anhydro-β-D-arabinofuranosyl-5-fluorouracil (**11**) where the angle between the pyrimidine ring and the C-1′ proton is estimated to be 110° shows $J_{H-1',F} = 0$ Hz. That is, the geometrical requirements seem to be the reverse of that expected if a $\sigma-\pi$ through-bond mechanism is operative. It therefore appears that a $\sigma-\pi$ through-bond mechanism is not operative in the case of long-range couplings in the 5-fluoropyrimidine nucleosides.

If a through-space mechanism and a $\sigma-\pi$ through-bond mechanism can be ruled out, the best explanation is that a mechanism is operative which is much like that found for proton–proton long-range couplings in

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heterocyclic, polynuclear aromatic compounds such as indoles and benzothiophenes,[32-34] N-benzylthieno-[3,2-*b*]pyrrole,[35] and various aromatic aldehydes.[32,36] Such couplings have been found for protons separated by five bonds and they are maximal when the planar zig-zag or "W" pattern is accomplished.[33] Replacement of the vinyl proton by a methyl group in several of these instances also results in no long-range coupling being observed.[33] These systems are all those in which electron localization has taken place. Resonance or canonical structures have been invoked to explain long-range couplings of such systems. The strongest argument for the long-range proton–fluorine spin–spin couplings we have observed can therefore be made for a mechanism involving, at least to a large extent, σ-induced spin–orbital interactions.[37]

It has previously been shown[38] that the pyrimidine residues of nucleosides exist as the oxo rather than the hydroxy form; that is, these compounds do not exist in the aromatic form but in the more localized oxo form.

One might have expected to see an effect on the magnitude of $J_{H-1',F}$ due to the different pyrimidine ring systems found in compounds like 1-(2′-deoxy-β-D-*erythro*-pentofuranosyl)-5-fluorouracil (**14**) and 1-(2′-deoxy-β-D-*erythro*-pentofuranosyl)-5-fluorocytosine (**12**). However, there appears to be little difference in the magnitude of the long-range coupling constant on going from the α,β-unsaturated ketone system found in the uracil compounds and **8** to the conjugated diene system found in the cytosine compounds and **9**. The question may be raised that the 5-fluorouracil nucleosides used in this study exist to a substantial extent as monoanions at the pD of D_2O solution (pD 7.25) since their pK_a values are ~7.7.[2] That this phenomenon has no significant effect on the long-range coupling is shown by the following: $J_{H-1',F}$ for 1-(β-D-arabinofuranosyl)-5-fluorouracil (**18**) run in D_2O and NaOD (pD 10.2) solutions were identical (1.7 Hz) and, further, the magnitude of this coupling was the same as that of its 3-methyl derivative **3**. The 5-fluorocytosine compounds whose pK_a values are ~2.3[2,6] would exist completely in the undissociated form in D_2O solution.

Analysis of 6-substituted derivatives of course would be most enlightening on the choice between the two mechanisms. Inductive effects should not effect π-induced couplings but should have a substantial affect upon σ-induced couplings. Unfortunately 5-fluoro-6-substituted pentosylpyrimidine nucleosides are not available. Perhaps more information can therefore be garnered by a determination of the signs of the long-range proton–fluorine coupling constant.

Experimental Section

5-Fluoro-4-methoxy-1-methyluracil. One gram (5.6 mmol) of 2,4-dimethoxy-5-fluorouracil and 5 ml of methyl iodide were combined in a small glass-lined bomb and heated at 65° for 18 hr. The bomb was cooled and opened and the suspension diluted with anhydrous ether and filtered. The crude crystalline precipitate, 390 mg (78%), was recrystallized from hot ethanol. The pure product was obtained as microscopic iridescent prisms which were dried in an Abderhalden apparatus. The melting point was not sharp, sintered *ca.* 171°, liquified at 188°. Thin layer chromatography on silica gel using butyl alcohol–water (86:14) as solvent showed only one substance.

Anal. Calcd for $C_6H_7FN_2O_2$: C, 45.57; H, 4.46; F, 12.01; N, 17.72. Found: C, 45.52; H, 4.40; F, 12.08; N, 17.72.

5-Fluoro-1-methyluracil (2). 5-Fluoro-4-methoxy-1-methyluracil (100 mg) was refluxed for 0.5 hr in 4 ml of concentrated hydrochloric acid. The hydrolysis was shown to be complete by thin layer chromatography on silica gel using butyl alcohol–water (86:14) as solvent. The acid was removed by repeated evaporations under vacuum with portions of water. The resulting solid was recrystallized from hot water. The yield of pure product **2** was 81 mg (88%), mp 256–257°.

Anal. Calcd for $C_5H_5FN_2O_2$: C, 41.67; H, 3.50; F, 13.18; N, 19.44. Found: C, 41.65; H, 3.52; F, 13.14; N, 19.42.

1-(β-D-Arabinofuranosyl)-5-fluoro-4-thiouracil (8). Compound **8** was obtained previously[6] as a syrup and was characterized as the disulfide. Subsequently, **8** was obtained as a solid, mp 173–175°.

Anal. Calcd for $C_9H_{11}FN_2O_5S$: C, 38.84; H, 3.98; F, 6.83; N, 10.07; S, 11.51. Found: C, 38.75; H, 4.09; F, 6.95; N, 9.95; S, 11.65.

1-(2′-Deoxy-3′,5′-di-*O*-*p*-toluyl-α-D-ribofuranosyl)-5-fluoro-4-thiouracil. 1-(2′-Deoxy-3′,5′-di-*O*-*p*-toluyl-α-D-ribofuranosyl)-5-fluorouracil (15 g, 0.06 mol) and 34 g (0.18 mol) of phosphorus pentasulfide in 800 ml of reagent grade pyridine were stirred vigorously and heated. As the temperature rose, solution gradually began. Sufficient water was added *dropwise* until turbidity was obtained. The reaction mixture was refluxed for 7 hr and allowed to stand overnight. The pyridine was decanted, the residual solid washed with fresh pyridine, and the combined solvent evaporated under vacuum to a thin syrup. The syrup was poured slowly into a well-stirred slurry of water–ice. Stirring was continued for 0.5 hr. The solid was filtered and washed thoroughly with fresh water. The damp precipitate was dissolved in *ca.* 2 l. of hot methylene chloride and the insoluble material removed by filtration. The water layer was separated and the solvent dried with anhydrous sodium sulfate at room temperature. The drying agent was removed and the solvent evaporated under vacuum. As the volume of methylene chloride dropped and precipitation began, ethanol was added and the evaporation continued. This process was repeated until all the methylene chloride was replaced by ethanol. The suspension was then chilled thoroughly and the precipitate filtered. The yield of yellow solid was 11 g (71%), mp 233–235°, sintering at 230°. A further quantity of product was obtained by evaporation of the mother liquors and recrystallization of the crude solid from hot ethanol.

1-(2′-Deoxy-α-D-ribofuranosyl)-5-fluorocytosine (13). 1-(2′-Deoxy-3′,5′-di-*O*-*p*-toluyl-α-D-ribofuranosyl)-5-fluoro-4-thiouracil (10 g, 0.02 mol), 50 ml of 2 *N* KOH, and 100 ml of ethanol were combined and stirred at room temperature for 1 hr. The reaction mixture was acidified to Congo red paper with concentrated hydrochloric acid (*ca.* 9 ml). The ethanol was removed under vacuum whereupon precipitation occurred; the solid was filtered, and the filtrate was neutralized with ammonium hydroxide and evaporated under vacuum. The syrupy residue was reevaporated several times with ethanol to remove residual water and finally leached repeatedly with hot acetone. The combined acetone filtrates were evaporated under vacuum to a syrup which was used directly without further purification.

The above syrup was dissolved in a mixture of 70 ml of methanol and 50 ml of water, containing 4 ml of methyl iodide, and treated slowly with 1 *N* sodium hydroxide to pH 8. Progress of the methylation was monitored spectrophotometrically by the change of the ratio 275:315 mμ. When this ratio became stable, the methanol was removed under vacuum. The resulting suspension was thoroughly chilled and filtered. Recrystallization of the crude product from ethanol containing a few drops of water gave a solid gel on cooling. The gel was pulled dry on a filter under a rubber dam and a white amorphous product was obtained which appeared to be somewhat solvated.

The amorphous solid (3 g) and *ca.* 40 ml of liquid ammonia were combined in the glass liner of a steel bomb which was then sealed and allowed to stand *ca.* 40 hr at room temperature. The bomb was opened and the ammonia evaporated under a stream of air. The syrupy residue was then repeatedly reconcentrated with ethanol

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until the last traces of ammonia were removed. The residue was dissolved in 100 ml of water; the pH was adjusted to pH 5 with acetic acid, and the solution was put on a column of Dowex 50 (H^+) 100–200 mesh (previously washed free of ultraviolet-absorbing contaminants). The column was washed with water until the washings were free of absorbing material, then the product was eluted with 1 *N* ammonium hydroxide. The combined fractions were evaporated rapidly under high vacuum with a bath temperature <40°, and the residual syrup was reconcentrated with ethanol until a white glass resulted. The glass was dissolved in hot ethanol which on cooling deposited a crystalline product, 1.0 g, mp 195–197°, $[\alpha]^{25}D$ −62° (*c* 2.73, water). A mixture melting point with **12** gave 174–185°; ultraviolet absorption in water: maxima at 213 and 291 mμ (ε 11,300 and 12,280, respectively), minimum at 247 mμ (ε 1315).

Anal. Calcd for $C_9H_{12}FN_3O_4$: C, 44.08; H, 4.93; N, 17.14; F, 7.75. Found: C, 44.09; H, 4.94; N, 17.14; F, 7.72.

The synthesis of **13** by another route has been reported.[39] The product has a reported mp 186–187° and $[\alpha]^{25}D$ −92°. A private communication from one of the authors has corrected their rotation value to −59°.

1-(Tri-*O*-acetyl-α-D-arabinofuranosyl)-5-fluorouracil. (Tri-*O*-acetyl-19). A solution of 500 mg of 1-α-D-arabinofuranosyl-5-fluorocytosine (**17**) in 25 ml of 1 *N* NaOH was heated 30 min at 120°. The solution was cooled to room temperature and passed through a column of 15 g of Dowex 50 (H^+) resin. The resulting solution was evaporated under vacuum to about 5 ml, decolorized with Norit, filtered through a pad of Celite, and evaporated under vacuum to yield 386 mg of **19** (77%) as an amber syrup, λ_{max} 265 mμ in ethanol.

The syrup did not crystallize and was acetylated with 1.0 ml of acetic anhydride (10.6 mequiv) in 2.5 ml of pyridine. The mixture was heated (bath temperature = 130°) until the syrup was dissolved and then placed in the refrigerator for 22 hr. Water (5 ml) was added, and after 0.5 hr the solution was evaporated to dryness to yield an amber syrup. Tlc showed a slight impurity was present. The syrup was placed on a column of silica gel G (1 × 21 mm) and eluted with 5% methanol–chloroform. Fractions (2 ml) were collected and fractions 2–11 gave, upon evaporation of solvents, a slightly yellow syrup (138 mg, 25%) of the tri-*O*-acetyl derivative of **19**. Tlc (silica gel GF_{254}) in 5% MeOH–$CHCl_3$ showed one spot, R_f 0.61; in 5% MeOH–benzene (three times) one spot showed, R_f 0.25. The spots were developed using uv and a 10% H_2SO_4 spray. The tlc and uv data for tri-*O*-acetyl **19** were identical with that for tri-*O*-acetyl **18**, the β anomer of **19**.

Anal. Calcd for $C_{15}H_{17}FN_2O_9$: C, 46.40; H, 4.42. Found: C, 46.69; H, 4.62.

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Proton Magnetic Resonance Spectra of Ethylene Phosphites and Ethylene Sulfite[1]

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Abstract: Complete analyses of proton magnetic resonance spectra are reported for three ethylene phosphites and for ethylene sulfite neat, in benzene, and in chloroform. The vicinal H–C–C–H and P–O–C–H coupling constants indicate that the ethylene phosphites appear to prefer twist–envelope conformations. This result may be generally applicable to the conformation of five-membered rings.

Our interest in the chemistry presented in this paper was aroused by the unusual properties of 1,3,2-dioxaphospholane rings (**1**). Ethylene phosphates[4] (**2**), intermediates in the alkaline hydrolysis of ribonucleic acid,[5] have been shown to undergo very rapid hydrolysis relative to their acyclic analogs.[6] These

1 2

results prompted structural analysis studies of the cyclic phosphates: methyl ethylene phosphate[7] and methyl pinacol phosphate.[8]

Complex pmr spectra have been obtained for compounds related to **1**, including phosphites (**3**),[9,10] sulfites (**4**),[11] and dioxolanes (**5**).[12] The spectra

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(4) Although Ring Index nomenclature has been employed for these cyclic compounds, we believe that they are best named as derivatives of the appropriate phosphorus acids. The fact that the acid form of **2** is a cyclic ester of phosphoric acid is not readily apparent from the Ring Index name, 2-hydroxy-2-oxo-1,3,2-dioxaphospholane, and **2** is not readily and clearly named as an anion. The same argument holds for other compounds considered in this paper.

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