Synthetic Applications of Cyclic α-Chloro-ethers and -thioethers. Part 5.[1] Tetrahydrofuranyluracil Derivatives: Conformational Properties in Solution

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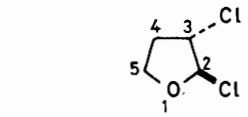
With the aid of high-frequency n.m.r. spectroscopy (360 MHz) and computer simulation all chemical shift and coupling constant parameters of tetrahydrofuranyluracil derivatives (3a and b) and (4a and b) have been obtained. By comparison with model compounds (1) and (2) and with literature studies of (deoxy)ribonucleosides a conformational analysis of (3a and b) and (4a and b) has been carried out. Vicinal coupling constants between THF protons are consistent with an $N \rightleftharpoons S$ conformational equilibrium, the former being preferred in (3a and b) and the latter in (4a and b). Finally, the relative orientation of THF and uracil rings in (3a and b) is described.

1′-(2-TETRAHYDROFURANYL)URACIL derivatives (hereafter 1′-THF-uracil) † are known to possess a high antitumor and carcinostatic activity.[2,3] Application for chemotherapeutic purposes has been reported, in particular for 1′-THF-5′-fluorouracil (Ftorafur).[3]

In a previous paper a synthetic route for these compounds was presented which also produced 3′-THF-uracil and 1′,3′-$(THF)_2$-uracil derivatives.[4] A detailed conformational analysis of the title compounds was undertaken because of their physiological activity as well as their structural resemblance to natural (deoxy)-ribonucleosides.



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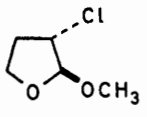

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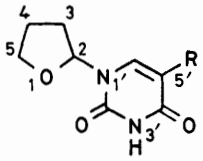

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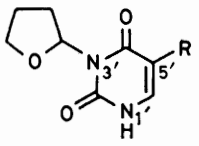
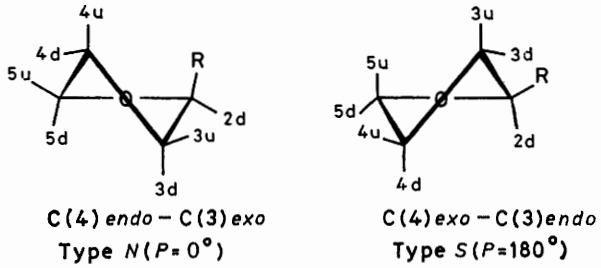


(4)

a, R = H
b, R = F

The conformational properties of the constituents of naturally occurring (deoxy)ribonucleic acids, both in the solid state and in solution, have been studied extensively in recent years.[5-8] It is the aim of the present paper to show that such studies can also provide the basis for a description of the conformational properties in solution of 1′-THF-(5′-fluoro)uracil (3a and b) and 3′-THF-(5′-fluoro)uracil (4a and b).‡

First, one should examine whether the concept of an equilibrium between two relatively low-energy type *N* and type *S* conformers can be used in the present case.[6,8] Indications justifying this approach are (i) the *X*-ray data of (3a), presented in the following paper, which reveal an *N*-type geometry in the solid state and (ii) *ab initio* calculations for tetrahydrofuran, which predict two energetically favoured geometries, characterized by the pseudorotation parameter $P = 0°$ (*N*-type) and $P = 180°$ (*S*-type).[9] To obtain further evidence for



C(4) *endo* − C(3) *exo* Type *N* ($P = 0°$)

C(4) *exo* − C(3) *endo* Type *S* ($P = 180°$)

d = down, u = up

this study, two model compounds were also analysed, namely *trans*-2,3-dichlorotetrahydrofuran (1) and *trans*-3-chloro-2-methoxytetrahydrofuran (2). Literature data suggest that these compounds adopt *one* fixed *N*-type conformation in solution.[10,11]

Secondly, concerning the relative orientation of the two rings, it should be investigated if a preference for the *anti*-conformation, as found in pyrimidine (deoxy)-ribonucleosides, is also present in compounds lacking the hydroxy and hydroxymethylene substituents in the oxacyclopentane ring. Comparison with (4a and b), where one of the two carbonyl functions has to be located over the five-membered ring, should yield information about the presence of a possible *syn*-conformer of (3a and b).

In order to simplify the direct comparison of the n.m.r. data obtained for (1)—(4), with the corresponding data reported for (deoxy)ribonucleosides, the numbering commonly used in nucleoside chemistry for atoms in the THF-ring is added in parentheses in Tables 1—5.

EXPERIMENTAL

trans-2,3-Dichlorotetrahydrofuran (1) [12] and *trans*-3-chloro-2-methoxytetrahydrofuran (2) [10] were synthesized and purified according to literature procedures. THF-(5′-fluoro)uracil derivatives (3) and (4) were prepared by

† Throughout this study the numbering depicted in the Figure is used.

‡ A detailed *X*-ray crystallographic structure determination of (3a) is presented in the following paper.

reaction of (5-fluoro)uracil with 2-chlorotetrahydrofuran, as described in ref. 4. The n.m.r. shift reagent [$^2H_{27}$]-Eu(fod)$_3$ was obtained from Merck.

The ^1H n.m.r. spectra of *ca.* 10% solutions of (1) and (2) in $CDCl_3$ were recorded on a JEOL PS-100 instrument, operating in the continuous wave mode at 99.5 MHz (probe temperature 20 °C; tetramethylsilane as internal standard). Sufficient signal separation and resolution (0.8 and 1.0 Hz linewidth respectively) were obtained.

Preliminary investigations of the 99.5 MHz ^1H n.m.r. spectra of (3a) and (4a) revealed considerable overlap of resonances. Therefore, n.m.r. spectra of (3) and (4) (0.05M solutions in $CDCl_3$; tetramethylsilane as internal reference; 25 °C) were recorded on a Bruker HX-360 spectrometer, employing the Fourier transform technique at 360 MHz. The free induction decay signals (100 accumulations) were stored in a Bruker BNC-12 computer using a spectral window of 3 600 Hz with 16 K data points.

Spectral parameters were obtained by careful simulation of the expanded THF proton regions using the computer program LAME. Chemical shifts and coupling constants for (1) and (2) were refined by iterative procedures and an accuracy of 0.001 p.p.m. and 0.05 Hz respectively was obtained (see Tables 1 and 2). The chemical shifts and couplings constants of (3a) and (4a) were estimated to be reproducible to *ca.* 0.001 p.p.m. and 0.1 Hz. In all cases, agreement between experimental and calculated spectra is quite satisfactory (see Figures 1—4).

The long-range coupling interaction of H(5′) and H(2d) in (3a) was determined from the expanded 100 MHz n.m.r. spectrum, recorded on a JEOL PFT-100 instrument, operating in the Fourier transform mode. To the *ca.* 1.0M solution in $CDCl_3$ a few drops of [$^2H_4$]methanol were added, in order to eliminate a possible H(3′)—H(5′) coupling.

* 360 MHz N.m.r. spectra of 1′,3′-(THF)$_2$-(5′-fluoro)uracil were also recorded. Both 1′-THF and 3′-THF rings displayed the same multiplet patterns as in (3a) and (4a) respectively.

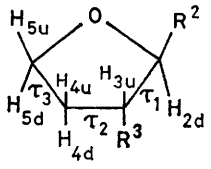
RESULTS

trans-2,3-*Dichlorotetrahydrofuran* (1).—Some of the n.m.r. characteristics of (1) have been described by Holik and Borkovkova, using first-order considerations.[11] The absence of a spin–spin coupling between H(2d) and H(3u) was demonstrated unambiguously by double irradiation and this technique also indicated ' a weak long-range interaction ' between H(2d) and the two H(4) protons. We have substantiated all spectral parameters by iterative simulation procedures. The results are presented in Tables 1 and 2.

The signal at highest field exhibits a small ^3J (0.82 Hz)

TABLE 1

Chemical shifts [a] of compounds (1), (2), (3a and b), and (4a and b) in $CDCl_3$ [b]



(1) $R^2 = R^3 = Cl$
(2) $R^2 = OCH_3$; $R^3 = Cl$
(3a) R^2 = 1′-uracil ; R^3 = 3d-H
(3b) R^2 = 1′-(5′-fluorouracil); R^3 = 3d-H
(4a) R^2 = 3′-uracil ; R^3 = 3d-H
(4b) R^2 = 3′-(5-fluorouracil); R^3 = 3d-H

	Chemical shift (δ)							
Proton	(1) [c]	(2)	(3a)	(3a) + Eu(fod)$_3$	Δδ (Hz)	(4a)	(3b) [d]	(4b) [d]
2d-H (1′d)	6.195	4.954	6.005	6.128	44.3	6.608	5.99	6.57
3u-H (2′u)	4.611	4.182	2.066	2.143	27.7	2.493	2.08	2.50
3d-H (2′d)			2.408	2.465	20.4	2.225	2.42	2.26
4u-H (3′u)	2.792	2.489	1.936	1.975	13.9	2.323	1.93	2.35
4d-H (3′d)	2.221	2.085	2.061	2.081	7.2	1.991	2.07	2.01
5u-H (4′u)	4.313	4.118	4.203	4.234	11.3	4.283	4.22	4.30
5d-H (4′d)		4.002	3.991	4.019	10.0	3.936	4.00	3.97
1′-H (1)						9.6		9.7
3′-H (3)			10.1				9.4	
5′-H (5)			5.72	5.90		5.71		
6′-H (6)			7.35	7.40		7.10	7.42	7.19

[a] Expressed in p.p.m. relative to tetramethylsilane; accuracy 0.001 p.p.m. [b] Only one of the two enantiomers of each compound is shown. [c] Lit.,[11] δ(CCl_4) 6.14 (2d-H), 4.57 (3u-H), 2.83 (4u-H), 2.19 (4d-H), and 4.31 (5u-, 5d-H). [d] First-order analysis; accuracy *ca.* 0.01 p.p.m.

TABLE 2

Coupling constants (J/Hz) of (1), (2), (3a and b), and (4a and b) in $CDCl_3$

	J/Hz			
Couple	(1) [a,b]	(2) [c]	(3a) [d]	(4a) [d]
2d, 3u (1′d, 2′u)	<0.1	<0.1	3.4	6.0
2d, 3d (1′d, 2′d)			6.3	8.3
3u, 3d (2′u, 2′d)			−13.6	−12.3
3u, 4u (2′u, 3′u)	5.66	5.8	7.8	8.8
3u, 4d (2′u, 3′d)	0.82	1.65	4.8	8.5
3d, 4u (2′d, 3′u)			8.7	4.4
3d, 4d (2′d, 3′d)			8.1	9.3
4u, 4d (3′u, 3′d)	−14.24	−13.6	−12.5	−11.9
4u, 5u (3′u, 4 u)	Σ18.35	8.3	7.7	6.6
4u, 5d (3′u, 4′d)		8.3	8.1	4.2
4d, 5u (3′d, 4′u)	Σ10.67	3.6	4.7	8.2
4d, 5d (3′d, 4′d)		7.25	6.9	8.1
5u, 5d (4′u, 4′d)		−8.3	−8.3	−7.7

	J/Hz			
Couple	(3a) [d]	(4a) [d]	(3b) [d]	(4b) [d]
5′, 6′ (5, 6)	8.0	7.6		
1′, 6′ (1, 6)		5.8		6.6
1′, 5′ (1, 5)		1.7		
F5′, 6′ (F5, 6)			6.4	4.6
2d, 5′ (1′d, 5)	0.25	<0.1		
2d, F5′ (1′d, F5)			1.4	<0.2

[a] Accuracy *ca.* 0.01 Hz. [b] $^4J_{2d,4u}$ 0.19, $^4J_{2d,4d}$ 0.60 Hz. [c] Accuracy *ca.* 0.05 Hz. [d] Accuracy *ca.* 0.1 Hz.

with H(3u), combined with a relatively large ^4J (0.60 Hz) with H(2d). Consequently, this signal should be attributed to H(4d), which apparently occupies a pseudoequatorial position. The small *trans*-vicinal coupling constants ($J_{2d,3u}$ and $J_{3u,4d}$) and the perceptible four-bond spin–spin coupling interactions 2d,4u and 2d,4d are consistent with a fixed *N*-type geometry. Because of the chemical shift equivalence of H(5u) and H(5d) no detailed information of the separate coupling constants in the C(4)—C(5) part could be obtained in this case.

trans-3-*Chloro*-2-*methoxytetrahydrofuran* (2).—Expanded plots from the relevant parts of the observed (A) and the simulated (B) 99.5 MHz spectrum of (2) are shown in Figure 1.

Assignments of the signals were based on straightforward chemical shift and coupling constant considerations. From the results compiled in Table 2 it can be concluded that (2) exists in a similar *N*-type conformation as (1). Moreover, as

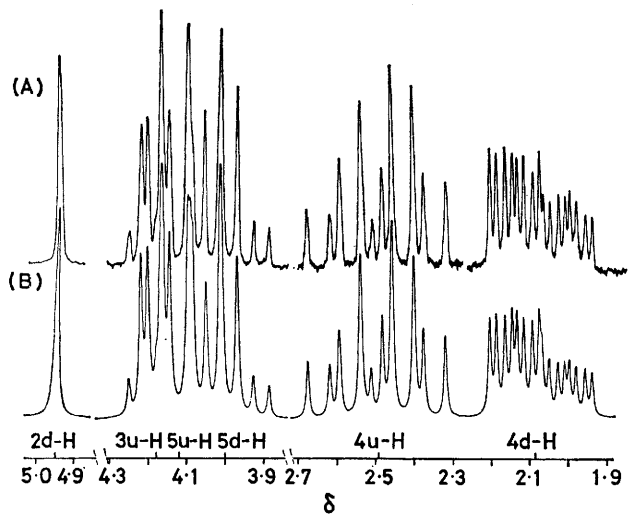


FIGURE 1 Observed (A) and computer-simulated (B) 99.5 MHz n.m.r. spectrum of *trans*-3-chloro-2-methoxytetrahydrofuran (2) in $CDCl_3$ at 25 °C. Methoxy protons are omitted. The values are relative to internal tetramethylsilane

a consequence of the nonequivalency of H(5u) and H(5d), all coupling constants of the C(4)—C(5) part could be deduced. Since the structural fragment O–C(5)H_2–C(4)H_2–C is also present in (3) and (4), these values can serve as a model for *N*-type conformations of THF-uracil isomers (3) and (4) (see Discussion section).

1′-THF-(5′-*fluoro*)*uracil* (3a *and* b).—Figure 2A shows expanded parts of the n.m.r. spectrum of (3a). Although a high-frequency n.m.r. technique (360 MHz) was used, considerable overlap of resonances from two protons in the high-field region occurred. As a consequence, highly complicated second-order multiplet patterns were observed, which were not directly amenable to computer simulation.

Incremental addition of the n.m.r. shift reagent Eu(fod)$_3$ was employed, in order to achieve a suitable chemical shift difference between these two protons without affecting the spectral resolution.[13] The spectrum after addition of the appropriate amount of shift reagent is depicted in Figure 3A. Indeed a partial separation of the relevant resonance signals and consequently a minimisation of the virtual coupling phenomena was observed [*cf.* H(3d) and H(4u) in Figures 3A and 2A respectively]. Thus, analysable

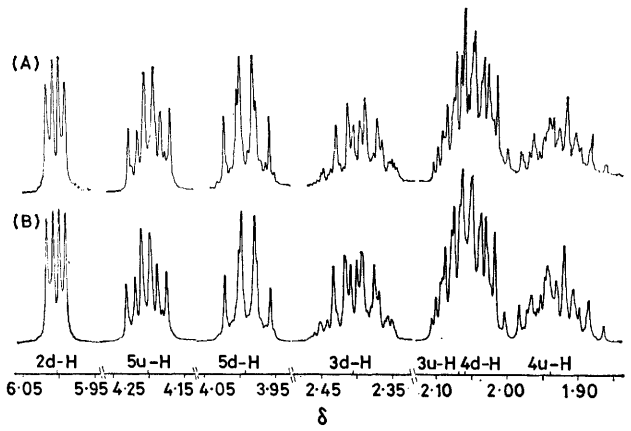


FIGURE 2 Observed (A) and computer-simulated (B) 360 MHz n.m.r. spectrum of 0.05M-1-THF-uracil (3a) in $CDCl_3$ at 25 °C. Uracil protons are omitted. The values are relative to internal tetramethylsilane

coupling patterns were obtained and the simulated spectrum is shown in Figure 3B.

Final values for all 31 THF proton–proton spin coupling constants were used as fixed parameters for the analysis of the original n.m.r. spectrum (Figure 2A). Good agreement between simulated and observed spectra (Figures 2B and 2A respectively) was obtained by variation of only the chemical shift parameters, indicating that our presumption that Eu(fod)$_3$ would not affect the coupling constants was correct.

The values for chemical shifts and coupling constants thus obtained are listed in Tables 1 and 2. Assignment of the proton multiplets to protons at C(3)—C(5) was easily performed by counting the number of coupling interactions. A reasonable assignment to individual protons at a given carbon atom was made from consideration of coupling constant magnitudes, expected for likely ring conformations (see Discussion section).

The 360 MHz n.m.r. spectrum of the 5′-fluoro derivative (3b) exhibited essentially the same characteristic multiplets for the C(3)—C(5) protons. Only small differences in chemical shifts were noted (see Table 1). In the signal of

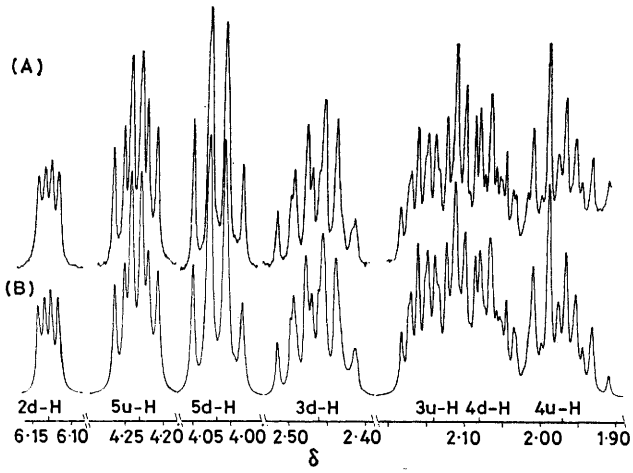


FIGURE 3 Observed (A) and computer-simulated (B) 360 MHz n.m.r. spectrum of 0.05M-1-THF-uracil (3a) in $CDCl_3$ at 25 °C after addition of [$^2H_{27}$]Eu(fod)$_3$. Uracil protons are omitted. The values are relative to internal tetramethylsilane

H(2d) an extra splitting appeared, due to a long-range five bond coupling with F(5′) (^5J 1.4 Hz). A similar, but strongly reduced coupling between H(2d) and H(5′) in (3a) (*ca.* 0.25 Hz) was determined from an expanded 100 MHz spectrum. These data are similar to those reported for the corresponding ribonucleosides (1.5 and 0.41 Hz) and deoxyribonucleosides (1.7 and 0.45 Hz).[14,15]

3′-THF-(5′-*fluoro*)*uracil* (4a *and* b).—The 360 MHz spectrum of (4a) is shown in Figure 4A. Complete separation of proton resonance signals enabled a direct computer simulation (Figure 4B). In Tables 1 and 2 the accurate values of chemical shifts and coupling constants are reported. Attribution of the multiplets to individual protons followed from comparison of the observed coupling constants with the values obtained for (1), (2), and (3a) and with reported values for deoxyribonucleosides (see Discussion section).[6,8] Similarity of the multiplet patterns in the n.m.r. spectrum of (4b) was observed; the slightly different chemical shifts are given in Table 1. In contrast

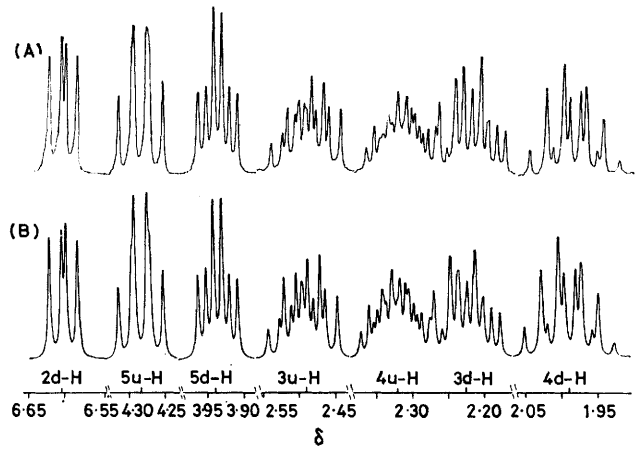


FIGURE 4 Observed (A) and computer-simulated (B) 360 MHz n.m.r. spectrum of 0.05M-3-THF-uracil (4a) in $CDCl_3$ at 25 °C. Uracil protons are omitted. The values are relative to internal tetramethylsilane

to the 1′-THF-uracil derivatives (3a and b) no long range H(2d)–F(5′) or H(2d)–H(5′) interaction was evident from the spectra of 3′-THF-uracil derivatives (4a and b).

DISCUSSION

In analysing the data from Tables 1 and 2 in more detail, a few restrictions should be kept in mind. First, comparison with published coupling constants is hampered by the fact that a different solvent ($CDCl_3$) was employed in this study. Secondly, it should be noted that quantitative description of the observed vicinal coupling constants in terms of a conformational $N \rightleftharpoons S$ equilibrium by using a modified Karplus equation is limited to the C(2)—C(3) fragments in (3a) and (4a). For the corresponding fragments in (1) and (2) and for all C(3)—C(4) and C(4)—C(5) parts, quantitative values for the electronegativity effect on vicinal coupling constants are lacking.

However, it will be shown that a satisfactory description of the conformational properties of the compounds studied here may still be obtained by a qualitative analysis of the observed coupling constants in these fragments.

Conformations of (1) *and* (2).—In the preceding section it was shown that the data presented in Table 2 were in agreement with the existence of only *one* *N*-type conformation of (1) and (2) in solution. The individual coupling constant values for the C(4)—C(5) part in (2) allow a more accurate description in terms of the phase angle of pseudorotation *P*. The coupling constants between the pseudoaxial and the pseudoequatorial pair (4u)—(5d) and (4d)—(5u) were found to be 8.3 and 3.6 Hz, respectively. Comparison of $J_{4d,5u}$ with the appreciably smaller $J_{2d,3u}$ and $J_{3u,4d}$ indicates a flattening of the THF ring in the C(4)—C(5) fragment. The most probable *P* values should then occur between 0 and −18° [C(3)*exo*].[5]

Conformation of the THF Ring in (3a *and* b).—Inspection of the *trans*-vicinal coupling constants, given in Table 2, reveals the presence of three small values of 3.4, 4.8, and 4.7 Hz [(2d)—(3u), (3u)—(4d), and (4d)—(5u), respectively], combined with two relatively large values of 8.7 and 8.1 Hz [(3d)—(4u) and (4u)—(5d)]. These data suggest the presence of a conformational equilibrium with a distinct preference for an *N*-type conformer, having 2d-, 3u-, 4d-, and 5u-protons in pseudoequatorial positions.

The most plausible *N*-type conformer is the one found in the *X*-ray structure determination, characterised by *P* 0.3° and τ_m 37°. An approximate model geometry of the other (*S*-type) participant of the equilibrium can be deduced by analysing the coupling constants of the C(2)—C(3) fragment.

In the case of deoxyribonucleosides, a modified Karplus equation $^3J_{HH} = 10.5\cos^2\phi_{HH} - 1.2\cos\phi/_{HH} + 0.3$ has been applied successfully to account for the observed coupling constants within this fragment.[6] Therefore, this equation is used; proton–proton torsion

TABLE 3

Calculated coupling constants for individual conformer of (3a) [a]

Conformer	$\phi_{2d,3u}$ (°) (1′d, 2′u)	$J_{2d,3u}$/Hz (1′d ,2′u)	$\phi_{2d,3d}$ (°) (1′d, 2′d)	$J_{2d,3d}$/Hz (1′d, 2′d
Type *N* *P* 0°				
(1) τ_m 37°	90	0.3	−32	6.8
(2) τ_m 41°	87	0.2	−35	6.3
Type *S* *P* 180°				
(1) τ_m 37°	154	9.9	32	6.8
(2) τ_m 41°	157	10.3	35	6.3
68% *N*1–32% *S*1 [b]		3.4		6.8
68% *N*2–32% *S*2 [b]		3.4		6.3
Experimental		3.4		6.3

[a] Utilizing the Karplus equation $^3J = 10.5\cos^2\phi_{HH} - 1.2\cos\phi_{HH} + 0.3$. [b] Calculated with $J_{2d,3u} = (1 - X_N)J_{2d,3u}(S)\ X_N J_{2d,3u}(N)$.

angles (ϕ_{HH}) can be deduced from the crystal structure [16] and the calculated values $J_{2d,3u}$ and $J_{2d,3d}$ are shown in Table 3 (*N*1). By virtue of symmetry considerations an *S*-type conformer having nearly the opposite geometrical structure (*P* 180°) seems most likely (*S*1);

calculated values for this hypothetical conformer are also given.

The calculated values for the *cis*-coupling (6.8 Hz) are 0.5 Hz higher than the experimental value. Although this is a minor anomaly, taking into account the approximations in the Karplus equation,[6-8] one could rationalize these data by assuming a slightly higher amplitude of puckering (τ_m 41°; *N*2 and *S*2 in Table 3).

From the data in Table 3 it is evident that the observed coupling constant magnitudes enable a reasonably accurate determination of the equilibrium composition, namely *ca.* 68% *N*-conformer. This result may seem surprising, because whereas uridine displays only *ca.* 50% *N*-type, deoxyuridine shows a definite preference for a type *S* conformation in solution.[6,17] However, in the absence of any electronegative substituent at other carbon atoms, it is a demonstration of the 'anomeric effect' at C(2).[18]

Conformation of the THF Ring in (4a *and* b).—Comparison of the 'equilibrium-sensitive' *trans*-vicinal coupling constants of (3) and (4) indicates that a conformational interchange between individual protons located at C(3)—C(5) has occurred. Consequently, the dominant conformer is of the *S*-type. By analogy with the guidelines, developed in the literature for conformational studies of nucleosides, we can use two probes for the ring geometry of this *S*-type conformer.[19,20]

Firstly, the *cis*-coupling constants show markedly higher values for (4a) (mean value 8.2 Hz) compared with (3a) (mean value 7.4 Hz). Secondly, the time-average values of $J_{2d,3u} + J_{4u,5d}$ and $J_{3u,4d} + J_{3d,4u}$ (which should to a good approximation be independent of the equilibrium constant *K*) amount to 10.2 and 12.9 Hz, being 1.3 and 0.6 Hz smaller than the corresponding values for (3a). Such a combination of results strongly indicates that relative flattening of the THF ring in (4a) occurs ($\tau_m < 37°$).

In order to develop further conditions for the geometry of the *S*-type conformer, a more accurate comparative analysis of the *cis*-coupling constants in (3a) and (4a) is presented in Table 4.

TABLE 4

cis-Vicinal coupling constants (Hz) of fragments of (3a) and (4a)

Fragment	(3a)		(4a)		Difference
C(2)—C(3)	6.3		8.3		+2.0
[C(1')—C(2')]					
C(3)—C(4)	7.8	8.0	8.8	9.1	+1.1
[C(2')—C(3')]	8.1		9.3		
C(4)—C(5)	7.7	7.3	6.6	7.4	+0.1
[C(3')—C(4')]	6.9		8.1		

The interesting fact is noted that agreement is good for the C(4)—C(5) fragment, whereas appreciable discrepancies occur in the other fragments. Consequently, the endocyclic torsion angles should be: $\tau_1(4a) \ll \tau_1(3a)$; $\tau_2(4a) < \tau_2(3a)$; and $\tau_3(4a) \simeq \tau_3(3a)$. Taking into account these conditions, acceptable parameter combinations are found within a small range of *P* values between 180 and 200° and τ_m values between 30 and 34°.

TABLE 5

Calculated coupling constants for individual conformers of (4a) [a]

Conformer Type *S*	$\phi_{2d,3u}$ (°) (1'd, 2'u)	$J_{2d,3u}$/Hz (1'd, 2'u)	$\phi_{2d,3d}$ (°) (1'd, 2'd)	$J_{2d,3d}$/Hz (1'd, 2'd)
P 198°, τ_m 32°	143	8.0	21	8.3
Type *N*				
P 18°, τ_m 32°	101	0.6	21	8.3
73% *S*–27% *N* [b]		6.0		8.3
Experimental		6.0		8.3

[a] See Table 3, note *a*. [b] See Table 3, note *b*.

A quantitative description of the C(2)—C(3) part of such an *S*-type conformer is given in Table 5.

This *S*-type conformation [C(4)*exo*] shows a small puckering at C(3), apparently caused by the 'bulky' C(2) substituent, which has always one carbonyl group above the ring. Therefore a likely candidate for an *N*-type counterpart in the conformational equilibrium is characterized by *P* 18° [C(4)*endo*]. The value for τ_m of this conformer is given as 32° in Table 5, but a wide range (30—40°) is possible, without affecting markedly the equilibrium population, *i.e.* 73% *S*, 27% *N* conformer.

Effects of Electronegativity on Vicinal Coupling Constants.—The influence of substituent electronegativities on coupling constants in ribose rings is well documented, but not fully understood.[6,8,20] Indeed, these effects are often obscured by the consequences of a concomitant change of the conformational equilibrium,[6] especially if *trans* coupling constants are compared. With the present data (Table 2), at least a qualitative assessment of the electronegativity effect on the less sensitive *cis*-coupling constants may be obtained.

Taking into account that the values of the *cis*-coupling constants of the C(4)—C(5) parts in (2) and (3a) are comparable (see Table 2), it can be concluded that the large difference (2.0 Hz) within $J_{3u,4u}$ of these compounds should mainly be attributed to the different electronegativities of the 3d substituents (Cl and H respectively).

A similar reasoning can be given to account for the increase of $J_{3u,4u}$ (that is $J_{2',3'}$ in riboses) in the series of uridine (5.2 Hz),[17] deoxyuridine (6.8 Hz),[17] and 1'-THF-uracil (7.8 Hz). Apparently, the substitution of each hydroxy by hydrogen causes an increase of >1 Hz.

Considering the individual *cis*-couples in the C(4)—C(5) parts of (3a) and (4a) (Table 4), information can be obtained regarding the influence of the orientation of an electronegative substituent. In Figure 5 the Newman projections of the C(5)—C(4) fragments of the major conformers of (3a) and (4a) are depicted. The orientation of O(1) with respect to H(4u) and H(4d) is characterized by the angles ϕ_1 and ϕ_2 respectively.

Inspection of the *J* values in Table 4 reveals that both in (3a) and in (4a) the smaller value (*ca.* 6.8 Hz) corresponds with ϕ *ca.* 150° and the larger value (*ca.* 7.9 Hz) with ϕ *ca.* 90°. The interesting observation that in both compounds the individual *cis*-coupling constants of the C(3)—C(4) parts are almost equal [7.8 and 8.1 Hz

in (3a); 8.8 and 9.3 Hz in (4a)] is a further indication of the effect of orientation of electronegative groups on couplings in the C(4)—C(5) parts.[21,22]

Relative Orientation of Uracil and THF Rings.—The orientation of the heterocyclic base relative to the sugar ring in (deoxy)ribonucleosides has been studied extensively.[23] In the solid state as well as in solution, pyrimidine nucleosides are known to prefer the *anti*-conformation. It has been argued that ' the hydroxymethyl group at C(4') [in our notation C(5)] seems to be responsible for the conformational weighting '.[14]

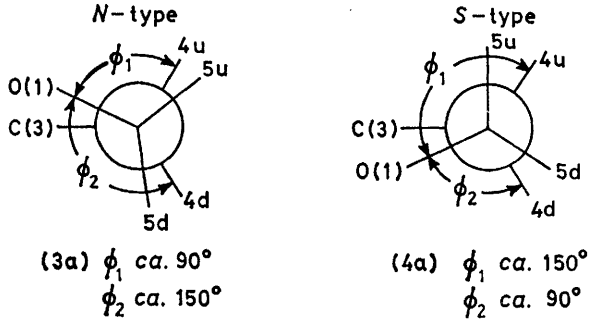


FIGURE 5 Newman projections of C(5)—C(4) fragments in (3a) and (4a), showing the orientation of the electronegative substituent with respect to the C(4) protons

One of the most interesting conclusions from the *X*-ray analysis of (3a) is that the ' sugar–base ' torsion angle (χ_{CN} 15.4°) falls well within the narrow range described for β-pyrimidine nucleosides in the *N*-type conformation.[5]

In solution the long-range coupling ($^5J_{H-H}$ 0.25 ± 0.1, $^5J_{H-F}$ 1.4 ± 0.1 Hz) found in (3a and b) respectively points to a similar conclusion. Also the pronounced changes, both in chemical shifts and in $N \rightleftharpoons S$ equilibrium composition that occur when a carbonyl function is located over the THF ring [*cf.* (4a and b) with (3a and b)] illustrate the preference for an *anti*-conformation of (3a and b) in solution.

Apparently, the preference for this orientation is not governed by substitution in the THF ring, but can be considered to be an intrinsic property of this type of ring junction.

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