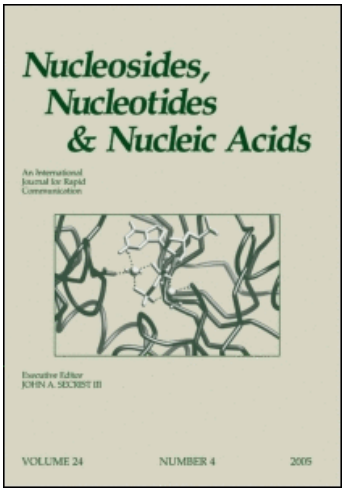

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Online publication date: 31 March 2001

To cite this Article Acharya, Parag , Thibaudeau, Christophe and Chattopadhyaya, Jyoti(2001) 'AN ENERGETIC CORRELATION OF *AB INITIO* AND NMR STUDIES OF THE 3'-*GAUCHE* EFFECT IN 3'-SUBSTITUTED THYMIDINES', Nucleosides, Nucleotides and Nucleic Acids, 20: 4, 1229 — 1233
To link to this Article: DOI: 10.1081/NCN-100002524
URL: http://dx.doi.org/10.1081/NCN-100002524

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(4–7), 1229–1233 (2001)

AN ENERGETIC CORRELATION OF *AB INITIO* AND NMR STUDIES OF THE 3′-*GAUCHE* EFFECT IN 3′-SUBSTITUTED THYMIDINES

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ABSTRACT

A straightforward correlation of our experimental NMR findings on 3′-substituted thymidine derivatives with that of the *ab initio* calculations shows that (i) the $\Delta G^{\circ 298k}_{NRM}$ of N ⇆ S equilibrium in nucleoside can be predicted from the *ab initio* calculated $\Delta E_{S\text{-}N}$ obtained from 6-311++G** level of theory; (ii) the substituent-dependent steric and stereoelectronic effects on the bias of the two-state N ⇆ S equilibrium in nucleosides can also be predicted from the *ab initio* calculations with sufficiently large basis functions, and (iii) the necessity of mimicking the solvation behaviour of the experimental NMR measurement condition in the *ab initio* calculations of biomolecules is also emphasized.

INTRODUCTION

The drive of the two-state (1,2b–e) N ⇆ S pseudorotational equilibrium of the sugar moiety of β-D-nucleos(t)ides in solution [Scheme 1A] is energetically controlled by the interplay of the steric and stereoelectronic [*gauche* (2,3) and anomeric effects (2,3a)] contributions of various sugar substituents (2a) depending upon their electronic nature and the relative configuration. In β-D-2′-deoxynucleosides, the strength of 3′-*gauche* effect [3′-GE] dominantly prevails over the counteracting anomeric effect [AE] of the aglycone in the overall drive of the sugar conformation

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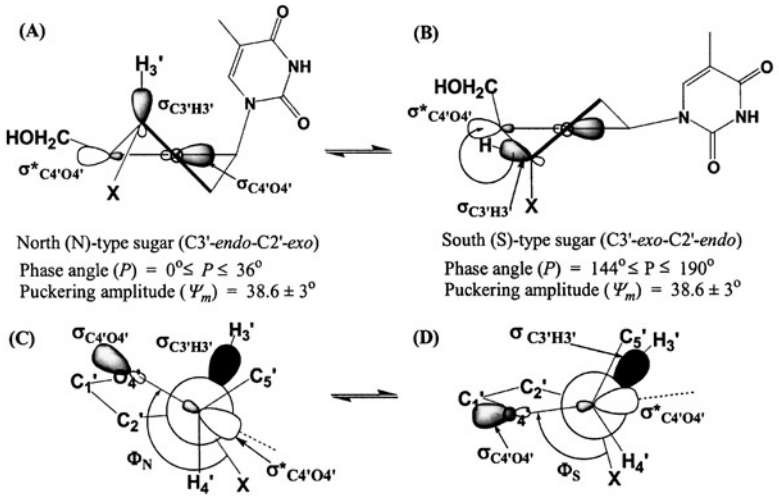

	X = H (1)	X = NH_2 (2)	X = OH (3)	X = OCH_3 (4)	X = NO_2 (5)	X = OCF_3 (6)	X = F (7)
Φ_N ‡	-158.1°	-160.1°	-154.3°	-155.0°	-156.2°	-154.6°	-152.9°
Φ_S ‡	-88.3°	-105.6°	-98.4°	-99.7°	-104.7°	-98.2°	-95.8°

‡ It is noteworthy that Φ_S is more *gauche* than Φ_N in compounds **1 – 7**.

Scheme 1. Panel (**A**) and (**B**) shows the schematic representation of the dymanic two-state (N ⇆S) pseudorotational equilibrium (1,2) of the β-D-pentofuranose moity in **1**–**7** and the 3′-*gauche* effect (X3′-C3′-C4′-O4′) owing to the $\sigma_{C3'-H3'} \rightarrow \sigma^*_{C4'-O4'}$ orbital mixing (2a,3b). The representative Newman projections in Panel (**C**) and (**D**) of the N- and S-type pseudorotamers respectively are drawn on the basis of the PDB structures obtained from the solution phase geometry optimisation at HF/6-311++G** for **1**–**7**. It shows that the preferential orbital overlap is dictated by the relative *gauche* orientation of Φ_S and Φ_N representing the torsion $\Phi_{X3'-C3'-C4'-O4'}$ in the S- and the N-type pseudorotamers respectively.

towards the S-type (2a,c). The 3′-GE stabilises (2) the S-type [Scheme 1(B) and (D)] over the N-type [Scheme 1(A) and (C)] pseudorotamers owing to the fact that X3′-C3′ and O4′-C4′ bonds are preferentially in more *gauche* orientation across the X3′-C3′-C4′-O4′ torsion in the S-type pseudorotamers (Φ_S) compared to the one in the N-type pseudorotamers (Φ_N) [Φ_N are relatively more trans compared to Φ_S in **1**–**7**, see Table in Scheme 1].

RESULTS AND DISCUSSIONS

The NMR estimation of the free-energy (2b,d) of the N ⇆ S pseudorotational equilibrium ($\Delta G^{\circ 298K}_{NMR}$) has earlier shown that this 3′-GE preferentially stabilises the S- over the N-type pseudorotamers in 3′-substituted thymidine derivatives in which the GE of 5′-CH_2OH and the AE of the nucleobase remain as the constant factor. It has also been clearly demonstrated that the conformational preference for

the S-type sugar conformation linearly increases with the increasing strength of the electronegetivity of the 3′-substitutent [H < NH_2 < OCF_3 < OH < OCH_3 < NO_2 < F] (2b,d). We argued that since we already have a dependable experimental means for the estimation of $\Delta G^{\circ 298K}_{NMR}$ (2b,d), which actually signifies (2,4) the difference in the thermodynamic stability between the S- and N-type pseudorotamer populations (1,2b–e), we could challenge the *ab initio* theory with this by calculating the total energy difference (ΔE) of N-type and S-type geometries ($\Delta E_{S\text{-}N}$) of **1–7** (Fig. 1) using high level calculations. The Gaussian calculations (5,6) of both N- and S-type pseudorotamers of potential anti-HIV (2b) 2′,3′-dideoxy 3′-substituted thymidine derivatives **1–7** have been performed using systemetic variation of different basis functions at Hatree-Fock level. With the lower basis functions such as 6-31G* or even with 6-311+G* basis sets (Table 1), we failed to observe any colinearity of the *ab initio* calculated $\Delta E_{S\text{-}N}$ in the gas phase with our $\Delta G^{\circ 298K}_{NMR}$. This pilot study showed the necessity of introducing diffuse function with higher basis set in order to reduce the basis set superposition error (6), which also illustrated the caveats of using a low-level *ab initio* method for structural calculation of flexible biomolecules.

The use of higher basis set, such as HF/6-311++G**, showed a marked improvement of correlation of $\Delta E_{S\text{-}N}$ with the experimental $\Delta G^{\circ 298K}_{NMR}$ for **1–7** (Table 1). Thus a plot of $\Delta E_{S\text{-}N}$ (gas phase HF/6-311++G**) as a function of $\Delta G^{\circ 298K}_{NMR}$ showed a Pearson's correlation coeffecient of 0.92 (Graph I in Fig. 1A). In order to mimick the solvation behaviour of the experimental NMR analyses, the solution phase ($\varepsilon = 78.3$) *ab initio* calculations (6) was performed at HF/6-311++G** level using Onsager solvation model. Remarkably, this gave even better correlation compared to the gas phase calculations as evidenced from the Graph II

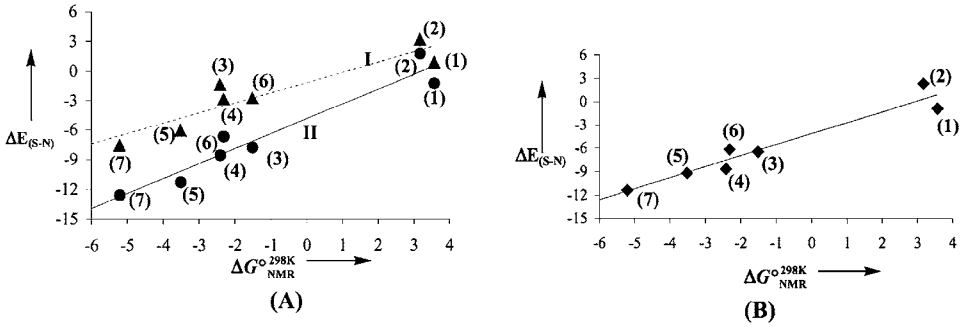

Figure 1. Panel (**A**) shows the plot of $\Delta G^{\circ 298K}_{NMR}$ (in kJ mol^{-1}) (2b,d) as a function of *ab initio* calculated $\Delta E_{S\text{-}N}$ (in kJ mol^{-1}) at HF/6-311++G** level for **1–7**, both in the gas phase [▲, dotted line, garph I] as well as in the solution [•, solid line, garph II] gives straight lines with slope = 1.03 ($\sigma = 0.11$), intercept = −1.22 ($\sigma = 0.31$) and R = 0.92 for I and slope = 1.50 ($\sigma = 0.09$), intercept = −4.92 ($\sigma = 0.30$) and R = 0.97 for II respectively. Panel (**B**) shows the plot of $\Delta G^{\circ 298K}_{NMR}$ (in kJ mol^{-1}) (2b,d) as a function $\Delta E_{S\text{-}N}$ (in kJ mol^{-1}) derived from the single point calculation at B3LYP/6-311++G**//HF/6-311++G** level in solution phase for **1–7** (indicated in parenthesis in the figure) gives the straight line with slope = 1.41 ($\sigma = 0.11$), intercept = −4.17 ($\sigma = 0.35$) and R = 0.97.

Table 1. The *ab initio* and DFT Calculated $\Delta E_{(S\text{-}N)}$[a] for **1–7** Using Gaussian 98 (5,6)

Compd.	HF/6–31G* (Gas Phase)	HF/6-311+G** (Gas Phase)	HF/6-311++G** (Gas Phase)	HF/6-311++G** (Solution Phase)	B3LYP/6-311++G** (Solution Phase)[b]	$\Delta G^{0\,298K\,c}_{NMR}$
1	−1.5	0.3	0.8	−1.3	−0.9	3.6
2	3.8	3.2	3.1	1.7	2.3	3.2
3	−2.7	−2.6	−2.8	−7.8	−6.5	−1.5
4	−1.1	−1.1	−1.4	−8.6	−8.7	−2.4
5	−4.9	−6.3	−6.1	−11.3	−9.2	−3.5
6	−2.4	−2.6	−2.9	−6.7	−6.2	−2.5
7	−7.3	−7.6	−7.6	−12.6	−11.4	−5.2

[a] The energy differences $\Delta E_{(S\text{-}N)}$ between geometry optimised S- and N-type conformers are given in kJ mol^{-1} [b] Single point calculation at B3LYP/6-311++G** using the optimised geometries at HF/6-311++G**. [c] $\Delta G^{\circ 298K}_{NMR}$ are given in kJ mol^{-1}. See Ref. 2b and 2d for the details of NMR analyses.

in Figure 1A, giving Pearson's correlation coeffecient of 0.97, as a result of improved colinearity of the energies from the solution phase *ab initio* calculations with the experimental NMR data. Moreover, the single point *ab initio* calculations at B3LYP/6-311++G** level of theory in solution phase with Onsager solvation model (6) have been performed using the optimised geometry at HF/6-311++G** level (6) for **1–7** (Table 1). The plot of $\Delta E_{S\text{-}N}$ calculated from this solution phase B3LYP/6-311++G**//HF/6-311++G** calculation as a function of experimental $\Delta G^{\circ 298K}_{NMR}$ gives the Pearson's correlation coeffecient as 0.97 (Fig. 1B). This correlation between the theory and the experiment would give much deeper insight into the molecular orbital basis of the role of the stereoelectronic forces in modulating the conformation of nucleosides and nucleotides as well as shed light in their ubiquitous self-assembly process governing the chemistry of life in general.

COMPUTATIONAL METHODS

All *ab initio* calculations were performed on Silicon Graphics Indigo R4000 work station and DEC Alpha XP1000 Professional work station with Gaussian 98 (5) programs. The initial geometry optimisation for both N- and S-type pseudorotamers of **1–7** has been done by constraining endocyclic torsion values in such a way that P and Ψ_m^4 of each conformers were in the middle of the NMR derived pseudorotational hyperspace (2b,d). All free geometry optimisations in gas phase have been performed in a stepwise manner upto the highest level at HF/6-311++G**.

ACKNOWLEDGMENTS

We thank the Swedish Board for Technical Development (TFR), the Swedish Natural Science Research Council (NFR), and the Swedish Board for Technical

Development (NUTEK) for generous financial support. Thanks are due to the Wallenbergstiftelsen, ForskningsraÊ dsnämnden and the University of Uppsala for funds to purchase of 500-MHz and 600-MHz Bruker DRX NMR spectrometers.

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