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STRUCTURAL STUDIES ON 1-(1-DEOXY-β-D-PSICOFURANOSYL)THYMINE

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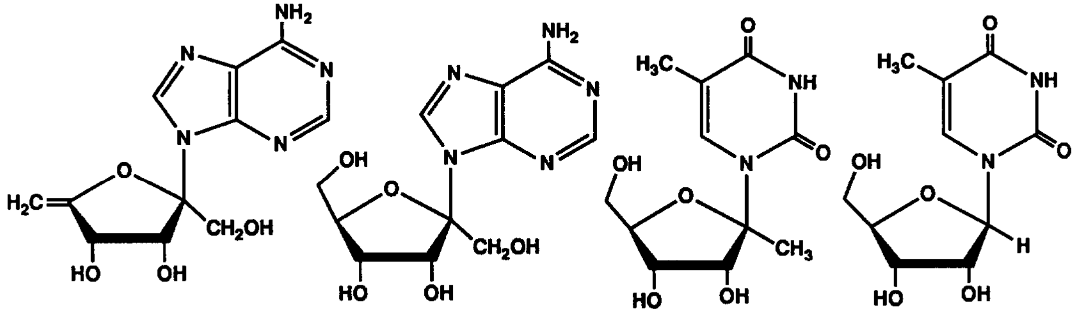
Abstract *Conformational analysis of a novel nucleoside analogue, 1-(1-Deoxy-β-D-psicofuranosyl)thymine (3) is described The structure of 3 differs from the natural ribonucleoside counterpart 4 in that a methyl group replaces H1' Conformational analysis of 3 was based on the vicinal proton-proton J-coupling constants* $J_{2'3'}$, $J_{3'4'}$, $J_{4'5'}$, *and* $J_{4'5''}$, *which were measured at 500 MHz for different solvents, and at different sample temperatures Although merely two J-coupling constants are available for conformational analysis of the furanose ring in 3, it can be concluded that a preference exists for a North-type puckered conformation A comparison is made with 1-(β-D-ribofuranosyl)thymine (4) which shows almost an equal population of pseudorotamers in North ⇄ South conformational equilibrium of the ribose moiety Molecular mechanics calculations using the MM2 force field yield molecular structures that are in excellent agreement with the NMR data, both for compounds 3 and 4 Thus, it can be safely concluded that the Me group on C1' in 3 has a pronounced impact on the furanose conformation by driving its conformational equilibrium towards the North form The North conformation of 3 appears to correspond with pseudo-equatorial location of the Me group, which is sterically favoured*

Decoyinine (Angustmycin A) **1** and Psicofuranine (Angustmycin C) **2** are well known adenine ketose naturally occurring nucleosides[1] They have antibacterial and antitumor activity, and are noncompetitive inhibitors of xanthinemonophosphate aminase[2] They are extremely susceptible to hydrolysis under acidic condition The additional hydroxymethyl group at C1' in the sugar moieties of both Decoyinine **1** and Psicofuranine **2** make them unique amongst all naturally-occurring nucleosides[3] We have been interested to incorporate this unique one extra carbon appendage at the anomeric center in pyrimidine nucleosides which have exhibited HIV-specific anti-retroviral activities[4-23] We reasoned that this unique functionalization at C1' by a single carbon homologation may dictate some specificity against HIV reverse transcriptase In our attempts to do so we chose to prepare the corresponding C1'-(Me) derivative[24] instead of C1'-(CH_2OH) simply because of the steric considerations We herein report our studies on the conformational implication of introduction of the C1'-(Me) group, as in 1-(1-Deoxy-β-D-psicofuranosyl)thymine (3)[24], compared to 1-(β-D-ribofuranosyl)thymine (4)[40], first by 500 MHz ^{1}H-NMR spectroscopy and the data analysis by well-known pseudorotation concept, and finally we arrive at an explicit model of the preferred conformation of 3 in solution through a set of molecular mechanics calculation using Allinger's MM2 force field

(A) Conformational analysis based on vicinal proton-proton J-coupling constants Our 500 MHz ^{1}H NMR studies on compound **1** were focussed primarily on the vicinal proton-proton coupling constants, i e , $J_{2'3'}$, $J_{3'4'}$, $J_{4'5'}$ and $J_{4'5''}$ The couplings $J_{4'5'}$ and $J_{4'5''}$ provide a direct means to determine the conformation around the C4'-C5' bond[25,26] As is well known, the conformation around this bond can be interpreted in terms of a rapid equilibrium over the staggered rotamers γ^+, γ^t and γ^- The calculated rotamer populations for the C4'-C5'



1 2 3 4

bond in 3, as measured under different experimental conditions, show that γ^+ and γ^t rotamers are approximately equally populated (47% and 48%, respectively) and prefered to γ^- rotamer (5%) The data on compound 3 are summarized in Table 1. The coupling constants $J_{2'3'}$ and $J_{3'4'}$ were used to monitor the conformation of the modified ribose ring in 3 Clearly, the introduction of the Me group at C1' cuts down the number of vicinal proton-proton constants from three (in ribonucleosides) to two in 3 The well-known pseudorotation concept [27] provides the most convenient way to describe the conformation of (modified)

Table 1 J-couplings (Hz) of 1-(1-Deoxy-β-D-psicofuranosyl)thymine (3)

Solvent		D_2O		DMSO-d_6	Pyridine-d_5
Temp =	8°C	19°C	30°C	19°C	19°C
$J_{2'3'}$	4 7	4 8	4 8	4 4	4 5
$J_{3'4'}$	7 1	7 1	7 0	8 7	8 3
$J_{4'5'}$	2 9	3 1	3 2	2 6	2 6
$J_{4'5''}$	5 8	5 8	5 9	4 3	4 0

furanose rings Only two parameters are needed to characterize the ring geometry a maximum puckering amplitude ν_m which defines the extent of puckering of the furanose ring, and a so-called phase angle of pseudorotation (P) which indicates which part of the ring is bent The parameters ν_m and P are directly related to the set of endocyclic torsion angles ν_0[C4'-O4'-C1'-C2'], ν_1[O4'-C1'-C2'-C3'], ν_2[C1'-C2'-C3'-C4'], ν_3[C2'-C3'-C4'-O4'], and ν_4[C3'-C4'-O4'-C1'][28] The dynamic behaviour of nucleosides and nucleotides in solution can often be interpreted in terms of a two-state equilibrium, form I ⇄ form II Clearly, five parameters are needed to describe such a conformational equilibrum ν_m and P of forms I and II and a mole fraction showing the relative participations of forms I and II

Although nothing is known *a priori* about the pseudorotational dynamics of compound 3, it is clear that even the simplest case of a two-state conformational equilibrium poses a serious problem to conformational analysis, since only two observables ($J_{2'3'}$ and $J_{3'4'}$) are available The common remedy to this situation is to measure vicinal coupling constants over a range of temperatures[29] Varying the sample temperature will change the position of the equilibrium, rather than the conformational properties of the individual forms For structure 3 this would mean that each new sample temperature adds two values to the experimental J-coupling data set, while only one extra parameter has to be calculated (i e the mole fraction for that particular temperature)

Table 2 J-couplings (Hz) of 1-(β-D-ribofuranosyl)thymine (4)

Solvent			D_2O			DMSO-d6	Pyridine-d_5
Temp =	8°C	19°C	30°C	45°C	80°C	19°C	19°C
$J_{1'2'}$	4 7	4 8	4 8	5 1	4 8	5 8	4 8
$J_{2'3'}$	5 4	5 5	5 5	5 4	5 6	5 2	5 1
$J_{3'4'}$	5 2	5 2	5 2	5 3	5 1	-	4 5
$J_{4'5'}$	2 9	3 0	3 1	3 1	3 1	-	2 7
$J_{4'5''}$	4 2	4 3	4 4	4 5	4 5	3 4	2 7

For this reason, we have attempted to measure $J_{2'3'}$ and $J_{3'4'}$ at different temperatures It was found, however, that compound **3** decomposes for temperatures higher than 35 °C, while for lower temperatures only minute changes of the J couplings could be detected Essentially, this means that the conformational analysis of the modified ribose ring in **3** poses a severely underdetermined problem

Initially, a graphical method was chosen to translate our values for $J_{2'3'}$ and $J_{3'4'}$ into a rough structural model of the modified ribose ring Figure 1 shows the calculated dependence of $J_{2'3'}$ and $J_{3'4'}$ on P, the phase angle of pseudorotation The three curves in Figure 1a correspond to fixed values of ν_m at 35°, 40° and 45°, respectively The calculations were based on (i) the empirically generalized Karplus equation as developed by Altona *et al*,[25] which relates vicinal proton-proton J-coupling constants to proton-proton torsion angles, and (ii) the relations ϕ[H2'-C2'-C3'-H3'] = 2 4° + 1.06 ν_2 and ϕ[H3'-C3'-C4'-H4'] = -124 0° + 1 09 ν_3 [30] Closed curves are obtained as P varies from 0° (North region) via 180° (South region), to 360° (North region) The experimental data points, which represent time-averaged values of the J-coupling constants in each of the participating conformers, nearly coincide at the spot ($J_{2'3'}$ = 4 7-4 8 Hz, $J_{3'4'}$ = 7 0-7 1 Hz), which is close to the North region in all three graphs This shows that the modified ribose ring in **3** is biased towards a North-type conformation Clearly, the position of the experimental data points is determined by the J-values in each of the conformers participating in the conformational equilibrium, and their mole fractions In the case of a two-state equilibrium, this means that the experimental data points are found on the line (conode) that connects the P-values for the two participating conformers [31,32] In this respect, it is of interest to note that the experimental data points are offset from any conode that can be drawn between the points on the curve for ν_m = 35° This means that the puckering amplitude of the furanose ring in **3** must exceed 35° For the curves ν_m = 40° and ν_m = 45° it is possible to construct conodes between e g the North and South regions, such that the experimental data points fall on the conodes If done so, it follows that the conformation is biased towards the North-type conformation (> ca 80 %) It is of interest to note that this conclusion remain valid if the modified ribose ring in structure **3** would be involved in a more complex conformational equilibrium (e g between three states) In a subsequent alternative analysis, we used the program PSEUROT[29] for the translation of our J-couplings into a conformational picture of the modified ribose ring in **3** PSEUROT calculates the best fit of the five conformational parameters needed to characterize a two-state conformational equilibrium (*vide supra*) to the set of experimental vicinal couplings PSEUROT was run under the assumption that the puckering amplitudes in both participating conformers are equal Minimal root-mean-square error was found for ν_m = 38 5°, the two

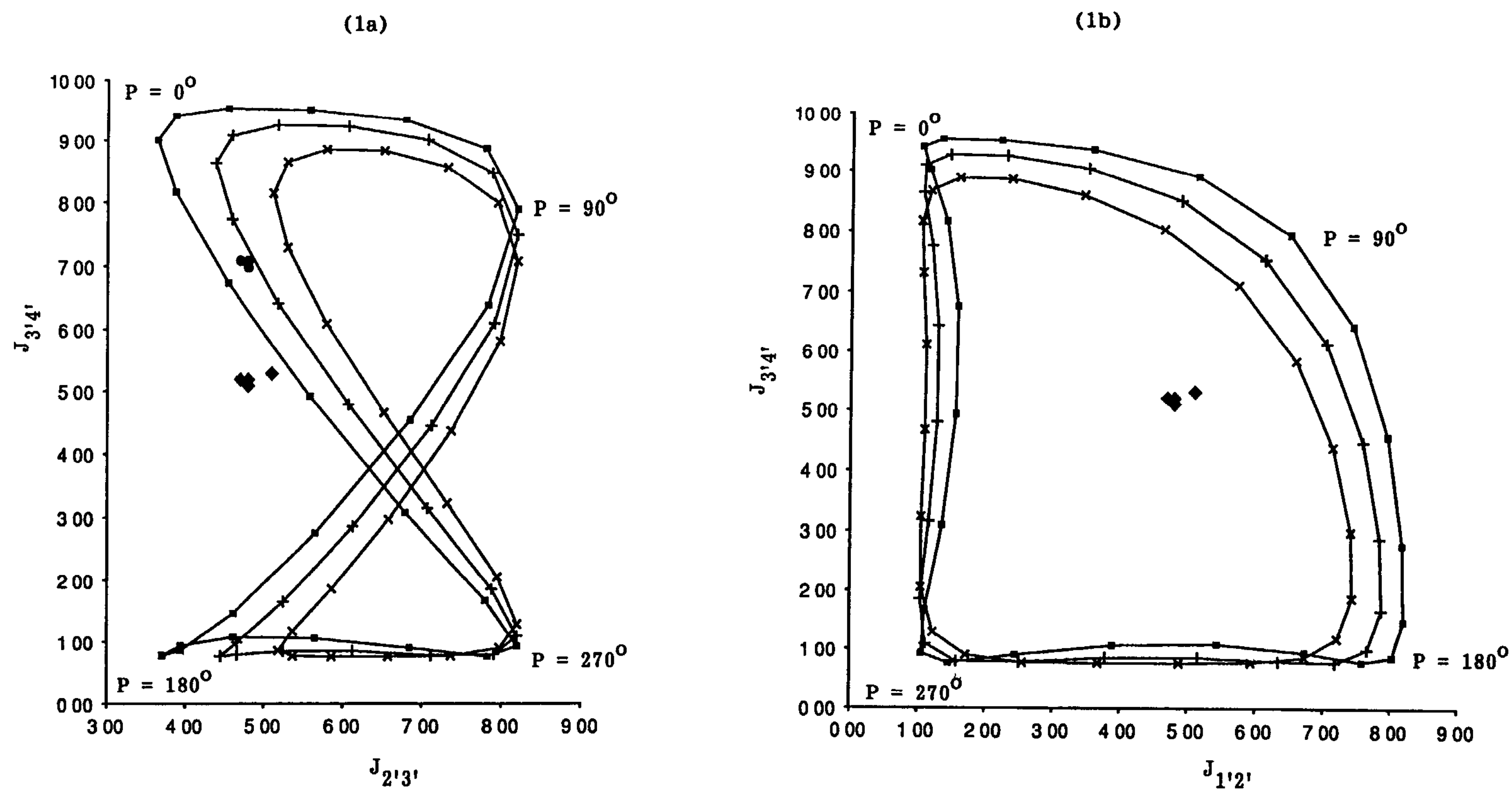
Table 3 Pseudorotational & MM2 Calculations 1-(1-Deoxy-β-D-psicofuranosyl)thymine (3)

	PSEUROT Analysis	Pseudorotational parameters from MM2 Calculations			
		Syn, γ^+ (Fig 2a)	*Anti*, γ^+ (Fig 2b)	*Syn*, γ^t (Fig 2c)	*Anti*, γ^t (Fig 2d)
φ[H2'-H3']*	42.1°	47 5°	45 6°	46 3°	47 0°
φ[H3'-H4']#	-157 5°	-160 6°	-161 0°	-158 3°	-159 0°
ν_0	14 05°	17 0°	14 6°	17 7°	17 8°
ν_1	-32 43°	-36 9°	-34.8°	-36 8°	-37.2°
ν_2	38 43°	41 3°	40 2°	40 6°	41 2°
ν_3	-29 75°	-33 0°	-33 2°	-31 8°	-32 3°
ν_4	9 70°	10 2°	11 8°	8 9°	9 2°
P	-3 4°	-4 8°	-2 0°	-6 3°	-6 1°
ν_m	38 5°	41 4°	40 2°	40 9°	41 4°
% N	80				
Steric Energy (Kcal/mol)		25 857	24 373	25 74	24 085
γ (deg)¢		56 8°	56 7°	178 9°	-177.6°
χ (deg)⁎		-24 6°	173 4°	-12 7°	174 6°

* φ[H2'-C2'-C3'-H3'], # φ[H3'-C3'-C4'-H4'], ¢ φ[O5'-C5'-C4'-C3'], ⁎ φ[C2-N1-C1'-O4']

participating conformers are predicted to have the phase angles P = -3 4° (North) , and P = 150 3° (South), with a mole fraction x(North) = 80% The calculated proton-proton torsion angles φ[H2'-C2'-C3'-H3') and φ[H3'-C3'-C4'-H4'] in the North form are 42 1° and -157 5°, respectively At this point, we have compared the structure of 3 with the conformational features derived from the 500 MHz ^{1}H-NMR of 1-(β-D-ribofuranosyl)thymine (4) The PSEUROT analysis of J-couplings of **4** showed that the population of North and South conformers is approximately equal (Table 4), and the rapid equilibrium over the staggered rotamers γ^+, γ^t and γ^- population for the C4'-C5' bond is favoured to γ^+ (65%) while the population of γ^t is 30% and γ^- rotamer is 5%

(B) Molecular Mechanics Calculations In order to arrive at a more explicit model of the preferred conformation of 3 in solution, a set of molecular mechanics calculation were carried out, using Allinger's MM2 method[33] Starting geometries were generated on the basis of the conformational information as deduced from J-coupling analysis (vide supra) Thus, the MM2 calculations served to refine the experimental data We decided to examine four distinct starting structures, taking into account that structure **3** poseses three important



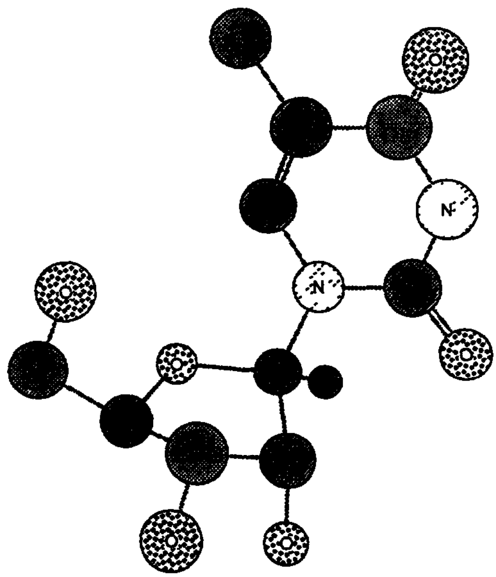
Figures 1a & 1b Values for $J_{1'2'}$, $J_{2'3'}$, $J_{3'4'}$ were calculated by varying the Phase angle of pseudorotation (P) from 0 - 360° at fixed Puckering amplitude (v_m) of 35° (x), of 40° (+) and of 45° (■) using Karplus-type equation as developed by Altona et al (ref. 30) for ribofuranosyl nucleosides Data points for compounds 3 (represented by ●) and 4 (represented by ◆) were obtained through the experimental J-couplings measured at 500 MHz in D_2O at different temperatures.

Table 4 Pseudorotational & MM2 Calculations of 1-(β-D-ribofuranosyl)thymine (4)

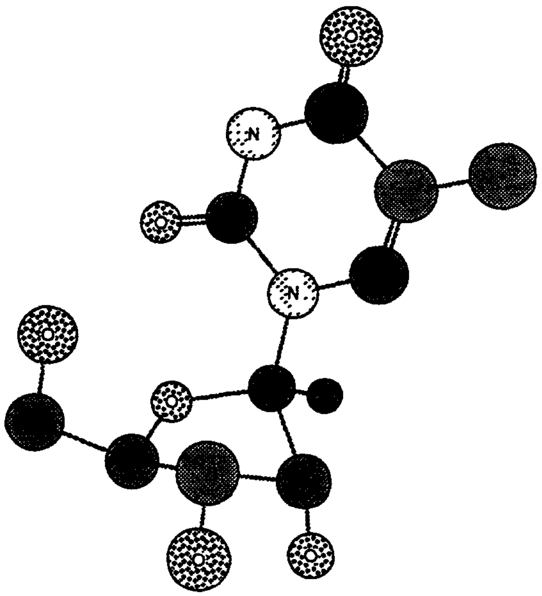
	North conformer		South conformer	
	PSEUROT analysis	Parameters from MM2 Calculations	PSEUROT analysis	Parameters from MM2 Calculations
ν_0	9 9°	2 3°	−33 0°	−32 9°
ν_1	-29 7°	-26 1°	38.0°	38 7°
ν_2	38.15°	37 7°	-28 5°	-29 4°
ν_3	-32 04°	-38 4°	8 1°	11 35°
ν_4	13.7°	22 9°	15 4°	13 5°
P	3 0°	15 9°	138 2°	140 8°
ν_m	38 2°	39 2°	38 2°	37 9°
% N	45		55	
Steric Energy (Kcal/mol)		20 403		20 37
γ (deg)¢		59 4°		58 3°
χ (deg)≠		-162 0°		−147 5°

¢ ϕ[O5'-C5'-C4'-C3'], ≠ ϕ[C2-N1-C1'-O4']

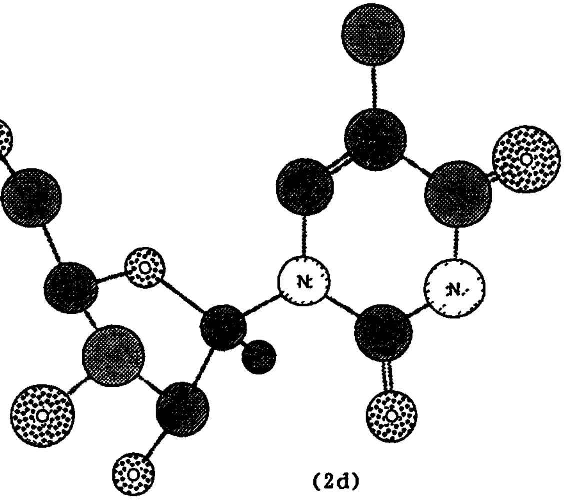
degrees of conformational freedom, namely pseudorotation of the furanose moiety, rotation around the C4'-C5' bond, and rotation around the C1'-N1 bond[34] In view of the NMR results, all calculations were started from a North-type puckered furanose ring, and either a γ^+ or γ^t conformation around the C4'-C5' bond The conformation around the glycosidic C1'-N1 bond was put in either the *anti* or the *syn* range since it was not possible to obtain any three-bond J-couplings between C2-H1' or C6-H1' [37,38] While it is known that pyrimidine bases have a strong tendency for *anti* conformation, we anticipated that a *syn* conformation for 3 can not be disregarded Space-filling models seem to indicate that the presence of the Me group on C1' can sterically interfere with O2 in the case of *anti* conformation, i e the Me group on C1' could therefore induce a preference for *syn* The four distinct starting structures can be characterized as follows (i)· North furanose ring, γ^+ for the C4'-C5' bond, *syn* for the C1'-N1 conformation, (ii) North, γ^+, *anti*, (iii) North, γ^t, *syn*, (iv) North, γ^t, *anti* Table 3 summarizes the most important geometrical and energetic parameters that were obtained after optimalization of the geometry, using the MM2 force field The optimized structures are also graphically shown by ball and stick model in Figures 2a, 2b, 2c and 2d, respectively Comparing the steric energies, it is obvious that MM2 predicts *anti* orientation of the base to be preferred over *syn* orientation by ca 1 5 Kcal/mol (Table 3) The glycosidic torsion angle is predicted to be approximately 174° for *anti* structures (Figures 2b & 2d, Table 3) The molecular models corroborate that the steric hindrance between the Me group on C1' and the base moiety is not of major importance in this geometry Another important conclusion that can be drawn from the calculational results is that structures depicted in Figures 2a to 2d have virtually converged to the same



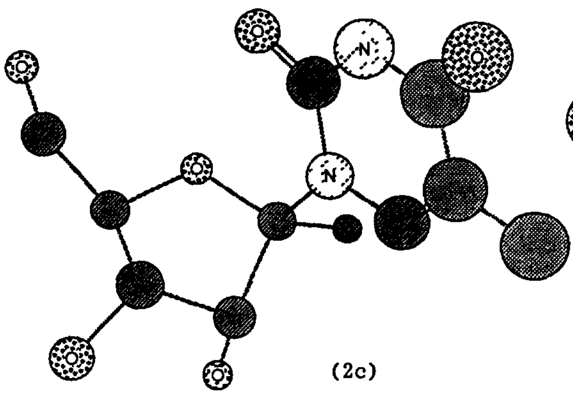
(2b)



(2a)



(2d)



(2c)

Figures 2a - 2d Molecular mechanics (Allinger's MM2 force field) optimized structures for 1-(1-Deoxy-β-D-psicofuranosyl)thymine (**3**) (2a) North, γ^{+}, *syn* , (2b) North, γ^{+}, *anti*, (2c) North, γ^{t}, *syn*, (2d) North, γ^{t}, *anti* Note the puckering amplitudes [ν_m] in all four optimized structures are between 40 2 and 41 4° and the phase angles (P) are between -6 3 to -2 0°, which correlate very favourably with the results from PSEUROT analysis [ν_m = 38.5° and P = -3 4° for the preferred North form (~80%)

geometry for the modified ribose. *The puckering amplitudes in all four optimized structures are between 40.2 and 41.4°, and also the phase angles fall in a very narrow range (-6.3 to -2.0°). Interestingly, these results correlate very favourably with the results from PSEUROT analysis (vide supra, Table 3), which yielded a puckering amplitude of 38.5° and a phase angle of -3.4° for the most preferred North form. Also, a comparison of the proton-proton torsion angles ϕ[H2'-C2'-C3'-H3'] and ϕ[H3'-C3'-C4'-H4'] shows a very close correspondence between the PSEUROT derived structure, and the MM2 calculated structure, started from geometries (i) - (iv)*.

Discussion. Despite the fact that only two vicinal J-coupling constants are available for conformational analysis of the modified ribose ring in **3**, it can be safely concluded that a preference exists for a North type ring conformation. NMR data and molecular mechanics calculations support this conclusion unequivocally. Examining the North conformation more in detail, it is clearly seen that the Me group assumes a pseudo-equatorial location with respect to the furanose ring. Conversely, the thymine base is in a pseudo-axial location. Perhaps the best visualization is given via the Newman projection along the C2'-C1' bond (Figure 3). Figure 3 clearly illustrates that the Me group is more remote from the furanose ring in the case of a North conformation, than for a South conformation. The conformational properties of compounds **3** (Table 3) and **4** (Table 4) should be discussed in terms of at least two effects. First, the aglycon base tends to adopt a pseudoaxial location, in which an antiperiplanar orientation of the C1'-N1 bond, and one of the lone-pairs on O4' is

(A)

(B)

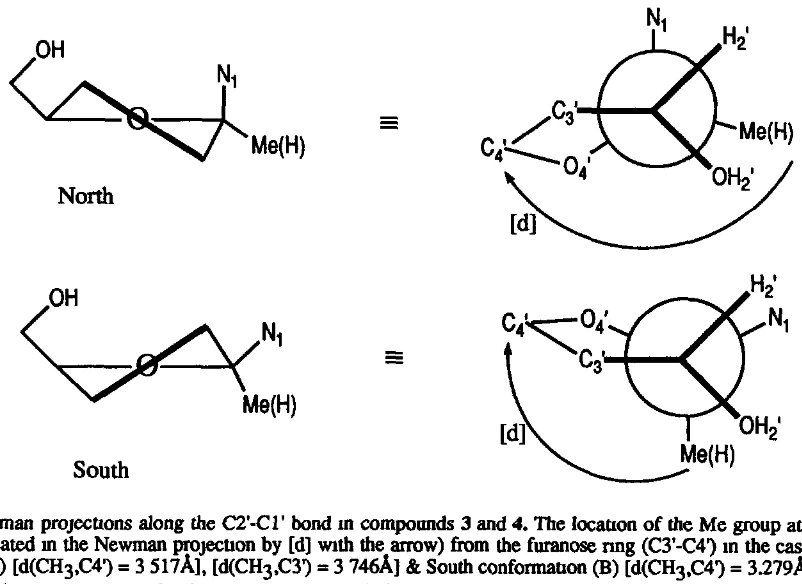


Figure 3. Newman projections along the C2'-C1' bond in compounds **3** and **4**. The location of the Me group at C1' is clearly distant (as indicated in the Newman projection by [d] with the arrow) from the furanose ring (C3'-C4') in the case of the North conformation (A) [d(CH_3,C4') = 3.517Å], [d(CH_3,C3') = 3.746Å] & South conformation (B) [d(CH_3,C4') = 3.279Å, [d(CH_3,C3') = 3.196Å]]. An alternative measure for the location of the methyl group with respect to the furanose ring is provided by the torsion angles ϕ[C3'-C2'-C1'-Me] and ϕ[C4'-O4'-C1'-Me]. For the North conformation (A) ϕ[C3'-C2'-C1'-Me] = -150.6° and ϕ[C4'-O4'-C1'-Me] = 135.4°, for South conformation (B) ϕ[C3'-C2'-C1'-Me] = -80.3° and ϕ[C4'-O4'-C1'-Me] = 94.0°

achieved. This geometry permits maximal n - σ* overlap (anomeric effect)[35]. Secondly, it is known that bulky ring-substituents tend to occupy a (pseudo-) equatorial location in order to minimize unfavourable steric interactions[39]. Interestingly, the encountered conformational properties of compounds **3** and **4** can be rationalized on the basis of *combined action of the anomeric and steric effects*. The preferred North conformation of **3** corresponds with pseudo-axial location of the base [favourable anomeric effect, unfavourable for steric reasons] and pseudo-equatorial location of the Me group [favourable for steric reasons] Clearly, an alternative South-type conformation would place the thymine base in a pseudo-equatorial location [loss of the anomeric effect, favourable for steric reasons, as well as unfavourable pseudo-axial location of the Me] Thus the overall favourable pseudo-equatorial location of the Me group drives the conformation of 3 to the preponderant North-type conformation

If we now turn to compound **4**, it is seen that North conformation corresponds with pseudo-axial location of the aglycon [anomeric effect operative, but disfavoured for steric reasons], and the alternative South conformation has pseudo-equatorial location of the base, in which virtually no stabilization occurs by the anomeric effect, while steric interactions with the ring would be minimized These opposing steric and anomeric effects do not provide any special driving force for either favoured North- or South-type conformation for **4** In fact, this simple rational illustrates that North and South conformation are approximately equally favourable in the case of ribothymidine **4** in solution (and, in fact also for other ribonucleosides)[38] Clearly, further experimental and theoretical studies are required to quantify the energetic aspects of the anomeric effect, and pseudo-axial/pseudo-equatorial location of substituents on furanose rings In fact, we have observed in previous work on C2'- and C3'-methylated modified nucleosides that Me has a relatively pronounced preference for pseudo-equatorial location, which can completely dictate the conformation of the furanose ring[36] Compound **4** represents a unique new example of a nucleoside analogue in which the furanose conformation is tuned via a methyl group on one of the furanose carbons

EXPERIMENTALS

Compounds **3** & **4** were prepared using the literature procedure (ref 24 & 40, respectively) All NMR spectra were recorded on a Bruker AMX-500 spectrometer ^{1}H-NMR spectra were collected with 32K data points in D_2O at different temperatures and zero filled to 64K data points A trace of dry acetonitrile was added as an internal reference for chemical shift measurements (δ 2 00 ppm). MM2 calculations were performed using Prof Allinger's MM2 force field as implented by J W Ponder [Chem3D plus (version 3 0) by Cambridge Scientific Computing, Cambridge, Massachusetts, USA]

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