How does the Steric Effect drive the Sugar Conformation in the 3′-*C*-branched Nucleosides?

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The steric effect of 3′-CH_2OH group drives the North ⇄ South pseudorotational equilibrium of the sugar moiety in the isomeric 1-(2′,3′-dideoxy-3′-hydroxymethyl-β-D-*erythro*-pentofuranosyl)cytosine **1** (80% North at 298 K; $\Delta H^\circ = +5.9$ kJ mol^{-1}, $\Delta S^\circ = +7.4$ J K^{-1} mol^{-1}), and 1-(2′,3′-dideoxy-3′-hydroxymethyl-β-D-*threo*-pentofuranosyl)cytosine **2** (82% South at 293 K; $\Delta H^\circ = -0.9$ kJ mol^{-1}, $\Delta S^\circ = +9.5$ J K^{-1} mol^{-1}) and it is found to be three times stronger in **2** ($\Delta H^\circ = -5.9$ kJ mol^{-1}) in comparison with that of **1** ($\Delta H^\circ = -2.1$ kJ mol^{-1}).

The pentofuranosyl moiety of nucleosides and nucleotides in solution is involved in a two-state conformational equilibrium between North [N (C3′-*endo*-C2′-*exo*] and South type [S (C2′-*endo*-C3′-*exo*] puckered pseudorotamers,[1,2] which can be monitored through the analysis of vicinal proton–proton coupling constants ($^3J_{HH}$).[1–7],† The geometry of individual pseudorotamers[2] is described by two parameters: a phase

† Phase angle (P) and puckering amplitude (ψ_m) are related to five endocyclic torsions ($\nu_0 - \nu_4$) by ($\nu_j = \psi_m \cos(P + 4(j\text{-}2)\pi/5)$, see ref. 7.

angle of pseudorotation (P), which defines the part of the ring which is mostly puckered and a puckering amplitude (ψ_m), which indicates the extent of puckering (Fig. 1).[1,2] The position of the pseudorotational N ⇄ S equilibrium is influenced by various steric and stereoelectronic effects of substituents that control the conformational preferences of pentofuranose moiety. Through the pseudorotational analyses of temperature-dependent $^3J_{HH}$ we have determined‡ the strength of anomeric effect ($\Delta H°$ = +5.0 kJ mol^{-1}) in 2′,3′-dideoxycytidine **3** (ddC) ($\Delta H°$ = +6.9 kJ mol^{-1}; $\Delta S°$ = +12.7 J K^{-1} mol^{-1})[8] which drives the pseudorotational equilibrium to the North type sugar.

The conformational behaviour of the 3′-hydroxymethyl-2′,3′-dideoxypentofuranose[9] ring in isomeric **1** and **2** has been analysed.§ This unique pair of isomeric nucleosides **1** and **2** has enabled us to evaluate how does the strength of the steric effect of a 3′-*C*-substituent on the α- or β-face drive the pseudorotational equilibrium of the pentofuranose ring. The anomeric effect of the cytosine base and the effect of 4′-CH_2OH group are common factors in **1** and **2** that can be isolated in comparison with ddC **3**.[8]‡

North sugar ($C_{3'}$-*endo*-$C_{2'}$-*exo*) South sugar ($C_{2'}$-*endo*-$C_{3'}$-*exo*)
$0° \leq P \leq 36°$ $144° \leq P \leq 190°$
$\psi_m = 38.6° \pm 3°$ $\psi_m = 38.6° \pm 3°$
Base = adenine-9-yl (A), guanine-9-yl (G), cytosine-1-yl (C), thymine-1-yl (T) or uracil-1-yl (U)

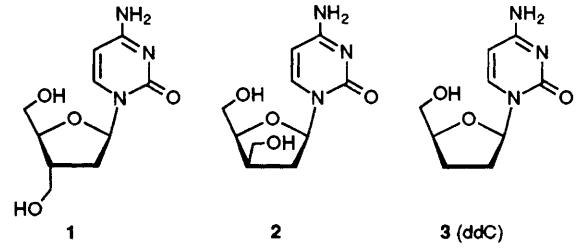
Fig. 1

‡ The strength of the anomeric effect of cytosine base as a driving force of pseudorotational equilibrium has been assessed in two ways by making van't Hoff plots of ([ln (X_S/X_N)] *vs.* 1/T) in order to determine the enthalpy ($\Delta H°$) and the entropy ($\Delta S°$) of the N ⇄ S equilibrium. First estimate of the anomeric effect of cytosine ($\Delta H°$ = +6.5 kJ mol^{-1}) has been obtained by the subtraction of the $\Delta H°$ values for N ⇄ S pseudorotational equilibrium in 2′,3′-ddC ($\Delta H°$ = +6.9 kJ mol^{-1}) and in (*S*)-tetrahydrofurfuryl alcohol ($\Delta H°$ = +0.4 kJ mol^{-1}). Second estimate ($\Delta H°$ = +3.4 kJ mol^{-1}) has been obtained by the subtraction of the $\Delta H°$ values in 1,2-dideoxy-D-*ribo*-furanose ($\Delta H°$ = −4.2 kJ mol^{-1}) from that in 2′-dC ($\Delta H°$ = −0.8 kJ mol^{-1}) with an average of $\Delta H°$ = +5.0 kJ mol^{-1}. The average estimate of $\Delta H°$ = +1.5 kJ mol^{-1} for the preference of pseudoequatorial orientation of 4′-CH_2OH group has been calculated by the regression analysis of $\Delta H°$ values of N ⇄ S equilibria in 12 nucleosides and abasic sugars (adenosine, 2′,3′-ddA, 2′-dA, guanosine, 2′,3′-ddG, 2′-dG, cytidine, 2′,3′-ddC, 2′-dC, (*S*)-tetrahydrofurfuryl alcohol, 1,2-dideoxy-D-*ribo*-furanose, 1,2,3-trideoxy-D-*ribo*-furanose).

§ The populations of the staggered rotamers across C4′-C5′ (γ$^+$, γ^t and γ$^-$) in epimers **1** and **2** were calculated from $^3J_{4'5'}$ and $^3J_{4'5''}$ according to C. A. G. Haasnoot, F. A. A. M. de Leeuw, H. P. M. de Leeuw and C. Altona, *Recl. Trav. Chim. Pays-Bas*, 1979, **98**, 576. The population of rotamers across C3′-CH_2 bond (ε [$C_{4'}$–$C_{3'}$–CH_2–O]: ε$^-$ ⇄ ε$^+$ ⇄ ε^t) in **1** and **2** has been calculated [$^3J_{H3',CH_2}$ = 6.0 Hz from 298 K to 353 K in **1**; $^3J_{H3',CH_a}$ and $^3J_{H3',CH_b}$ for **2** are 7.1 and 7.0 Hz at 293 K and 7.0 and 6.8 Hz at 353 K (the limiting coupling constants for **1**: ε = 60° ($^3J_{H3',CH_a}$ = $^3J_{H3',CH_b}$ = 1.9 Hz), ε = 180° ($^3J_{H3',CH_a}$ = 11.5 Hz and $^3J_{H3',CH_b}$ = 4.1 Hz) and ε = −60° ($^3J_{H3',CH_a}$ = 4.1 Hz and $^3J_{H3'CH_b}$ = 11.5 Hz) give the following rotamer populations: $x(\varepsilon^+)$ = 0.31, $x(\varepsilon^-)$ = 0.35 and $x(\varepsilon^t)$ = 0.35]. The limiting $^3J_{H,H}$ in **2** for ε = 60° ($^3J_{H3',CH_a}$ = 4.1 Hz and $^3J_{H3',CH_b}$ = 11.5 Hz), ε = −60° ($^3J_{H3',CH_a}$ = $^3J_{H3',CH_b}$ = 1.9 Hz), and ε = 180° ($^3J_{H3',CH_a}$ = 11.5 Hz and $^3J_{H3',CH_b}$ = 4.1 Hz) give at 293 K: $x(\varepsilon^+)$ = 0.43, $x(\varepsilon^-)$ = 0.13 and $x(\varepsilon^t)$ = 0.44, and at 353 K: $x(\varepsilon^+)$ = 0.41, $x(\varepsilon^-)$ = 0.15 and $x(\varepsilon^t)$ = 0.44. These populations do not change even with reverse assignment of 3′-CH_aH_bOH. On the basis of observed NOE enhancements at H1′ (2.3%), H2′ (2.7%), H3′ (2.6%) and H5″ (0.9%) upon saturation of H6 in **1**, it has been concluded that the pyrimidine base is *anti* which is consistent with $^3J_{C2,H1'}$ (2.0 Hz) and $^3J_{C6,H1'}$ (3.0 Hz) ref. 16).

Vicinal proton–proton coupling constants ($^3J_{HH}$) of 1-(2′,3′-dideoxy-3′-hydroxymethyl-β-D-*erythro*-pentofuranosyl)cytosine **1** and its epimer 1-(2′,3′-dideoxy-3′-hydroxymethyl-β-D-*threo*-pentofuranosyl)cytosine **2**[9],§ were obtained through ^{1}H NMR spectra at 500 MHz in D_2O at four temperatures in the range 293–353 K (Table 1). The computer program PSEUROT[7] has been used to calculate the best fit of the five conformational parameters[7]† (P and ψ_m for both North and South conformers and corresponding mole fractions) to the five experimental coupling constants ($^3J_{1'2'}$, $^3J_{1'2''}$, $^3J_{2'3'}$, $^3J_{2''3'}$ and $^3J_{3'4'}$). The sugar moiety of **1** is involved in [North (P = 5°, ψ_m = 30°)] ⇄ [South (P = 150 °, ψ = 30°)] equilibrium with the North conformer being preferred by 80% at 298 K. The geometry of the minor South conformer was constrained during optimisation.¶ The r.m.s. error of PSEUROT analysis of $^3J_{HH}$ in **1** was 0.5 Hz and the largest deviations between experimental and calculated $^3J_{HH}$ were 0.8 Hz for $^3J_{1'2''}$ and 0.7 Hz for $^3J_{2''3'}$. The population of the major North conformer in **1** is reduced from 80% at 298 K by increasing temperature to 77% at 313 K, 75% at 333 K and 73% at 353 K. In the case of **2** a high preference of 82% for the South sugar conformation (P = 177°, ψ_m = 34°) was found, which does not change with temperature. The pentofuranose ring of **2** is involved in [North (P = 0°, ψ_m = 34°)] ⇄ [South (P = 177°, ψ_m = 34°)] equilibrium. The geometry of the minor North conformer was kept fixed during optimisation.¶ The r.m.s. error of PSEUROT analysis was 0.3 Hz and the largest individual deviation between experimental and calculated $^3J_{HH}$ was 0.6 Hz for $^3J_{1'2''}$.

The conformational analysis of pentofuranosyl moieties in **1** and **2** was extended by making van't Hoff plots of ([ln (X_S/X_N)] *vs.* 1/T) in order to determine the enthalpy ($\Delta H°$) and the entropy ($\Delta S°$) of the N ⇄ S pseudorotational equilibria. The slope of the straight lines, calculated through the experimental data points, gave the $\Delta H°$ values for **1** and **2** of +5.9 (σ = 0.1) and −0.9 (σ = 0.2) kJ mol^{-1}, respectively (Table 2).¶ The corresponding $\Delta S°$ values of the N ⇄ S pseudorotational equilibrium in **1** and **2**, derived from the point of interception on the ordinate are +7.4 (σ = 0.6) and +9.5 (σ = 0.7) J mol^{-1} K^{-1}, respectively.¶ Note that at room temperature the enthalpy and entropy contributions to the $\Delta G°$ of pseudototational equilibrium in **1** and **2** are very different. Although the entropy contributions to the drive of the pseudorotational equilibrium in **1** and **2** (Table 2) are comparable, it is the significant $\Delta H°$ contribution (+5.9 kJ mol^{-1}) over the entropy in **1**, which drives the pseudorota-



1 **2** **3 (ddC)**

¶ The standard deviations of $\Delta H°$ and $\Delta S°$ are based on 12 calculations of slopes and intercepts of van't Hoff graphs on PSEUROT analyses of different geometries in which the minor conformers were kept fixed during optimisations. For **1**, P of the minor South conformer was increased from 140° to 190° in 10° steps at ψ_m = 30° and 35°. The population of the major North conformer of **1** (3° < P < 14°, 28° < ψ_m <31°) varied by ±3% at temps shown in Table 1 to give r.m.s. error in the range of 0.4 to 0.7 Hz. In the PSEUROT optimisations of $^3J_{HH}$ in **2**, P of the minor North conformer was varied in the range −20° < P < 20° at ψ_m = 30°, 34° and 39°. The population of the major (82%) South conformer of **2** (174° < P < 181°, 34° < ψ_m < 36°) varied by ±2% at temps shown in Table 1 to give r.m.s. error in the range of 0.3 to 0.4 Hz.

Table 1 $^3J_{H,H}$ coupling constants[a] (Hz) and populations of conformers around $C_{4'}$–$C_{5'}$, bond[b] for 2',3'-dideoxy-3'-hydroxymethyl-*erythro*-cytidine **1**[c] and its C3' epimer **2**[d]

Compd.	*T*/K	$J_{1'2'}$	$J_{1'2''}$	$J_{2'3'}$	$J_{2''3'}$	$J_{3'4'}$	$J_{4'5'}$	$J_{4'5''}$	$x(\gamma^+)$	$x(\gamma^t)$	$x(\gamma^-)$
1	298	3.8	7.1	8.1	8.9	8.1	2.9	5.4	0.52	0.43	0.05
	313	4.0	7.0	8.3	8.7	7.9	3.1	5.4	0.50	0.43	0.08
	333	4.2	6.9	8.2	8.3	8.0	3.2	5.5	0.48	0.43	0.09
	353	4.3	7.1	8.3	8.2	7.9	3.4	5.5	0.46	0.43	0.11
2	293	7.6	6.3	9.0	7.8	7.6	3.5	7.0	0.29	0.59	0.12
	313	7.7	6.1	9.0	7.7	7.6	3.6	6.9	0.29	0.57	0.13
	333	7.6	6.2	9.0	7.6	7.9	3.9	6.8	0.28	0.55	0.17
	353	7.6	6.3	8.8	7.8	7.8	3.9	6.6	0.30	0.53	0.17

[a] $^3J_{H,H}$ were extracted from one-dimensional ^1H NMR spectra recorded at 500 MHz in D_2O. [b] See note §. [c] δ (298 K) 6.00 (H-1'), 3.92 (H-4'), 3.83 (H-5'), 3.67 (H-5''), 3.59 (3'-CH_2OH; $^3J_{H3',CH_2}$ = 6.0 Hz, invariable with temp.), 2.32 (H-3'), 2.25 (H-2''), 2.14 (H-2'). [d] δ (293 K) 5.93 (H-1'), 4.20 (H-4'), 3.75 (H-5'), 3.65 (H-5''), 3.60 (3'-C*H*; $^3J_{H3',CH}$ = 7.1 Hz, J_{gem} = 11.3 Hz), 3.51 (3'-C*H*; $^3J_{H3',CH}$ = 7.0 Hz), 2.65 (H-3'), 2.45 (H-2''), 1.75 (H-2').

Table 2 Enthalpy and entropy contributions[a] of N ⇄ S pseudorotational equilibrium in **1**, **2** and ddC **3**

Compd.	$\Delta H°$	$-T\Delta S°$	ΔG^{298}	% North
1	5.9	−2.2	3.7	82
2	−0.9	−2.8	−3.7	18
3	6.9	−3.8	3.1	78

[a] Values of $\Delta H°$, $-T\Delta S°$ (at 298 K) and ΔG^{298} are in kJ mol^{-1}.

tional equilibrium to the North conformer. In contrast, the $\Delta H°$ (−0.9 kJ mol^{-1}) and entropy (−2.8 kJ mol^{-1}) contributions are working in a cooperative manner in **2** to drive the pseudorotational equilibrium to the South in D_2O solution.

The effect of 3'-CH_2OH group on the pseudorotational equilibrium in **1** and **2** has been analysed through the comparison of $\Delta H°$ values of **1** and **2** with that of ddC **3**.[8]‡ In all three compounds the anomeric effect of cytosine base and substituent effect of 4'-CH_2OH group (both effects drive the N ⇄ S equilibrium to North)‡ are equivalent. Clearly, 3'-CH_2OH group drives the pseudorotational equilibrium in both *erythro* and *threo* configuration in **1** and **2**, respectively, through its preference to occupy the pseudoequatorial orientation. In **1** the pseudoequatorial orientation of 3'-CH_2OH group is achieved in the North type conformations, while in **2** it is achieved in the South type sugar. This tendency of 3'-CH_2OH group to occupy pseudoequatorial orientation imposes distinct steric hindrances that have dramatic influence on the N ⇄ S pseudorotational equilibrium in **1** and **2** depending on the configuration at C3' (*vide infra*). It was shown before, that the strong preference for the North type conformation in 3'-dA (77% at 300 K)[10,11] can be dramatically altered to the South conformation by the introduction of the Me group at C3' on the β-face of the 3'-deoxy-*xylo*-pentofuranosyl moiety[12] (>95% South). It was also known that 9-(3'-*C*-methyl-β-D-*xylo*-furanosyl)adenine takes up preferentially North conformation (90% at 300 K), whereas 3'-*C*-methyl-adenosine adopts the South conformation (91% at 300 K).[13] In these works,[10–13] it was not possible to dissect the complex influence of various effects such as the preference of O2'/O3'–C–C–O4' fragments to adopt the *gauche* orientation, the effects of C2'/3'-substituents and the anomeric effect. In contrast, the presence of 3'-CH_2OH group in the α- or the β-face in the epimeric **1** and **2** and the absence of *gauche* effects provides unique opportunity to quantitatively assess for the first time the steric effect of 3'-*C*-substituent in the sugar moiety as one of the important forces that drive the N ⇄ S pseudorotational equilibrium.

That the steric effect of 3'-CH_2OH group in **1** and **2** was considerably different was recognized through the simple computer modelling.[14,15] The structures of **1** and **2** were built covering the North (−20° < *P* < 40°) and South (140° < *P* < 220°) part of the pseudorotational cycle[1,2] at ψ_m = 34°. The comparison of distances $d_{C5'-3'-C}$, $d_{N1-3'-C}$ and $d_{C5'-N1}$ in these pseudorotamers of **1** and **2** has revealed that in **1** the only distance that is different in North and South type puckered sugar ring is $d_{C5'-3'-C}$ (3.34 Å at *P* = 0° and 3.79 Å at *P* = 160°).‖ In **2** where 4'-CH_2OH, 3'-CH_2OH and the base are on the β-side of the pentofuranose ring the only distance that changes considerably along the pseudorotational cycle is $d_{N1-3'-C}$ (3.37 Å at *P* = 0° and 4.87 Å at *P* = 160°).‖ It is noteworthy that in **2** the distance $d_{C5'-3'-C}$ does not change (3.0 ± 0.1 Å) as *P* covers North and South part of the pseudorotational cycle. Therefore, the steric interactions alone between 3'-CH_2OH and 4'-CH_2OH group in **1** and 3'-CH_2OH and the cytosine base in **2** should theoretically drive their pseudorotational equilibria to the South type sugar conformations. Evidently, the preference of the 3'-CH_2OH group to adopt the pseudoequatorial orientation opposes the steric effect and works cooperatively with the anomeric effect in **1**, while in **2**, both the preference of the 3'-CH_2OH group to be pseudoequatorial (pseudoequatorial effect) and the steric effect work in a cooperative manner, but they oppose the anomeric effect, which results in very small $\Delta H°$ value for **2** (Table 2).

In order to determine the steric effect of 3'-CH_2OH in *erythro* and *threo* configuration in **1** and **2**, respectively, we have assumed that the pseudoequatorial preferences of 3'-CH_2OH and 4'-CH_2OH are comparable. This assumption enables the estimation of the relative strengths of the steric effects in **1** and **2** imposed by 3'-CH_2OH on the α- or on the β-face of the pentofuranose moiety, respectively. In the case of **1** the experimental $\Delta H°$ value of +5.9 kJ mol^{-1} can be dissected into the following $\Delta H°$ contributions that drive the psedorotational equilibrium: +1.5 kJ mol^{-1} for pseudoequatorial preference of 4'-CH_2OH,‡ +5.0 kJ mol^{-1} for the anomeric effect of cytosine base,‡ +1.5 kJ mol^{-1} for pseudoequatorial preference of 3'-CH_2OH and −2.1 kJ mol^{-1}

‖ In the North type pseudorotamers of **1** (−20° < *P* < 40°, ψ_m = 34°) the following distances have been found: $d_{C5'-3'-C}$ = 3.3 ± 0.1 Å, $d_{N1-3'-C}$ = 4.6 ± 0.1 Å and $d_{C5'-N1}$ = 4.3 ± 0.1 Å, while in the South conformers of **1** (140° < *P* < 220°, ψ_m = 34°) $d_{C5'-3'-C}$ = 3.8 ± 0.1 Å, $d_{N1-3'-C}$ = 4.6 ± 0.1 Å and $d_{C5'-N1}$ = 4.3 ± 0.1 Å. North type pseudorotamers of **2** (−20° < *P* < 40°, ψ_m = 34°) are characterised by the following distances: $d_{C5'-3'-C}$ = 3.0 ± 0.1 Å, $d_{N1-3'-C}$ = 3.4 ± 0.1 Å and $d_{C5'-N1}$ = 4.3 ± 0.1 Å, while in the South conformers of **2** (140° < *P* < 220°, ψ_m = 34°) $d_{C5'-3'-C}$ = 3.0 ± 0.1 Å, $d_{N1-3'-C}$ = 4.8 ± 0.1 Å and $d_{c5'-N1}$ = 4.3 ± 0.1 Å.

for the steric hindrance imposed by 3′-CH_2OH group on the α-face of pentofuranose moiety. Note, that the plus sign of the $\Delta H°$ contribution of particular steric or stereoelectronic effect denotes the tendency of that effect to drive the N ⇄ S conformational equilibrium to the North type sugar, while minus sign denotes the drive to the South type. Similarly, in **2** the experimental $\Delta H°$ value of −0.9 kJ mol^{-1} is constituted of following $\Delta H°$ contributions from various steric and stereoelectronic effects that drive pseudorotational equilibrium: +1.5 kJ mol^{-1} for pseudoequatorial preference of 4′-CH_2OH,‡ +5.0 kJ mol^{-1} for the anomeric effect of cytosine base,‡ −1.5 kJ mol^{-1} for pseudoequatorial preference of 3′-CH_2OH, and −5.9 kJ mol^{-1} due to the steric hindrance between 3′-CH_2OH on the β-face of pentofuranose moiety with other substituents, predominantly with the cytosine base. Therefore, the steric effect in the drive of pseudorotational equilibrium to the South is nearly three times stronger in **2** ($\Delta H°$ = −5.9 kJ mol^{-1}), where all substituents are on the same β-face, in comparison with the steric effect in **1** ($\Delta H°$ = −2.1 kJ mol) in which 3′-CH_2OH is away both from 4′-CH_2OH and the cytosine residue.

We thank Swedish Board for Technical Development and Swedish Natural Science Research Council and Medivir AB, Lunastigen 7, S-141 44 Huddinge, Sweden for generous financial support and Wallenbergstiftelsen, Forskningsrådsnåmnden (FRN) and University of Uppsala for funds for the purchase of a 500 MHz Bruker AMX NMR spectrometer.

Received, 18th March 1993; Com. 3/01579C

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