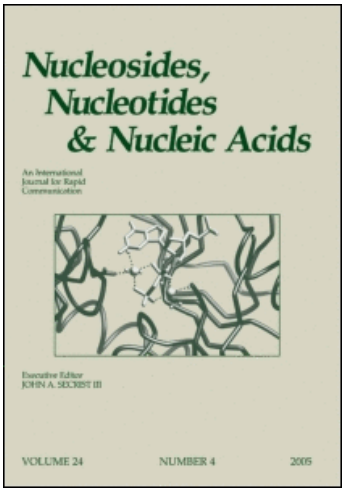

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The Discovery of Intramolecular Stereoelectronic Forces That Drive The Sugar Conformation in Nucleosides and Nucleotides

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THE DISCOVERY OF INTRAMOLECULAR STEREOELECTRONIC FORCES THAT DRIVE THE SUGAR CONFORMATION IN NUCLEOSIDES AND NUCLEOTIDES

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ABSTRACT. This report summarizes our results[8] on how the determination of the thermodynamics of the two-state North (N,*C2'-exo-C3'-endo*) ⇄ South (S,*C2'-endo-C3'-exo*) pseudorotational equilibrium in aqueous solution (pD 0.6 - 12.0) basing on vicinal $^3J_{HH}$ extracted from ^{1}H-NMR spectra measured at 500 MHz from 278K to 358K yields an experimental energy inventory of the unique stereoelectronic forces that dictate the conformation of the sugar moiety in β-D-ribonucleosides (rNs), β-D-nucleotides, in the mirror-image β-D- versus β-L-2'-deoxynucleosides (dNs) as well as in α-D- or L- versus β-D- or L-2'-dNs. Our work shows for the first time that the free-energies of the inherent internal flexibilities of β-D- versus β-L-2'-dNs and α-D- versus α-L-2'-dNs are identical, whereas the aglycone promoted tunability of the constituent sugar conformation is grossly affected in the α-nucleosides compared to the β-counterparts.

(A) The validity of the two-state N ⇄ S pseudorotational equilibrium in aqueous solution. Our conformational analyses of nucleosides are based on the pseudorotational concept[1-3]. The furanose geometry is described by the phase angle of pseudorotation (P) and the puckering amplitude (Ψ_m)[2]. The assumption of the two-state N ($0° < P < 36°$) ⇄ S ($144° < P < 190°$) equilibrium in solution[2,3] was originally based on a statistical analysis showing that both N and S forms are predominantly found in the X-ray crystal structures of nucleosides and nucleotides (Scheme 1). It has been later on further evidenced by NMR studies showing clearly the presence of two distinctly identifiable (by their different chemical shifts and $^3J_{1'2'}$) dynamically interconverting N and S conformations of some sugar moieties owing to their different stereochemical environments in B ⇄ Z DNA[4] or A ⇄ Z RNA[5] or A-form ⇄ B-form lariat RNA[6] transformations as a result of change of concentration of salt or alcohol in the buffer or as a result of change of temperature. Recent work by Raman spectroscopy has also identified a similar two-state equilibrium in A and T-containing DNAs[7].

(B) The nature of the stereoelectronic forces which drive the two-state N ⇄ S equilibrium in β-D-nucleosides. We have uniquely shown[8] that the conformation of the sugar moiety in β-D-nucleosides is energetically controlled by the following stereoelectronic effects: (i) The anomeric effect[8,9-11] of the nucleobase which drives the N ⇄ S equilibrium toward N-type sugars. (ii) The [O3'-C3'-C4'-O4'] (in 2'-dNs, rNs and nucleotides) and [O2'-C2'-C1'-N_{base}] (in rNs and nucleotides) gauche effects[8,12] which push the N ⇄ S equilibrium toward S. (iii) The [C2'-C2'-C1'-O4'] gauche effect which favours N-type sugars in rNs and nucleotides. (iv) The [O2-C2'-C3'-O3'] gauche effect which operates both in N-type and S-type sugars in rNs and nucleotides and (v) the [O5'-C5'-C4'-O4'] gauche effect, which is minimal either in N- or S-type sugars. The thermodynamics of the N ⇄ S equilibrium have been calculated from van't Hoff type analysis of temperature and pD-dependent mole fractions of the N and S pseudorotamers derived from the PSEUROT analysis of vicinal $^3J_{HH}$ extracted from 1D-^{1}H spectra[8]. From our original[8] pairwise comparisons of the thermodynamics of the N⇄ S equilibrium based on our conformational studies on β-D-nucleosides and nucleotides, the following conclusions can be drawn:

(i) The energetics of the gauche effects that drive the N ⇄ S equilibrium in the pentofuranose moiety are nucleobase-dependent.[8a,i] The counteracting [O2'-C2'-C3'-O3'] and [O4'-C4'-C3'-O3'] gauche effects cancel each other both in rNs and abasic sugars (≈ 6 and -7 kJ/mol in the former, ≈ 5 and -5 kJ/mol, in the latter, respectively). The strengths of the anomeric effect and of the[O4'-C4'-C3'-O3'] gauche effect are interrelated as suggested by the fact that in β-D-2'-dNs and -rNs, the latter is significantly stronger (≈ -7 kJ/mol) than in 1,2-dideoxy-D-ribofuranose. Similarly, we have shown that the strength of the [O2'-C2'-C1'-N] gauche effect in rNs is nucleobase-dependent [stronger in purine (≈ -8 kJ/mol) than in pyrimidine rNs (≈ -4 kJ/mol)].

(ii) The interdependence of the phosphate backbone and pentofuranose conformation in ribonucleotides[8d,j]. This has been shown by comparing the thermodynamics of the N⇄ S equilibrium in β-D-rNs[8j] and their 3'-$OPO_3H^{-1/-2}$ (rNMPs) and 3'-OPO_3Et^- (rNMPEts) as well as in β-D-dNs[8d] and their 3'-$OPO_3H^{-1/-2}$ (dNMPs), 3'-OPO_3Et^- (dNMPEts). rNMPEts and dNMPEts have been used as the simplest model for dinucleoside(3'→5')-monophosphate, where intramolecular base-base stacking is completely absent.

(a) The additional stabilization of S-type conformations in rNMPs/dNMPs compared to rNs/dNs, respectively is slightly nucleobase-dependent and results from the enhanced gauche effect of [3'-phosphate-C3'-C4'-O4'] compared to that of [3'-OH-C3'-C4'-O4'] in the former compared to the latter[8j].

(b) In the case of rNMPEts[8j], S-type conformations are more stabilized than in the corresponding rNs and rNMPs as a result of a unique cooperative two-state (N,ε^t) ⇄ (S,ε^-) conformational equilibrium which is orchestrated by the interaction of 2'-OH with the vicinal 3'-OPO_3Et^-, whereas in dNMPEts[8d] for obvious reasons these cooperative conformational transitions are absent, so that the preference of dNMPEts for S-type sugars is comparable to that in the corresponding dNMPs.

(c) However, the extent of the additional stabilization of S-type sugars in pyrimidine rNMPEts compared to rNMPs counterparts is much more reduced than in purine rNMPEts, which means that the internucleotidyl phosphates of the pyrimidine nucleotide are more energetically predisposed to take up that conformation by rotating ε^- conformer with much lesser energy penalty than that of the purine nucleotides[8j]. This is consistent with the fact that the self-cleavage site in the hammerhead ribozyme is the conserved cytidine, and it is the uridine nucleotide in UA rich RNA sequence that undergoes most frequent self-cleavage reaction.

(iii) The strength of the anomeric effect in nucleosides is specifically dictated by the unique electronic character of the constituent aglycone[8a,c]. (a) In β-D-2',3'-dideoxynucleosides (ddNs) the strength of the combined steric and stereoelectronic contributions of the anomeric effect of the nucleobases increases in the following order: adenine ≈ guanine < thymine < uracil < cytosine (from 4.4 to 7.6 kJ/mol), most likely owing to the fact that the $n(O4') \rightarrow \sigma^*C1'\text{-}N$ delocalization is more effective in the π-deficient pyrimidine moiety compared to relatively more electron-rich purine, although dipole-dipole repulsion as the origin of anomeric effect in nucleosides cannot be ruled out.

(b) The strength of the anomeric effect in β-D-2'-dNs is considerably weaker (from ≈ 0.0 kJ/mol for β-D-2'-dA to 3.5 kJ/mol for β-D-2'-dU) than in the corresponding β-D-2',3'-ddNs due to the presence of the electron-withdrawing 3'-OH group in the latter. However, the strength of the nucleobase-specific anomeric effect is comparable in β-D-2',3'-ddNs and in β-D-rNs as a result of the fact that the influences of 3'- and 2'-OH groups in the latter are cancelling each other.

(iv) The strength of the anomeric effect in β-D-nucleosides can be modulated upon protonation and/or deprotonation of the constituent nucleobase as a result of the efficient transfer of the protonation ⇄ deprotonation energy to drive the conformation of the pentofuranose moiety (energy pump).[8k] (a) This has been experimentally evidenced by the sigmoidal dependence of the thermodynamics of the N⇄ S equilibrium for all β-D-rNs and 2'-dNs on the pD of the aqueous solution. Correlation plots of the pD-dependent aromatic and anomeric ^1H chemical shift versus $\Delta G°$ of the N⇄ S equilibrium are straight lines with correlation coefficients larger than 0.97 in all cases.

(b) The validity of the two-state model in solution has been confirmed by the fact that the pD-dependent energetics of two-state N⇄ S equilibrium in β-D-nucleosides can indeed be used independently to reproduce the literature values[13] of the pK_a of nucleobases in nucleosides from Hill plots or curve fitting of the experimental $\Delta G°$ values of the equilibrium to the Henderson-Hasselbach equation.

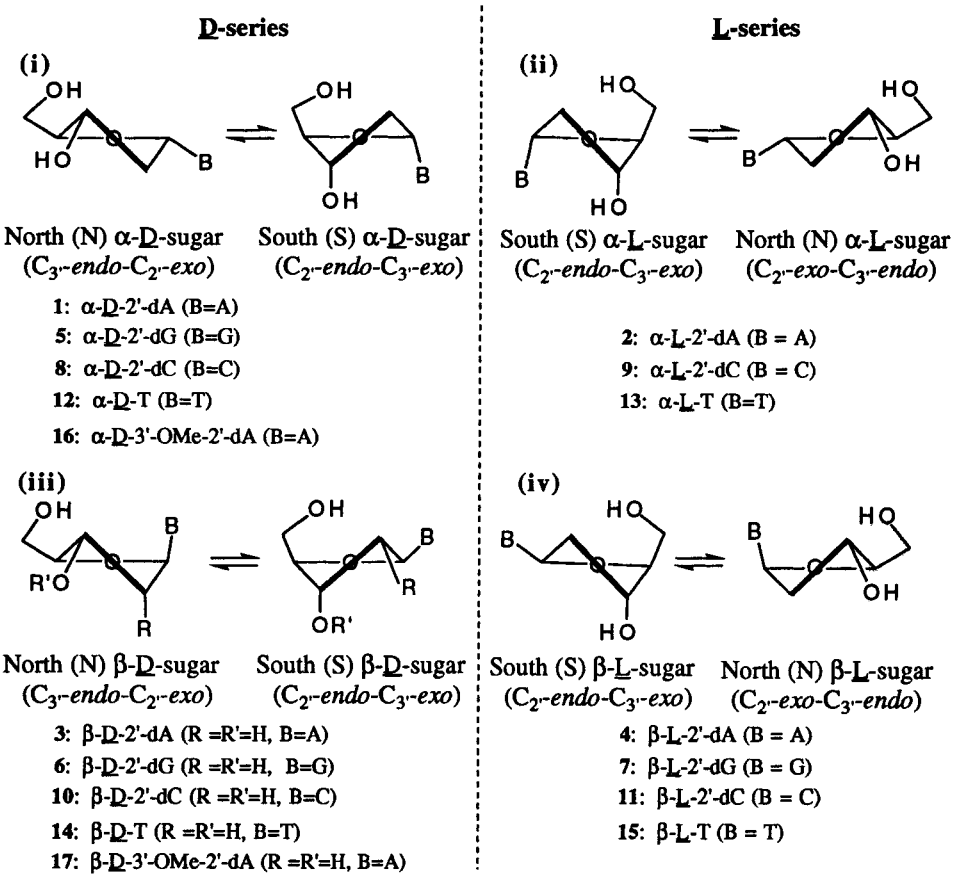
(c) This means that any change of the pK_a of a specific nucleobase due to DNA/RNA folding, or H-bonding or any site-specific metal-ion complexation would promote specific local change of DNA/RNA conformation by transmission of the energetics of the altered electronic character of the heterocyclic agycone to steer the sugar-phosphate backbone conformation through the tuning of the strength of anomeric effect.

(C) The nature of stereoelectronic forces in α-D/L- versus β-DL- 2'-dNs[8n]. The main structural difference between α-D- or L- and β-D- or L-2'-dN pair lies in the reverse configurational relationship at C1' (Scheme 1). In α-D- and α-L-2'-dNs *both* the anomeric effect and the [O3'-C3'-C4'-O4'] gauche effect drive the sugar conformation toward S-type pseudorotamers whereas, in the β counterparts, the anomeric effect drives the sugar to N-type and 3'-gauche effect to the S-type conformation. One other main structural difference between α- and β-nucleosides lies in the fact that in the former 3'-OH and the aglycone at C1' are on the same side of the constituent pentofuranose ring. As in the case of β-D-2'-dNs, the sugar conformation in α-D/L-2'-dNs and β-L-2'-dNs has been assumed to be solely controlled by: (i) the anomeric effect of the nucleobase; (ii) the [O4'-C4'-C3'-O3'] gauche effect and (iii)the [O5'-C5'-C4'-O4'] gauche effect which is negligible (see above).

(D) The strengths of stereoelectronic forces to drive the N ⇄ S pseudorotational equilibrium depends on the anomeric configuration[8n]. No experimental comparison of the energetics of β-D-2'-dNs as building blocks of Nature vis-a-vis their mirror-image β-L counterparts has been reported hithertofore, or why β-D-2'-dNs have been chosen as the molecules for the storage of genetic information over their α-D counterparts (α-D-2'-dNs). This has been investigated by us by comparison of the energy inventory of pD-dependent conformational preferences of the sugar moieties in the D versus L or α versus β in following nucleosides: α-D-2'-dNs **1, 5, 8, 12** and **16**, α-L-2'-dNs **2, 9** and **13**, β-D-2'-dNs **3, 6, 10, 14** and **17** as well as β-L-2'-dNs **4, 7, 11** and **15**.

(i) ΔH° contribution[8n] is much larger compared to $-T\Delta S^\circ$ in α- versus β-2'-dNs. In each of the protonated, neutral and deprotonated states for all α-D and α-L-2'-dNs, ΔH° contribution to the ΔG° of the N⇄ S pseudorotational equilibrium clearly prevails over the weaker $-T\Delta S^\circ$ term; it is the main factor responsible for the drive of the sugar conformation and is much more efficient than in the β counterparts[8k], as evident by the larger flexibility of the conformation of the sugar moiety in α-D and α-L-2'-dNs than in the β counterparts from 278 to 358K, with only exception being in the neutral and deprotonated α-D-2'-dG (**5**).

(ii) The thermodynamics of the N ⇄ S equilibrium in the mirror image D- and L-2'-dNs in either α- or β-forms are identical within the timeframe and accuracy of NMR spectroscopy.[8n] For each nucleobase, the pairwise comparison of the ΔH° and ΔS° values of the N ⇄ S pseudorotational equilibria in α-D and α-L-2'-dNs, on one hand, in β-D and β-L-2'-dNs, on the other, clearly shows that the D- and L-nucleosides pairs within either α- or β-forms cannot be energetically distinguished as they exhibit identical pD-dependent conformational preferences (For α-D/L-2'-dA : ΔG°_N = -2.7 ± 0.1 kJ/mol; ΔG°_P = -2.8 ± 0.1 kJ/mol; For α-D/L-2'-dC: ΔG°_N = -3.0 ± 0.1 kJ/mol; ΔG°_P = -4.5 ± 0.2 kJ/mol; For α-D/L-T: ΔG°_N = -2.0 ± 0.1 kJ/mol; ΔG°_D = -1.2 ± 0.2 kJ/mol; For β-D/L-2'-dA: ΔG°_N = -2.1 ± 0.1 kJ/mol; ΔG°_P = -1.1 ± 0.1 kJ/mol; For β-D/L-2'-dG: ΔG°_N = -1.7 ± 0.1 kJ/mol; ΔG°_P = -0.1± 0.1 kJ/mol; ΔG°_D = -2.6± 0.1 kJ/mol; For β-D/L-2'-dC: ΔG°_N = -1.3 ± 0.1 kJ/mol; ΔG°_P = -0.8 ± 0.1 kJ/mol and for β-D/L-T: ΔG°_N = -1.3 ± 0.1 kJ/mol; ΔG°_D = -1.7 ± 0.1 kJ/mol).



1: α-D-2'-dA (B=A)
5: α-D-2'-dG (B=G)
8: α-D-2'-dC (B=C)
12: α-D-T (B=T)
16: α-D-3'-OMe-2'-dA (B=A)

2: α-L-2'-dA (B = A)
9: α-L-2'-dC (B = C)
13: α-L-T (B=T)

3: β-D-2'-dA (R =R'=H, B=A)
6: β-D-2'-dG (R =R'=H, B=G)
10: β-D-2'-dC (R =R'=H, B=C)
14: β-D-T (R =R'=H, B=T)
17: β-D-3'-OMe-2'-dA (R =R'=H, B=A)
18: β-D-2'-dU (R =R'=H, B=U)
19: β-D-A (R =R'=H, B=A)
20: β-D-G (R =R'=H, B=G)
21: β-D-C (R =R'=H, B=C)
22: β-D-rT (R =R'=H, B=T)
23: β-D-U (R =R'=H, B=U)

4: β-L-2'-dA (B = A)
7: β-L-2'-dG (B = G)
11: β-L-2'-dC (B = C)
15: β-L-T (B = T)

R = H, R' = $OPO_3H^{-1/-2}$: β-D-dNMPs with B = A, G, C, T, U
R = H, R' = OPO_3Et^-: β-D-dNMPEts with B = A, G, C, T, U
R = OH, R' = $OPO_3H^{-1/-2}$: β-D-rNMPs with B = A, G, C, T, U
R = OH, R' = OPO_3Et^-: β-D-rNMPEts with B = A, G, C, T, U

A = adenine-9-yl G = guanine-9-yl C = cytosine-1-yl T = thymine-1-yl

Scheme 1 : The D- and L- mirror image relationship for the two-state dynamic N⇌S sugar equilibrium in α-D-2'-dNs **(i)** , α-L-2'-dNs **(ii)**, β-D-2'-dNs **(iii)** and β-L-2'-dNs or β-D-rNs **(iv)**. In L-nucleosides, the N sugar is redifined as being the form with maximal negative value for the endocyclic torsion [C1'-C2'-C3'-C4'][14]. *Note that in α-D-2'-dNs (i) and α-L-2'-dNs (ii), the aglycone B becomes more pseudoaxial as the anomeric effect becomes stronger in the S-type conformation, whereas in β-D-2'-dNs (iii) and β-L-2'-dNs (iv), this is achieved in the N-type conformation. Hence, the signs for the energetic drive of the anomeric effect in α-nucleosides is opposite to that of β-counterparts.*

(iii) The extent of the preference for S-type sugars in α-D-2'-dNs in each of the protonated (P), neutral (N) and deprotonated (D) states is reduced owing to their inherent weaker anomeric effect compared to β-counterparts[8k,n]. (a) We have calculated the experimental pK_as of the nucleobases in α-D-2'-dNs **1**, **5**, **8** and **12** both from the sigmoidal plots of the pD-dependent ΔG° (298K) of their N ⇄ S equilibria and from Hill plots as described by us in the β-D series[8k]. These experimental pK_as are completely consistent with those calculated from the pD-dependent anomeric and aromatic ^1H chemical shifts in α-D-2'-dNs according to the procedure described previously[8k] and are identical to the values previously obtained for the nucleobases in β-D-2'-dNs, which means that the nucleobases in α- and β-D-2'-dNs have the identical electronic character.

(b) On the assumption that the mechanism and strength of the stereoelectronic effects that control the N ⇄ S equilibria of the pentofuranose moiety are the same in α-D-2'-dNs **1**, **5**, **8**, **12** and **16** and in β-D-counterparts[8k], we could anticipate large negative values for ΔG° of the N ⇄ S equilibrium of the former in each of the P, N and D states of their nucleobases. However, at any pD, the experimental drive of the N ⇄ S equilibrium of α-D-2'-dNs **1**, **5**, **8**, **12** and **16** has been found to be less biased than expected. This means that the nucleobase-dependent anomeric effect is weakened in α-D-2'-dNs compared to the β-counterparts.

(iv) The amplitudes of the nucleobase-dependent changes of the thermodynamics of the N ⇄ S equilibrium as a function of pD are different in α-D-2'-dNs and in β-D-2'-dNs and show the lack of flexibility of the former. Protonation of adenine in α-D-2'-dNs **1** and **16** results in the *slightly smaller increase of the anomeric effect* than in β-D-2'-dNs **3** and **17**. Any H-bonding contribution between 3'-OH and the nucleobase in α-D-2'-dA **1** as origin of its lack of flexibility upon protonation has been ruled out by the fact that the sugar conformation in its 3'-OMe analog **16** is almost not affected upon protonation either. However, protonation of guanine and cytosine in α-D-2'-dNs **5** and **8** yields a *slightly larger enhancement of the anomeric effect* than in the β-counterparts **6** and **10**. Deprotonation of guanine in α-D-2'-dG **5** *does not* affect its N⇄ S equilibrium, whereas deprotonation in β-D-2'-dG 6 counterpart results in the *weakening of the anomeric effect* . On the other hand, deprotonation of thymine yields a *larger weakening of the anomeric effect* in α-D-T **12** than in the corresponding β-D-T **14** counterpart.

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