Ground-State Properties of Nucleic Acid Constituents Studied by Density Functional Calculations. 3. Role of Sugar Puckering and Base Orientation on the Energetics and Geometry of 2′-Deoxyribonucleosides and Ribonucleosides

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In the present paper, we have analyzed the conformational energy and geometrical parameters of the isolated 2′-deoxyribonucleosides and ribonucleosides. Geometry optimization of these nucleic acid constituents has been undertaken by means of density functional theory with the Becke−Lee−Yang−Parr exchange and correlation functional and split valence basis sets, 6-31G(*), including nonstandard polarization functions on carbon, nitrogen, and oxygen atoms. For each nucleoside, three major conformers, i.e., C2′-endo/anti, C3′-endo/anti, and C3′-endo/syn, have been taken into consideration, where C3′-endo and C2′-endo refer to the north (N)-type and south (S)-type sugar puckering, respectively, and anti and syn designate the orientation of the base with respect to the sugar. In both families (2′-deoxyribonucleosides and ribonucleosides) the anti orientation of the base stabilized by an intramolecular C−H···O hydrogen bond formed between the base and the O5′ atom of the sugar moiety corresponds to the lowest energy states. In the 2′-deoxyribonucleosides including uracil, guanine, and adenine bases the lowest energy conformer is C2′-endo/anti, whereas in 2′-deoxycytidine the most stable conformer is C3′-endo/anti. In ribonucleosides, the C3′-endo/anti and C2′-endo/anti conformers nearly have the same energy, except in cytidine, where the most stable conformer is C3′-endo/anti. Therefore, a general discussion has been devoted to the exceptional cases of 2′-deoxycytidine and cytidine compared to the other nucleosides. The present calculated results have also been compared with those recently reported at the MP2 level by other authors on the 2′-deoxyribonucleosides or smaller model compounds on one hand, and with the experimental results based on a statistical survey of nucleoside crystal structures on the other hand.

I. Introduction

Analysis of the structural properties of nucleic acid constituents is a fundamental task to understand their biological functions. This task can be partly achieved by studying the energetic and conformational properties of the elementary building blocks of the nucleic acids, i.e., nucleosides and nucleotides.

Recently, in the first paper of this series,[1] we analyzed the ground-state properties of ribonucleosides and ribonucleotides, such as uridine, cytidine, 5′-methyl phosphate uridine, and 3′-methyl phosphate uridine, which can be considered as RNA building blocks. The energy and geometry[1] of these moieties as well as the harmonic vibrations[2] of uridine and cytidine have been estimated at the density functional level of theory. On the basis of the above-mentioned theoretical investigations[1,2] and previous reports on the same subject,[3,4] one can conclude that the density functional theory (DFT) calculations performed by means of the hybrid exchange and correlation functional (Becke−Lee−Parr, B3LYP) and sufficiently extended basis functions, such as 6-31G*, can now be regarded as a cost-effective alternative to the sophisticated and time-consuming MP2 (second-order perturbative Moller−Plesset method), as far as the analysis of the ground-state properties of nucleic acid constituents is concerned.

To our knowledge, a complete set of theoretical calculations including electronic correlation effects concerning the energy and geometry of all the ribonucleosides and 2′-deoxyribonucleosides containing the four major nucleic acid bases are still lacking in the literature. Thus, in this paper, our aim is to report the results concerning adenosine and guanosine, completing the main results of the previous investigations on uridine and cytidine,[1] as well as those corresponding to all four major 2′-deoxyribonucleosides (building blocks of DNA) at the DFT/B3LYP/6-31G(*) level of theory. The only existing theoretical results at the MP2/6-31G* level of theory on 2′-deoxyribonucleosides with an anti orientation of the base with respect to the sugar[5] as well as those on smaller nucleoside model compounds[6,7] have been carefully overviewed in the present paper and used here for comparison. The comparison between the calculated and experimental results is based on the statistical analysis of nucleoside X-ray structures in the solid state.[8]

II. Theoretical Details

Figure 1 displays the atom numbering and chemical structure of the major 2′-deoxyribonucleosides and ribonucleosides. Each of these eight molecules has been defined by a β-junction of one of the DNA bases (T, A, C, and G) or the RNA bases (U, A, C, and G) to a sugar, i.e., 2′-deoxyribose (in 2′-deoxyribonucleosides) and ribose (in ribonucleosides), respectively. For the sake of brevity, these molecules are hereafter referred to as

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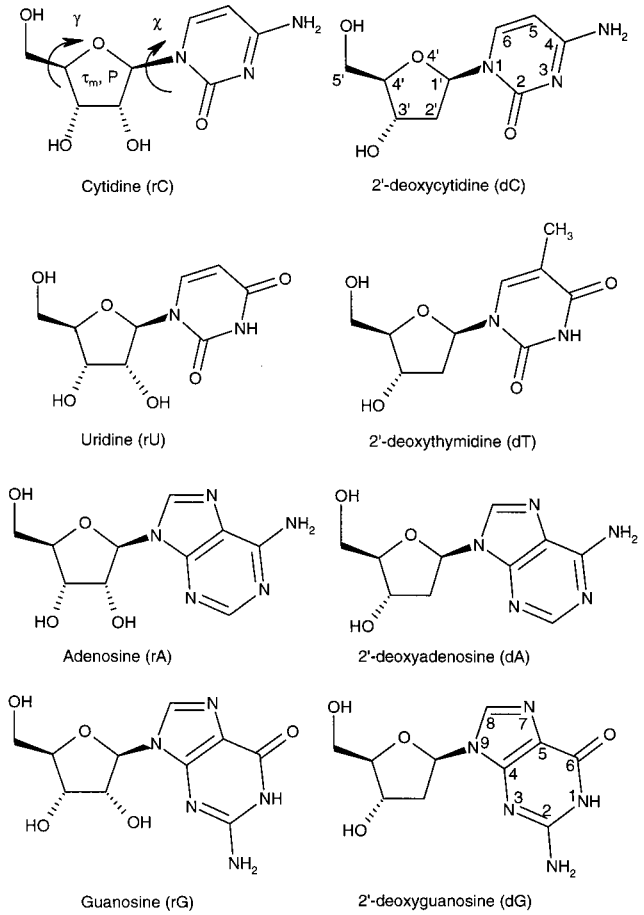

Figure 1. Chemical structure and atom numbering of the (left) four ribonucleosides (rC, rU, rA, rG) and (right) four 2′-deoxyribonucleosides (dC, dT, dA, dG). The conformational torsion angles have also been shown in rC.

dT, dC, dA, and dG (for the 2′-deoxyribonucleosides) and rC, rU, rA, and rG (for the ribonucleosides).

The main conformations of a 2′-deoxyribonucleoside or ribonucleoside can be defined by means of the following:[9] (i) The glycosyl torsion angle χ defined as $\chi = \phi$(O4′−C1′−N1−C2) in pyrimidine nucleosides and as $\chi = \phi$(O4′−C1′−N9−C4) in purine nucleosides, allowing the orientation of the base with respect to the sugar to be determined. This angle is found between 90° and 270° for the anti orientation and between −90° and +90° for the syn orientation. (ii) τ_m and P angles, named pseudorotation angles, representing, respectively, the puckering amplitude and phase angle of pseudorotation of the sugar ring. The most occurring conformations of the sugar correspond to the following P angle values: from 0° to 36° for the C3′-endo (N-type) conformation and from 144° to 180° for the C2′-endo (S-type) conformation. (iii) $\gamma = \phi$(C3′−C4′−C5′−O5′) torsion angle, which defines the orientation of the O5′ atom with respect to the ribose ring (generally gauche$^+$ or trans).

Our calculations have been performed on three major conformers of these nucleosides, i.e., C2′-endo/anti, C3′-endo/anti, and C3′-endo/syn. The first two are the most common conformers encountered in right-handed and left-handed nucleic acid helices.[9] The latter is less common but can be encountered in purine nucleosides involved in left-handed (*Z* form) helices of RNA[10] and DNA[11] or in UNCG tetraloops of 16S RNA.[12] The initial value of the τ_m angle was 35° for all nucleosides. For the P angle, we have started the calculations with $P = 18°$ and $P = 162°$ for C3′-endo and C2′-endo sugar conformations, respectively. The initial value of the γ angle was 60° (gauche$^+$ orientation of O5′), except in the purine nucleosides (dA, dG, rA, and rG) with a syn orientation of the base, where an initial value of $\gamma = 180°$ (trans orientation of O5′) was adopted to minimize the steric conflicts between the O5′−H hydroxyl group and purine bases. This latter choice is in agreement with the experimental observations on purine nucleosides involved in *Z* form helices,[10,11] where the syn orientation of the base is always accompanied by a trans orientation of the O5′ atom. Hereafter this special purine nucleoside conformation will be referred to as C3′-endo/syn/trans. It should also be mentioned that pyrimidine nucleosides with a syn base orientation constitute a low population of experimentally observed nucleoside conformations.[9]

All of our quantum mechanical calculations have been performed using the Gaussian98 code[13] at the DFT/B3LYP level of theory.[14] As in our previous investigations on the nucleic acid constituents,[1,2] double-ζ, split valence 6-31G Gaussian basis sets[15] enlarged with d-type polarization functions[16] have been used. The exponents of the polarization functions were 0.75, 0.80, and 0.85 for carbon, nitrogen, and oxygen, respectively.[17] Hereafter this special atomic basis set will be referred to as 6-31G(*). Quantum mechanical computations have been performed on Cray C90 and C98 supercomputers or on Silicon Graphics workstations.

No degrees of freedom (bond lengths, valence angles, or torsion angles) have been frozen in the course of the geometry optimization of a given nucleoside.

III. Results and Discussion

Before the analysis of the results obtained in the present calculations, we should point out that the amino group (NH_2) appearing in the chemical structure of guanine, adenine, and cytosine (Figure 1) is pyramidalized upon geometry optimization. It is now known that this effect appears at all theoretical levels when polarized basis sets, such as 6-31G*, are used.[18,19] Preliminary calculations at the HF/6-31G* level have shown that the amino group is nonplanar in cytosine, guanine, and adenine.[18] This fact has also been proved at the MP2/6-31G* [19] and DFT/6-31G* [20] levels of theory. Upon harmonic vibrational calculations on nucleic acid bases, it has been shown that the planar geometry of the amino group corresponds to a transition state.[18]

Another point which should be emphasized here is the privileged orientation of the methyl group hydrogens in the thymine residue involved in dT. We have selected this particular orientation on the basis of our previous ab initio calculations at the MP2/6-31G* level on thymine that have shown that the energy minimum corresponds to a conformation where one of the hydrogens of the CH_3 group is located in the plane of the base and oriented toward the C5═C6 bond and the other two hydrogens lie symmetrically with respect to the ring plane.[21]

To give typical examples of the analyzed nucleosides, Figure 2 shows the graphical representation of the three optimized conformers of dC and rG. In Figure 2, the intermolecular O2′−H···O3′ (C3′-endo conformation) and O3′−H···O2′ (C2′-endo conformation) hydrogen bonds in ribose, are drawn in broken lines. Their features will be commented on in paragraph III.3 of this paper.

III.1. Conformational Energies. Values of the electronic energies (hartrees) obtained at the DFT level for the four major 2′-deoxyribonucleosides (dT, dC, dG, and dA) are displayed in Table 1 and compared with those of the four major ribonucleosides (rU, rC, rG, and rA). To facilitate the lecture of these results, the relative energies of different conformers of a given

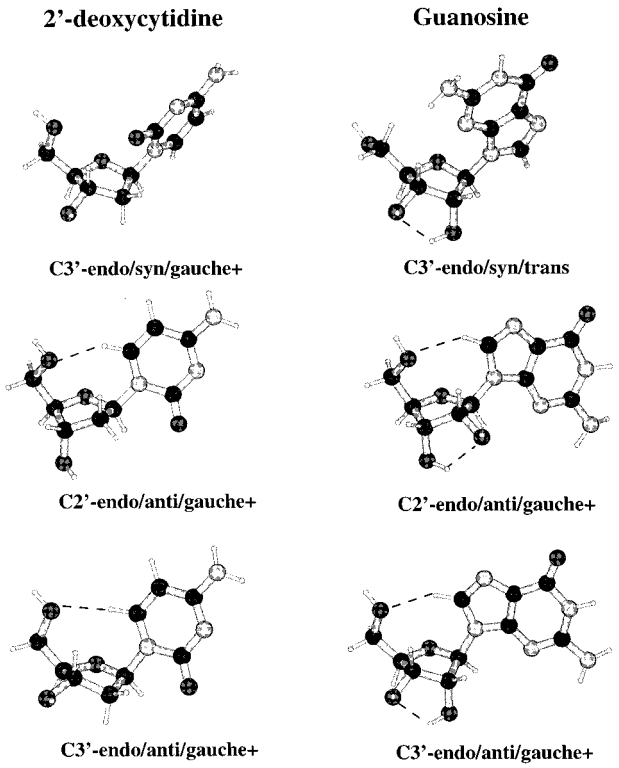

Figure 2. Geometry optimized structures of 2′-deoxycytidine (dC) and guanosine (rG) at the DFT/B3LYP/6-31G(*) level in three different conformations, i.e., C3′-endo/anti, C2′-endo/anti, and C3′-endo/syn. The values of the electronic energies and of the conformational angles are indicated in Table 1. The main conformational angles of these optimized conformers are reported in Table 2. Intermolecular hydrogen bonds are represented with dashed lines. Note that the γ torsion angle is trans in the C3′-endo/syn conformation of guanosine. This is also the case in the same conformation of other purine nucleosides (dA, rA, dG; see the text and Table 2).

2′-deoxyribonucleoside or ribonucleoside, called ΔE_e (in kcal/mol), have been calculated with respect to the energy of the C3′-endo/anti conformer. To confirm the reliability of our theoretical results at the DFT level, available ΔE_e values obtained for the 2′-deoxyribonucleosides with anti bases at the MP2 level[5] have also been indicated in Table 1. It is worth mentioning that both DFT- and MP2-calculated results have been obtained by similar basis sets, i.e., 6-31G* and 6-31G(*). To our knowledge, no attempt has been devoted up to now to estimate at the MP2 level the electronic energy of 2′-deoxyribonucleosides with a base in the syn conformation. MP2 calculations on ribonucleosides are also lacking in the literature. The only available MP2 calculations are based on ribonucleoside model compounds formed by a sugar connected to a structurally simple molecule, such as pyrrole[6] and imidazole,[7] which mimic the chemical structure of nucleic acid bases.

III.1.1. 2′-Deoxyribonucleosides and Ribonucleosides with a Base in an Anti Orientation. In 2′-deoxyribonucleosides, the signs of ΔE_e values have been reproduced similarly by both theoretical calculations (DFT or MP2), and their absolute values differ from one another by less than 0.4 kcal/mol (Table 1). The most important difference (ΔE_e) between the two theoretical methods is encountered in dT and dC, where the DFT calculations tend to favor the C3′-endo/anti conformers. In dT, dG, and dA, the lowest energy conformer is C2′-endo/anti, whereas in dC, C3′-endo/anti is the most stable one. On the basis of the DFT calculations, in 2′-deoxyribonucleosides the energy difference between the C2′-endo/anti and C3′-endo/anti conformers is generally greater than that found in ribonucleosides. The exceptional case of rC should be emphasized here, where the ΔE_e value reaches its maximum value (+1.25 kcal/mol), showing that the C3′-endo/anti conformer corresponds to the deepest energy minima, whereas, in other ribonucleosides (rU, rA, and rG), the C3′-endo/anti and C2′-endo/anti conformers are energetically identical ($\Delta E_e < 0.15$ kcal/mol). Note that this difference is well below the thermal energy at room temperature ($kT \approx 0.6$ kcal/mol).

Thus, one can mention that dC and rC behave differently from the other nucleosides, favoring the C3′-endo/anti conformation (Figure 3). This fact has been evidenced previously[5] in the case of dC through the theoretical calculations performed at the MP2 level (Table 1).

III.1.2. 2′-Deoxyribonucleosides and Ribonucleosides with a Base in a Syn Orientation. All ribonucleosides and 2′-deoxyribonucleosides in the C3′-endo/syn conformation have a higher energy than those of the above-mentioned C2′-endo/anti and C3′-endo/anti conformers. The rotation of the base to a syn orientation in a nucleoside costs between 1 and 6 kcal/mol as compared to the energy of the C3′-endo/anti conformer. The lowest ΔE_e value is obtained for rA and the highest one for dC. Moreover, the energy difference between the C3′-endo/syn and C3′-endo/anti conformers is higher in dG and rG than that found in dA and rA. This result contradicts somehow the previous reports indicating the higher tendency of guanine to adopt a syn orientation compared to adenine.[5,22]

III.2. Analysis of the Sugar Conformations through the Pseudorotation Angles. τ_m and P values obtained from the geometry-optimized nucleosides at the DFT level are reported in Table 2. Those values issued from recent MP2 calculations on the C2′-endo/anti and C3′-endo/anti conformers of 2′-deoxyribonucleosides[5] are also reported in Table 2 for comparison. The main difference between the DFT- and MP2-calculated results can be summarized as follows:

(i) Both MP2 and DFT calculations give rise to τ_m values which are compatible with the variation range estimated experimentally for C3′-endo (36.2 ± 3.3°) and C2′-endo (37.3 ± 2.4°) conformations.[8] However, τ_m values obtained at the MP2 level are slightly higher by 4−7°, than those calculated at the DFT level.

(ii) P angles calculated at the MP2 level are systematically lower than those estimated by DFT calculations. But in both levels of theory, the P values for pyrimidine C2′-endo/anti conformers are slightly higher than those for purine C2′-endo/anti conformers. No such trend has been found for the nucleosides with C3′-endo sugars. Moreover, P values are rather small for C3′-endo/anti conformations (<18°), whereas for C3′-endo/syn conformations, these values are found distributed around 30°. We can conclude that anti (respectively syn) bases favor C3′-endo sugars, tending toward C2′-exo (respectively C4′-exo). Previous calculations[7] on nucleoside model compounds reported higher P values for C3′-endo sugars in ribonucleosides than in 2′-deoxyribonucleosides. The present calculations based on the real nucleosides do not reflect this kind of separation.

III.3. Intramolecular C−H···O and O−H···O Hydrogen Bonds. Our aim in this section is to mention and discuss the existence of particular intramolecular hydrogen bonds found in 2′-deoxyribonucleosides and ribonucleosides at the theoretical levels which consider explicitly the electronic correlation effects. However, we are conscious that further improvement of the calculated results concerning H-bonding effects needs the use of more extended basis sets, such as those containing diffuse orbitals.[23,24]

TABLE 1: Energy Values Obtained by Geometry Optimization at the DFT Level for the Eight Nucleosides in the Three Different Conformations[a]

pyrimidine nucleosides			purine nucleosides[b]		
conformation	E_e/hartrees	ΔE/(kcal/mol)	conformation	E_e/hartrees	ΔE/(kcal/mol)
2′-Deoxythymidine (dT)			2′-Deoxyguanosine (dG)		
C3′-endo/anti/gauche$^+$	−875.108 75	0 (0)	C3′-endo/anti/gauche$^+$	−963.520 40	0 (0)
C2′-endo/anti/gauche$^+$	−875.109 64	−0.56 (−0.9)	C2′-endo/anti/gauche$^+$	−963.521 59	−0.75 (−0.7)
C3′-endo/syn/gauche$^+$	−875.101 23	+4.72	C3′-endo/syn/trans	−963.514 55	+3.67
Uridine (rU)[b]			Guanosine (rG)		
C3′-endo/anti/gauche$^+$	−910.998 59	0	C3′-endo/anti/gauche$^+$	−1038.730 77	0
C2′-endo/anti/gauche$^+$	−910.998 59	+0.00	C2′-endo/anti/gauche$^+$	−1038.730 64	+0.08
C3′-endo/syn/gauche$^+$	−910.994 69	+2.45	C3′-endo/syn/trans	−1038.725 15	+3.53
2′-Deoxycytidine (dC)			2′-Deoxyadenosine (dA)		
C3′-endo/anti/gauche$^+$	−815.903 17	0 (0)	C3′-endo/anti/gauche$^+$	−888.290 26	0 (0)
C2′-endo/anti/gauche$^+$	−815.902 32	+0.53 (+0.3)	C2′-endo/anti/gauche$^+$	−888.290 992	−0.46 (−0.4)
C3′-endo/syn/gauche$^+$	−815.893 31	+5.65	C3′-endo/syn/trans	−888.286 410	+2.42
Cytidine (rC)[b]			Adenosine (rA)		
C3′-endo/anti/gauche$^+$	−891.111 439	0	C3′-endo/anti/gauche$^+$	−963.499 70	0
C2′-endo/anti/gauche$^+$	−891.109 443	+1.25	C2′-endo/anti/gauche$^+$	−963.499 48	+0.14
C3′-endo/syn/gauche$^+$	−891.107 050	+2.75	C3′-endo/syn/trans	−963.497 75	+1.23

[a] E_e represents the electronic energy of a given conformer. ΔE_e represents the difference between the electronic energies as calculated with respect to the electronic energy of the C3′-endo/anti conformer of a given nucleoside ($\Delta E_e = 0$). In parentheses, the ΔE_e values obtained at the MP2 level for the 2′-deoxynucleosides with an anti orientation of the base, are reported.[5] Gauche$^+$ and trans refer to the orientation of the O5′ atom with respect to the sugar orientation as defined by means of the γ torsion angle (see the text and Figure 2). [b] Extracted from ref 1.

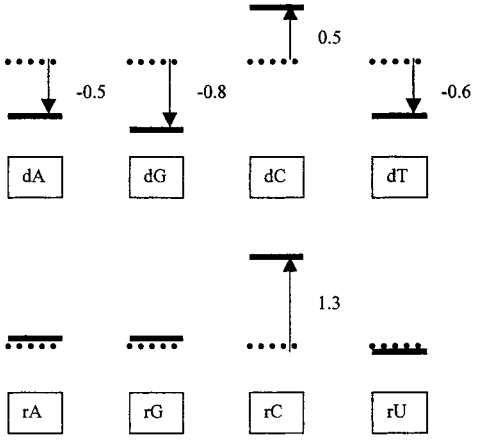

Figure 3. Comparative energy scheme for 2′-deoxyribonucleosides (top) and ribonucleosides (bottom). The difference in electronic energy (ΔE_e, kcal/mol) between the C2′-endo/anti (thick line) conformation and the C3′-endo/anti (dashed line) one has also been reported (see the text). Note the different behavior of dC and rC compared to the other 2′-deoxyribonucleosides and ribonucleosides, respectively: In both cases, cytosine favors the C3′-endo/anti (N-type) conformer by grossly 1 kcal/mol.

It should be mentioned that two types of particular intermolecular H-bonds, i.e., C6−H6···O5′ and C8−H8···O5′ in pyrimidine and purine nucleosides, respectively, have been experimentally confirmed in nucleosides[25] and nucleic acid chains.[26,27] The pivotal role of these intramolecular H-bonds is now well elucidated.[28] In our previous report on the geometry optimization of pyrimidine ribonucleosides and ribonucleotides,[1] the existence of intramolecular C−H···O hydrogen bonds between the O5′ atom of sugar and the H6 atom of the anti-oriented pyrimidine bases (uracil or cytosine) has been reported. Here, on the basis of the geometrical criteria derived from the whole set of the DFT calculations (Table 2), i.e., hydrogen−acceptor and donor−acceptor distances as well as donor−hydrogen−acceptor angles, we can also confirm the presence of the C6−H6···O5′ hydrogen bond in dT and dC (Figure 2, Table 2). We should also emphasize the presence of a C8−H8···O5′ hydrogen bond in rG, rA, dG, and dA (Figure 2, Table 2) when the purine base has an anti orientation. Obviously, in the nucleosides with a syn base these particular C−H···O hydrogen bonds cannot occur because of the inaccessibility of the H6/H8 (pyrimine/purine) donors from the O5′ acceptor site of sugar (Figure 2). This effect contributes to the fact already mentioned in this paper (see paragraph III.1) that the energy of the syn base nucleosides is systematically higher than that of the anti base nucleosides (Table 1). Similar C−H···O hydrogen bonds have also been predicted by MP2 calculations[29] (Table 2), but with shorter H6/8···O5′ distances as compared with those predicted by DFT calculations for all 2′-deoxyribonucleosides. The only exception is dC (Table 2). Moreover, in DFT-calculated results (Table 2), no significant difference has been found between the H-bond geometrical data in ribonucleosides and 2′-deoxyribonucleosides. But for all compounds, the C···O distances are shorter for the conformers containing C3′-endo sugars than those involving C2′-endo sugars. The difference in hydrogen bond length between N-type and S-type conformers appears to be more dramatic for purines than for pyrimidines, with again a notable exception in the case of dC (Table 2).

Recently, a systematic theoretical study of the C−H···O hydrogen bonds has been reported on methane and fluoromethanes at the MP2, MP4, CCSD, QCISD, and DFT/B3LYP levels of theory.[24] The main conclusion of this study is that the C−H···O interaction can be undoubtedly considered as a true hydrogen bond. Of course, the C−H···O interaction is weaker than the other H-bonds arising for instance from the O−H··· O-type interactions. It has also been shown[24] that the C−H··· O hydrogen bond features strongly depend on the existence of an electronegative atom covalently bonded to carbon. In nucleic acid bases, the atom next to C6 (in pyrimidine ring) or to C8 (in purine ring) is a nitrogen (respectively N1 and N7), and this fact may reinforce the C−H···O intermolecular H-bonding mentioned above. Moreover, theoretical analysis[24] has shown that the C···O distance in the C−H···O hydrogen bonding is located in a range between 3.3 and 3.6 Å, depending on the strength of this particular interaction. A scan of Table 2 shows that the C···O distance is well located between 3.3 and 3.5 Å

TABLE 2: Conformational Angles and Intramolecular Hydrogen Bond Parameters[a]

	conformational angles/deg				C−H···O hydrogen bond parameters		
	τ_m	P	γ	χ	d(H···O5′)	d(C···O5′)	θ(C−H···O5′)
				dT			
C3′-endo/anti	34 (39)	13 (12)	53	201 (198)	2.291 (2.223)	3.323 (3.242)	158 (156)
C2′-endo/anti	34 (38)	165 (163)	52	230 (231)	2.416 (2.379)	3.455 (3.419)	160 (160)
C3′-endo/syn	32	30	53	80			
				rU			
C3′-endo/anti	36	13	51	202	2.283	3.314	158
C2′-endo/anti	34	167	51	235	2.376	3.418	160
C3′-endo/syn	35	37	49	76			
				dC			
C3′-endo/anti	34 (39)	11 (9)	55	196 (195)	2.313 (2.257)	3.307 (3.250)	152 (151)
C2′-endo/anti	34 (37)	164 (162)	54	211 (207)	2.542 (2.565)	3.506 (3.476)	148 (141)
C3′-endo/syn	33	34	52	80			
				rC			
C3′-endo/anti	37	12	52	197	2.330	3.329	151
C2′-endo/anti	35	165	51	233	2.425	3.458	158
C3′-endo/syn	36	38	47	78			
				dA			
C3′-endo/anti	33 (40)	9 (7)	51	209 (193)	2.305 (2.309)	3.319 (3.219)	155 (141)
C2′-endo/anti	33 (37)	172 (168)	51	234 (230)	2.533 (2.518)	3.468 (3.441)	144 (143)
C3′-endo/syn/t	31	24	190	71			
				rA			
C3′-endo/anti	35	11	49	208	2.338	3.347	155
C2′-endo/anti	33	173	50	237	2.513	3.447	144
C3′-endo/syn/t	32	26	190	68			
				dG			
C3′-endo/anti	33 (39)	12 (10)	50	211 (198)	2.313 (2.284)	3.337 (3.255)	156 (149)
C2′-endo/anti	33 (37)	173 (169)	50	236 (232)	2.542 (2.521)	3.476 (3.447)	144 (143)
C3′-endo/syn/t	32	34	191	68			
				rG			
C3′-endo/anti	34	13	48	212	2.356	3.375	156
C2′-endo/anti	33	174	49	238	2.542	3.470	143
C3′-endo/syn/t	34	33	190	67			

[a] τ_m and P are the pseudorotation angles of the sugar pucker involved in a given nucleoside. $\gamma = \phi$(O5′−C5′−C4′−C3′) torsion angle. χ is the glycosyl torsion angle: $\chi = \Phi$(O4′−C1′−N1−C2) in pyrimidine nucleosides and $\chi = \Phi$(O4′−C1′−N9−C4) in purine nucleosides. d(H···O5′) (Å), d(C···O5′) (Å), and θ(C−H···O5′) (deg) represent the hydrogen−acceptor distance, donor−acceptor distance, and donor−hydrogen−acceptor angle, respectively. H and C refer to H6/H8 and C6/C8 (pyrimidine/purine), respectively. In parentheses, the values obtained at the MP2 level for the 2′-deoxynucleosides with an anti orientation of the base are reported.[5] t = trans orientation of the O5′ atom with respect to the sugar (see the text and Table 1).

in all cases, confirming the existence of the intermolecular C−H···O hydrogen bonds in 2′-deoxyribonucleosides and ribonucleosides.

Correspondingly, beyond the above-mentioned C−H···O hydrogen bonds occurring in the anti base conformers, we should point out the existence of O−H···O hydrogen bonds between the two adjacent hydroxyl groups attached to the C2′ and C3′ atoms of the sugar moiety included in ribonucleosides.[1] These O−H···O hydrogen bonds show a symmetrical character in terms of hydrogen bond lengths and donor−hydrogen−acceptor angle: C3′-endo sugars are stabilized by a O2′−H···O3′ hydrogen bond, whereas C2′-endo sugars are accompanied by a O3′−H···O2′ hydrogen bond (Figure 2). This result has also been confirmed elegantly by Brameld and Goddard[6] in their recent work based on the ribonucleoside model compounds where they did a systematic investigation as a function of the P angle and the relative orientation of the 2′- and 3′-hydroxyls. It should be pointed out that the other alternative for forming an intramolecular O−H···O hydrogen bond, especially in the C2′-endo/anti conformation, is to direct the O2′−H toward the O2 atom (pyrimidine base) or the N3 atom (purine base). Although these latter particular situations seem to be energetically favorable (data not shown), they have however been discarded on the basis of the vibrational mode calculations and their disagreement with experimental results.[2] Of course in RNA chains, the above-mentioned O3′−H···O2′ hydrogen bonds cannot exist because of the replacement of the 3′-hydroxyl group by a phosphate moiety. Nevertheless, the remaining O2′−H in a RNA chain can participate in the formation of intramolecular hydrogen bonds or intermolecular hydrogen bonds with the surrounding water molecules.[27]

III.4. Torsion Angle around the Glycosyl Bond. In a recent publication the energy variation of the nucleosides has been analyzed as a function of the χ angle.[30] The sugar was modeled just by a tetrahydrofuran, and the plot of energy versus χ angle has shown two wells corresponding to syn and anti rotamers. The results of this study have shown that the anti energy well is shallower for purines than for pyrimidines with an exceptional behavior for cytidine which presents the sharpest slope in the anti well region ($150° < \chi < 240°$). Thus, high values of the χ angle would be more disfavored for cytidine. It has to be noted though that this study[30] does not take into account the interactions between the bases and the O5′H hydroxyl group (leading to an intermolecular C−H···O hydrogen bond, see paragraph III.3, or to a steric clash between the base and the terminal CH_2-OH group of the sugar), nor does it take into account the difference between a ribose and a deoxyribose. It thus serves to show that, beyond the intramolecular C−H···O hydrogen bond, cytidine behaves differently as far as its intrinsic rotation about the glysosyl linkage is concerned.

TABLE 3: Comparison between the Observed and Calculated Values of Some Sugar Bond Lengths (Å) in Ribonucleosides and 2′-Deoxyribonucleosides

	observed[a]		calculated (DFT)[b]							
bonds/angles	ribonucleosides	2′-deoxyribonucleosides	rC	rU	rG	rA	dC	dT	dG	dA
			C3′-endo							
C1′−C2′	1.529	1.519	1.539	1.540	1.542	1.541	1.537	1.539	1.539	1.539
C3′−O3′	1.417	1.419	1.426	1.425	1.426	1.426	1.420	1.419	1.419	1.419
O4′−C1′−C2′	107.6	106.8	106.7	106.9	106.8	106.8	106.6	106.7	106.5	106.5
C1′−C2′−C3′	101.3	102.4	101.8	102.1	102.3	102.1	102.9	103.1	103.2	103.1
			C2′-endo							
C1′−C2′	1.526	1.518	1.540	1.540	1.541	1.542	1.535	1.536	1.538	1.538
C2′−C3′	1.525	1.516	1.541	1.541	1.540	1.541	1.530	1.531	1.531	1.531
C3′−O3′	1.427	1.435	1.414	1.414	1.415	1.414	1.426	1.425	1.427	1.426
C4′−O4′	1.454	1.446	1.439	1.442	1.441	1.440	1.435	1.435	1.434	1.434
C1′−C2′−C3′	101.5	102.5	102.2	101.9	102.2	102.3	102.4	102.3	102.6	102.6
C2′−C3′−C4′	102.6	103.1	102.5	102.5	102.4	102.4	102.6	102.5	102.4	102.4
C5′−C4′−C3′	115.2	114.1	114.8	114.9	114.8	114.8	115.2	114.9	114.8	114.9

[a] Observed data are those corresponding to the mean values of the sugar puckers involved in ribonucleosides and 2′-deoxyribonucleosides as analyzed by a statistical survey of the crystal structures.[8] Parameters in italics are supposed to be dependent on sugar dehydroxylation, according to ref 8. [b] Calculated values are those obtained at the DFT/B3LYP/6-31G(*) level (this work) for the ribonucleosides and 2′-deoxyribonucleosides containing a base with an anti orientation.

In the present paper, although the variation of the energy versus χ angle has not been studied, the calculations are based on real nucleosides. Thus, the chemical groups allowing to distinguish ribose from 2′-deoxyribose are explicitly present in the theoretical calculations. As Table 2 shows, χ angle values estimated by DFT calculations correlate very well with those observed in the crystal phase[8] for the conformers containing N-type (C3′-endo) and S-type (C2′-endo) sugars. However, the χ angle values obtained from DFT calculations are generally slightly higher than those from MP2 calculations.[5]

Furthermore, on the basis of the DFT calculations, in all nucleosides the anti χ angles associated with a sugar in the C3′-endo conformation are located in the $204 \pm 8°$ range, whereas with a C2′-endo sugar conformation the glycosyl torsion angle varies in the $234 \pm 4°$ domain, except for dC, which adopts a χ angle value of 211° in the C2′-endo/anti conformation. The sharpest slope of the potential well energy versus χ angle found in the above-mentioned calculations,[30] may explain this exceptional behavior of dC in comparison with other nucleosides. The above-mentioned substantial difference in χ angle value in going from C3′-endo/anti to C2′-endo/anti conformations (~30°) in all nucleosides (except in dC, where a lower difference between the two χ angle values is found) may also be interpreted in terms of the C−H···O hydrogen bond emphasized in paragraph III.3. In fact, to favor this particular hydrogen bond in C2′-endo/anti conformers, the base should turn around the glycosyl linkage to make possible the formation of the intramolecular C−H···O hydrogen bond.[1] This intramolecular hydrogen bond can then be considered as a driving force tending to shift the χ angle toward higher values in C2′-endo/anti conformers.

III.5. Sugar Bond Lengths and Valence Angles. As indicated in the previous investigations based on the statistical survey of the crystal structures of ribonucleosides and 2′-deoxyribonucleosides,[31] the important geometrical parameter changes occurring upon the nucleoside conformational transitions are those related to the sugar moiety, the bases being relatively rigid structurally.[8] For this reason, we will compare and discuss in this section the changes in geometrical parameters (bond lengths and valence angles) of N-type and S-type sugar puckering in 2′-deoxynucleosides and ribonucleosides.

III.5.1. Comparison between the Observed Values and Those Calculated at the DFT and MP2 Levels of Theory for 2′-Deoxyribonucleosides. A systematic comparison between the calculated (at both MP2 and DFT levels) bond lengths and valence angles for 2′-deoxyribose with those estimated experimentally[8] has been performed in Table 4. In DFT calculations, CC and CN bond lengths appear to be systematically longer (~0.01 Å) compared with those obtained at the MP2 level.[5] As mentioned previously in the case of a set of biomolecules,[4] DFT calculations tend to overestimate CC and CN bond lengths in the same order of magnitude. The calculated values of these bond lengths obtained at the MP2 level are longer (~0.01 Å) than those observed in the crystal phase. However, this kind of difference has been found in all molecules between the in vacuo calculated parameters ($T = 0$ K) and those obtained from the solid-state X-ray diffraction analysis performed at room temperature.[32] As far as the glycosyl bond length is concerned, although no distinct differentiation on C1′−N9 (purine) and C1′−N1 (pyrimidine) distances has been mentioned in the statistical survey of Gelbin et al.,[8] both methods of calculation (DFT and MP2) show a neat difference of ~0.02 Å between pyrimidine and purine bases. This fact is in agreement with detailed experimental structural analysis of pyrimidine and purine nucleosides.[9]

In contrast, the valence angles calculated by both DFT and MP2 calculations give comparable deviations with respect to the observed values in the solid state. The difference between the calculated and experimental values for valence angles seems to be less systematic and more scattered than that mentioned above for bond lengths. Whatever the level of theory is, the calculated results meet difficulties in reproducing the bond lengths and angles in the ether C1′−O4′−C4′ linkage (Table 4).

III.5.2. Influence of Sugar Type and Conformation on Geometrical Parameters. According to the above-mentioned statistical survey of nucleoside crystal structures,[8] some bond lengths or valence angles are dependent on the N-type (C3′-endo) and S-type (C2′-endo) conformations, and the nature (ribose or 2′-deoxyribose) of the sugar. We thus checked (Tables 3 and 4) whether these features can be reproduced by the calculated results.

Differences between 2′-Deoxyribonucleosides and Ribonucleosides. In Table 3, sugar pucker bond lengths and valence angles sensitive to sugar hydroxylation on the C2′ site are reported. As has been mentioned in the above paragraph and also shown in Table 3, the dispersion of the calculated valence angle values does not allow us to perform such detailed analysis. Thus, we limit our comparison to the key bond lengths because

TABLE 4: Comparison between the Bond Lengths and Valence Angles of the Sugar Pucker Included in 2′-Deoxuribonucleosides Calculated at the DFT (Present Work) and MP2[5] Levels[a]

	C3′-endo/anti									C2′-endo/anti								
	dC		dT		dG		dA			dC		dT		dG		dA		
	MP2	DFT	MP2	DFT	MP2	DFT	MP2	DFT	observed	MP2	DFT	MP2	DFT	MP2	DFT	MP2	DFT	observed
									Bonds									
C1′−C2′	1.527	1.537	1.527	1.539	1.526	1.539	1.524	1.539	1.519 (0.010)	1.524	1.535	1.525	1.536	1.527	1.538	1.527	1.538	1.518 (0.010)
C2′−C3′	1.525	1.535	1.526	1.536	1.527	1.536	1.526	1.536	1.518 (0.012)	1.519	1.530	1.521	1.531	1.521	1.531	1.520	1.531	1.516 (0.008)
C3′−C4′	1.521	1.534	1.521	1.534	1.522	1.535	1.523	1.535	1.521 (0.010)	1.532	1.543	1.532	1.543	1.530	1.541	1.530	1.541	1.529 (0.010)
C4′−O4′	1.440	1.436	1.441	1.437	1.441	1.435	1.443	1.435	1.449 (0.009)	1.441	1.435	1.439	1.435	1.439	1.434	1.439	1.434	1.446 (0.010)
O4′−C1′	1.423	1.418	1.420	1.413	1.421	1.418	1.420	1.417	1.418 (0.012)	1.426	1.423	1.429	1.423	1.426	1.423	1.426	1.423	1.420 (0.011)
C3′−O3′	1.424	1.420	1.423	1.419	1.423	1.419	1.423	1.419	1.419 (0.006)	1.431	1.426	1.430	1.425	1.431	1.427	1.430	1.426	1.435 (0.013)
C4′−C5′	1.508	1.518	1.508	1.518	1.509	1.519	1.508	1.519	1.509 (0.011)	1.512	1.522	1.512	1.522	1.513	1.524	1.513	1.523	1.512 (0.007)
C1′−N1/N9	1.478	1.485	1.480	1.488	1.463	1.466	1.465	1.467	1.488 (0.013)	1.461	1.466	1.455	1.465	1.446	1.451	1.446	1.452	1.468 (0.014)
C5′−O5′	1.429	1.425	1.429	1.424	1.427	1.423	1.427	1.424	1.423 (0.011)	1.429	1.426	1.431	1.427	1.430	1.426	1.430	1.426	1.418 (0.025)
									Valence Angles									
C1′−C2′−C3′	102.1	102.9	102.2	103.1	101.9	103.2	101.6	103.1	102.4 (0.8)	101.6	102.4	101.6	102.3	101.8	102.6	101.8	102.6	102.5 (1.2)
C2′−C3′−C4′	100.9	101.4	100.9	101.4	100.9	101.6	100.9	101.5	102.2 (0.7)	102.8	102.6	102.7	102.5	102.7	102.4	102.7	102.4	103.1 (0.9)
C3′−C4′−O4′	105.2	105.7	105.2	105.7	105.3	106.0	105.4	106.0	104.5 (0.4)	106.5	106.8	106.5	106.7	106.3	106.5	106.3	106.6	106.0 (0.6)
C4′−O4′−C1′	109.7	111.0	109.8	111.0	109.7	111.2	109.6	111.1	110.3 (0.7)	109.7	110.7	109.8	110.8	110.1	111.1	110.1	111.1	110.1 (1.0)
O4′−C1′−C2′	106.6	106.6	106.6	106.7	106.6	106.5	106.7	106.5	106.8 (0.5)	105.7	105.6	105.3	105.6	105.8	105.8	105.8	105.8	105.9 (0.8)
C2′−C3′−O3′	115.5	115.4	115.4	115.3	115.2	115.0	115.3	115.1	112.6 (3.3)	111.8	112.7	111.6	112.6	111.6	112.5	111.6	112.6	109.4 (2.5)
C4′−C3′−O3′	107.7	108.2	107.7	108.2	107.8	108.4	107.7	108.3	112.3 (2.0)	105.4	106.2	105.4	106.3	105.6	106.5	105.5	106.4	109.7 (2.5)
C5′−C4′−C3′	116.2	116.1	116.2	116.0	115.9	115.5	115.9	115.7	115.7 (1.2)	114.8	115.2	114.5	114.9	114.6	114.8	114.7	114.9	114.1 (1.8)
C5′−C4′−O4′	109.9	110.1	109.9	110.0	109.8	110.0	109.9	110.0	109.8 (1.1)	109.0	109.5	109.1	109.7	109.2	110.0	109.2	109.9	109.3 (1.9)
O4′−C1′−N1/N9	109.1	109.6	108.8	109.3	108.3	109.0	108.4	108.9	108.3 (0.3)	108.2	108.9	107.6	108.6	107.8	108.9	107.7	108.8	108.0 (0.7)
C2′−C1′−N1/N9	111.7	113.0	112.1	113.4	111.9	113.8	111.4	113.7	112.6 (1.9)	113.5	114.2	114.3	114.6	113.7	114.2	113.7	114.2	114.3 (1.4)
O5′−C5′−C4′	108.8	109.4	108.8	109.4	108.7	109.4	108.6	109.5	11.0 (2.5)	108.2	109.2	108.4	109.2	108.4	109.4	108.4	109.4	110.9 (1.7)
C1′−N9−C4					124.5	125.4	124.4	125.1	123.9 (1.0)					126.7	126.7	126.7	126.6	126.3 (1.2)
C1′−N1−C2	114.9	115.5	115.0	115.4					117.5 (1.4)	116.5	117.4	118.5	118.1					117.8 (1.1)

[a] Bond lengths and valence angles are in angstroms and degrees, respectively. Observed data are those corresponding to the mean values of the N-type (C3′-endo) and S-type (C2′-endo) sugar pucker geometrical parameters of the 2′-deoxyribonucleosides (for all bases) as analyzed by a statistical survey of the crystal structures.[8] In front of each mean value the standard deviation is reported in parentheses. Parameters in italics are those which are supposed to be dependent on the sugar conformation, according to ref 8.

according to the X-ray structures,[8] one bond length (C1′−C2′) in the N-type (C3′-endo) conformations and four bond lengths (C1′−C2′, C2′−C3′, C4′−O4′, and C3′−O3′) in the S-type (C2′-endo) conformations, are characteristic of the sugar hydroxylation on the C2′ site of nucleosides (Table 3). Note that this comparison is impossible at the MP2 level, due to the lack of results concerning ribonucleosides. It turns out that, for the C2′-endo conformation, the trends unveiled by the statistical survey[8] are confirmed by DFT calculations. Quantitatively, the calculated differences in bond lengths are however lower than those estimated experimentally. For the C3′-endo conformation the calculated difference between the C1′−C2′ bond length (∼0.002 Å) obtained for the two types of sugar pucker is well below that found in experimental observations.

Differences between N-Type and S-Type Conformations. Also reported by Gelbin et al.[8] for ribonucleosides and 2′-deoxyribonucleosides and further explored by calculations on nucleoside model compounds,[6] some of the bond lengths and valence angles depend on the sugar conformation. As far as the 2′-deoxyribonucleosides are concerned, six valence angles are thought to behave differently in S-type and N-type conformations. Both MP2 or DFT calculations show differences of about 1° in these angles (in italics in Table 4). But, the same kind of differences can also be found for other valence angle values (not mentioned by the experimental observations as characteristic angles). Thus, the use of these calculated differences to probe sugar pucker conformation remains questionable. However, more dramatic changes are found on the C3′−C4′, C1′−N1/N9, and C3′−O3′ bond lengths (∼0.01−0.02 Å) between C2′-endo and C3′-endo conformers (in italics in Table 4), regardless of the nature of the base connected to the sugar. The C3′−O3′ bond length is particularly important to explain the stability of a C2′-endo conformation: the O3′ atom being in a pseudoequatorial position, a gauche effect has been suggested previously[6] to reinforce an intrinsic preference for this conformation over C3′-endo. The fact that the calculated C3′−O3′ bond length at both levels of theory is actually greater for the C2′-endo conformation confirms this explanation since it corresponds to an interaction involving the σ^* C3′−O3′ orbital:[6] the partial occupancy of this orbital, owed to this gauche effect interaction, implies the lengthening of the C3′−O3′ bond.[33]

On the contrary, in the case of ribonucleosides, it has to be noted that the calculated C3′−O3′ bond length is greater in the C3′-endo conformation (Table 3). This is in contradiction with a structural characterization of the above-mentioned suspected gauche effect, and also with the statistical results of X-ray structures.[8] This discrepancy should imply extreme prudence in invoking electronic effects explaining the relative stability of N-type and S-type conformations, especially in the case of ribonucleosides where an intramolecular hydrogen bond strongly affects the concerned bond lengths.[34] One can also note that the C2′-endo conformer (the one characterized by a gauche effect) is actually energetically favored for 2′-deoxyribonucleosides (with the notable exception of dC) and not for ribonucleosides.

Whatever the nature of the nucleoside, the glycosyl C1′−N1/N9 bond shows a variation between N-type and S-type conformers. In C3′-endo conformations, this bond length is ∼0.02 Å shorter than in the C2′-endo ones. An anomeric effect involving the O4′−C1′−N1/N9 string of atoms has been invoked previously to explain this result.[6,35] This anomeric effect might also be responsible for the low P values in the C3′-endo conformation.[36] As a matter of fact, this effect would be fully expressed theoretically in an O4′-exo conformation ($P = 270°$). But in this case, it would be strongly counterbalanced by an important steric strain between the base and the O5′ hydroxyl. The low value of P (<13°) involved in all C3′-endo conforma-

tions (Table 2) thus appears to be the best compromise among intramolecular hydrogen bonding, steric strain, and anomeric effect.[34]

IV. Concluding Remarks

In this paper, we have discussed our main results concerning the analysis of the geometrical parameters of the major ribonucleosides and 2′-deoxyribonucleosides at the DFT/B3LYP/6-31G(*) level of theory. This survey led us to confirm the following:

(i) DFT calculations on the 2′-deoxyribonucleosides provide results which are quantitatively in good agreement with those obtained at the MP2 level for the same compounds.[5] The energy order of the C2′-endo/anti and C3′-endo/anti conformers as well as the important geometrical features related to them, such as pseudorotation angle *P*, glycosyl torsion angle χ, intramolecular C−H···O hydrogen bonds, and the sugar bond lengths and valence angles, are reproduced similarly by both theoretical approaches. On the other hand, the calculated results are in very good agreement with those observed experimentally on the nucleosides in the solid phase.[8]

(ii) Generally speaking, in ribonucleosides we can assume that both C2′-endo/anti and C3′-endo/anti constitute a couple of conformers with the same energy. In contrast, in 2′-deoxyribonucleosides, the C2′-endo/anti conformer is slightly more stable than the C3′-endo/anti one (Figure 3). However, among the nucleosides rC and dC are the striking exceptions which do not follow the same rules as the others. In fact in both of these nucleosides the cytosine residue favors energetically the C3′-endo/anti conformer. Thus, on the basis of the present results, a substantial difference exists between cytosine and other bases as first suggested by other authors,[5,35] and not between purine and pyrimidine bases as emphasized in previous publications.[6,37] This result is not at all in contradiction with NMR results which have shown that the population of the S-type sugar conformation in the nucleosides containing cytosine is well below that observed in nucleosides with U and T bases.[38] Of course, as usual upon the comparison between quantum mechanical calculations and NMR results, one must be aware of the difference in essence between the electronic energy given by theoretical methods and the Gibbs free energy estimated from NMR experiments.

The reason behind this exceptional fact cannot be found in the difference between N-type and S-type sugar puckering. As far as the 2′-deoxyribonucleosides are concerned, we have presented above the gauche effect as a possible reason for a C2′-endo conformer stabilization compared to a C3′-endo conformer stabilization. This reason cannot be retained for the exceptional behavior of dC and rC in which the C3′-endo sugar is considerably favored. As a matter of fact, rC and dC behave likewise to the other nucleosides as far as their sugar geometrical parameters (especially bond lengths) are concerned.

On the contrary, the glycosyl linkage of dC does not subscribe to the same behavior as the other 2′-deoxyribonucleosides. The difference between the χ angle values calculated in the C3′-endo/anti and C2′-endo/anti conformers is lower than those relative to the other 2′-deoxyribonucleosides. Correlatively, dC shows the weakest O5′−H···C6 intramolecular hydrogen bond (along with the longest O5′−H bond length) in the C2′-endo/anti conformer. We can thus speculate that in general the nucleosides present a relatively strong intramolecular hydrogen bond in the C3′endo/anti conformation and a weaker one in the C2′-endo/anti one. As stated above, the rotation of the base around the glycosyl bond toward higher χ angles leads to the strengthening of this hydrogen bond in the nucleosides. This general tendency has not been found in the case of dC in which the χ angle variation is lower than the one calculated for other nucleosides, and this fact is also certainly linked with the sharpest energy torsional profile evidenced for cytidine.[30] Thus, the C−H···O hydrogen bond is even weaker in the dC C2′-endo/anti conformer compared to the same conformation in other nucleosides. This effect might be considered as one of the reasons for which the C2′-endo/anti conformer is not favored in dC. Another surprising effect is that although the C2′-endo/anti conformer is also disfavored in rC, the χ angle in this conformer behaves like that in other nucleosides, and not like that in its parent molecule, dC. Therefore, additional calculations are necessary to bring some more clarification to the above-mentioned exceptional behaviors of dC and rC.[34]

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