Ab Initio Calculations of ^{1}H and ^{13}C Chemical Shifts in Anhydrodeoxythymidines

Jiří Czernek and Vladimír Sklenář*

*Laboratory of Biomolecular Structure and Dynamics, Masaryk University, Kotlářská 2,
CZ-611 37 Brno, Czech Republic*

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For relatively large (containing 16 non-hydrogen atoms each) organic molecules, anhydrodeoxythymidines, ^{1}H and ^{13}C NMR chemical shifts were predicted using CPHF-GIAO, DFT-GIAO, and SOS-DFPT-IGLO methods. Both ab initio optimized and experimentally derived geometries of studied compounds were investigated. In the majority of cases, good agreement of theoretical and experimental chemical shifts was obtained with an average rmsd for SOS-DFPT-IGLO, DFT-GIAO, and CPHF-GIAO calculations of 5.5, 5.2, and 6.6 ppm for ^{13}C and 0.233, 0.269, and 0.297 ppm for ^{1}H, respectively. The best overall performance was found with the SOS-DFPT-IGLO technique.

Introduction

Numerous studies (recently reviewed by A. C. de Dios[1]) have shown that ^{1}H and ^{13}C NMR chemical shifts can be successfully predicted for many organic systems with HF-GIAO,[2−4] DFT-GIAO,[4] HF-IGLO,[5,6] HF-LORG,[7,8] and SOS-DFPT-IGLO[9,10] methods. However, ab initio calculations of chemical shielding in molecules containing about 15 non-hydrogen atoms are still rare. To the best of our knowledge, results of such calculations on nucleosides are presented here for the first time; the data on their constituent parts (purine and pyrimidine bases[11,12] and ribose and deoxyribose[13]) has only recently been published. In this study, we report the proton and carbon chemical shifts for three anhydrodeoxythymidine derivatives: 2,3′-anhydrodeoxythymidine **1** (2,3′-anhydro-1-(2′-deoxy-*β*-D-xylofuranosyl)thymine, Figure 1), 2,5′-anhydrodeoxythymidine **2** (2,5′-anhydro-1-(2′-deoxy-*β*-D-ribofuranosyl)thymine, Figure 2), and 3′,5′-anhydrodeoxythymidine **3** (3′,5′-anhydro-1-(2′-deoxy-*β*-D-xylofuranosyl)thymine, Figure 3). Three different protocols, based on GIAO and DFPT-IGLO methods, and both experimentally derived and ab initio optimized geometries were used to evaluate the predictive power of ab initio calculations and to study the influence of geometrical parameters on computed chemical shifts. Parameters for the linear correlation of theoretically calculated and experimentally derived ^{1}H and ^{13}C chemical shifts were determined. Based on the obtained results, the following topics will be addressed: (1) overall agreement of experimental and computed shifts; (2) reliability of computational methods; (3) specific problems of proton and carbon chemical shift predictions; (4) influence of geometry on theoretical shielding, and (5) CPU time requirements of various computational protocols.

Since calculations were performed using relatively large basis sets (see following section for details), not only the relative performance of various methods but aspects other than wave function quality could also be assessed. One of the most important factors strongly affecting the values of calculated chemical shifts is the population averaging over the shielding values of various conformers, as recently studied in detail by Stahl et al.[14] To eliminate, at least partially, this influence, anhydrodeoxythymidines were chosen as molecules for investigation. Oxygen bridges restrict the conformational freedom, and the structures of studied compounds can be reliably predicted by a combination of molecular mechanics, ab initio calculations, and NMR measurements.[15] As a result, limits of present ab initio NMR shielding calculations when applied to

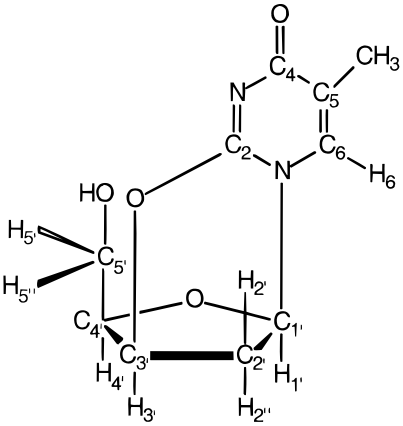

Figure 1. 2,3′-Anhydro-1-(2′-deoxy-*β*-D-xylofuranosyl)thymine. Only the numbering of atoms for which the chemical shifts were calculated is shown.

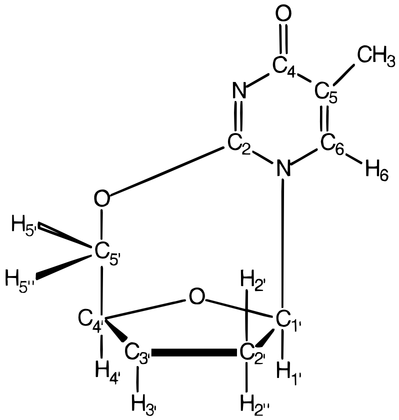

Figure 2. 2,5′-Anhydro-1-(2′-deoxy-*β*-D-ribofuranosyl)thymine. Only the numbering of atoms for which the chemical shifts were calculated is shown.

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* Corresponding author. E-mail: sklenar@chemi.muni.cz. Fax: +420-5-4112 9506.

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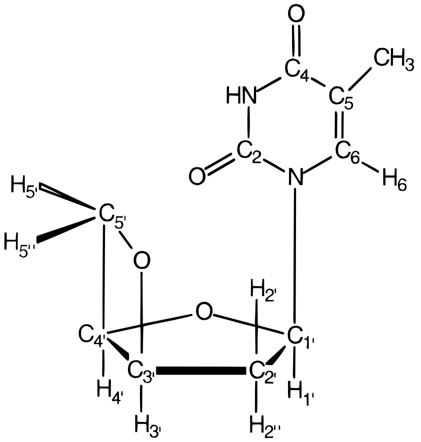

Figure 3. 3′,5′-Anhydro-1-(2′-deoxy-*β*-D-xylofuranosyl)thymine. Only the numbering of atoms for which the chemical shifts were calculated is shown.

relatively large molecular systems could be evaluated. These limits, together with answers to the topics specified above, are of interest not only to theoretical chemists but to NMR spectroscopists as well.

Theory and Computations

Two computer programs were used to obtain the values of the respective components of a nuclear magnetic shielding tensor.

(1) Values abbreviated as SOS-DFPT-IGLO were obtained with deMon-MASTER-CS code,[16] which implements sum-over-states density functional (Rayleigh−Schrodinger) perturbation theory with the IGLO[17] gauge choice. The Perdew−Wang-91 exchange-correlation potential,[18,19] the approximation Loc.1 SOS-DFPT,[9,10] and the basis set IGLO-III of Kutzelnigg et al.[17] were used for all computations. (IGLO-III is roughly of "quadruple-ζ" quality, the contraction pattern (6)/[3,3*1] with two sets of p polarization functions for hydrogen and (11;7)/[5,6*1;2,5*1] with two d sets for first-row atoms. Its use resulted in application of 712 basis functions for each structure.) To obtain more precise molecular orbital coefficients and one-electron energies after reaching convergence during SCF iterations, one extra iteration was performed without fitting the exchange-correlation potential and using an enlarged grid.[9]

(2) Values marked in the tables as DFT-GIAO and CPHF-GIAO were obtained with the GAUSSIAN94[20] suite of programs. Both CPHF (coupled-perturbed Hartree−Fock) and DFT (density functional theory) methods of shielding tensor calculations solve coupled-perturbed equations by using a magnetic field as a perturbation and apply the GIAO (gauge including atomic orbitals) method[21] to overcome the gauge problem. This implementation has been recently described by Cheeseman et al.[4]

Since experimental values are referenced to tetramethylsilane (TMS), the chemical shifts δ were calculated as a difference between the absolute isotropic shielding of TMS σ^i(TMS) and of a given nucleus σ^i: $\delta = \sigma^i(\text{TMS}) - \sigma^i$, where $\sigma^i = 1/3(\sigma_{xx} + \sigma_{yy} + \sigma_{zz})$ is calculated from the chemical shielding tensor of individual ^{1}H and ^{13}C atoms, respectively.

In Table 1, the absolute isotropic shieldings of ^{1}H and ^{13}C nuclei in TMS computed by three different approaches in two investigated geometries are summarized (vide infra). The convergence of the computed shifts in anhydrodeoxythymidines with respect to the quality of basis set was examined on the Hartree−Fock level. For the optimized structure of **1**, the calculations were performed with standard D95, D95*, and D95** basis sets,[22] with a TZ2P basis set (see below), and quadruple-ζ (QZ) basis set of Thakkar[23] with two polarization functions of Dunning.[20] Results obtained with D95 basis sets were less reliable for ^{1}H shielding (for two pairs of protons, the chemical shifts were interchanged in comparison with the experimental spectrum), whereas the large QZ2P basis set (584 basis functions for the studied molecule) gave practically the same results as the TZ2P. Therefore, a triple-ζ basis set with two polarization functions[24] (the contraction pattern (5)/[3] for hydrogen and (10;6)/[6;3] for the rest of the atoms in studied molecules; 508 basis functions for each structure) was employed in all remaining GIAO calculations.

TABLE 1: Absolute Isotropic Shielding of Tetramethylsilane in Molecular Mechanics (MM) and RHF/6-31G (HF) Geometry [ppm]**

		SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO
^{13}C	MM	184.6	182.6	192.0
	HF	185.5	184.0	193.7
^{1}H	MM	31.19	31.62	31.88
	HF	31.53	31.96	32.26

The DFT calculations applied a coupled perturbative scheme without including the magnetic field effects in the exchange correlation functional. Hybrid method B3LYP[25] in the framework of a DFT approach[4] successfully predicted ^{13}C shifts of paclitaxel ($C_{47}H_{51}NO_{14}$)[4] and also was used in this work.

Ab initio geometry optimizations were carried out on the RHF/6-31G** level with GAUSSIAN94. The experimentally derived geometries[15] (MM/NMR) for compounds **1** and **2** were obtained by combining simulations based on measured spin−spin coupling constants and molecular mechanics minimizations using Discover.[26] Since no useful geometrical constrains can be extracted from the NMR data of TMS, the "experimental" TMS geometry was generated by minimization using Discover with default settings. A similar approach was adopted in calculations of "experimental" geometry for molecule **3** because insufficient NMR data was available for structure refinement at the time of computations.

Calculations were carried out on the SGI Power Challenge computer with 1GB RAM and R8000 processors with a theoretical speed of 6 × 0.3 GFlops. Typical CPU times are discussed in Conclusions.

Results and Discussion

Generally, with the theoretical approach, one isolated molecule in vaccuo in its equilibrium geometry is studied. Consequently, the experimental counterparts to the calculated absolute shieldings should be those measured in the gas phase extrapolated to zero density and temperature. Because the NMR experiments for studied nucleosides had to be carried out on samples in aqueous solutions, the following issues complicated comparison of the theoretical and experimental data.

(1) Gas-to-liquid transition generates a large shift in shielding (e.g., 4.26 ppm[27] for protons in water).

(2) Solvation effects influence the shielding patterns considerably. This is especially true for protons with an extended intermolecular hydrogen bond network in nucleosides.

(3) With the theoretical approach, the conformational changes are normally not considered. For example, there is a substantial conformational freedom for the glycosidic ($C_{1'}$−N_1) bond and sugar conformations in 3′,5′-anhydrodeoxythymidine **3**.[15]

The computed and measured data is summarized in four tables for each compound (Tables 2−13). In each table, theoretical (SOS-DFPT-IGLO, DFT-GIAO, CPHF-GIAO) and experimentally measured ^{13}C or ^{1}H chemical shifts[15] are listed for ab initio

TABLE 2: ^{13}C NMR Chemical Shifts of 2,3′-Anhydrothymidine 1 [ppm] Obtained by IGLO and GIAO Calculations Using MM/NMR Geometry[a,b]

	SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO	δ(exp)
CH_3	19.8 (+3.6)	17.5 (+1.3)	14.7 (−1.5)	16.2
$C_{2'}$	45.0 (+7.9)	43.4 (+6.3)	38.7 (+1.6)	37.1
$C_{5'}$	74.0 (+10.0)	71.2 (+7.2)	62.3 (−1.7)	64.0
$C_{3'}$	93.6 (+9.9)	90.8 (+7.1)	79.4 (−4.3)	83.7
$C_{4'}$	101.6 (+12.5)	98.4 (+9.3)	84.8 (−4.3)	89.1
$C_{1'}$	104.3 (+12.7)	100.8 (+9.2)	87.5 (−4.1)	91.6
C_5	138.9 (+17.0)	139.5 (+17.6)	134.3 (+12.4)	121.9
C_6	146.1 (+1.9)	147.8 (+3.6)	151.3 (+7.1)	144.2
C_2	166.7 (+7.1)	170.8 (+11.2)	176.3 (+16.7)	159.6
C_4	174.8 (−4.5)	178.2 (−1.1)	184.0 (+4.7)	179.3

[a] The differences from experimental data (exp) are given in parentheses. [b] Linear relationships between experimentally obtained vs calculated chemical shifts: $\delta(\text{IGLO}) = 0.9625\delta(\text{exp}) + 11.5$ ($r^2 = 0.993$), rmsd = 6.22; $\delta(\text{DFT}) = 1.006\delta(\text{exp}) + 6.53$ ($r^2 = 0.995$), rmsd = 5.58; $\delta(\text{CPHF}) = 1.089\delta(\text{exp}) - 6.13$ ($r^2 = 0.995$), rmsd = 6.10.

TABLE 3: ^{1}H NMR Chemical Shifts of 2,3′-Anhydrothymidine 1 [ppm] Obtained by IGLO and GIAO Calculations Using MM/NMR Geometry[a,b]

	SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO	δ(exp)
H_6	7.47 (−0.11)	7.34 (−0.24)	7.47 (−0.11)	7.58
$H_{1'}$	5.80 (−0.14)	5.52 (−0.42)	5.17 (−0.77)	5.94
$H_{3'}$	5.31 (−0.15)	5.09 (−0.37)	4.85 (−0.61)	5.46
$H_{4'}$	4.41 (−0.06)	4.32 (−0.15)	3.87 (−0.60)	4.47
$H_{5'}$	4.31 (+0.44)	4.34 (+0.47)	3.87 (0.00)	3.87
$H_{5''}$	4.02 (+0.24)	3.99 (+0.21)	3.71 (−0.07)	3.78
$H_{2''}$	2.80 (+0.11)	2.61 (−0.08)	2.38 (−0.31)	2.69
$H_{2'}$	2.70 (+0.05)	2.69 (+0.04)	2.47 (−0.18)	2.65
CH_3	2.10 (+0.28)	2.16 (+0.34)	2.19 (+0.37)	1.82

[a] The differences from experimental data (exp) are given in parentheses. [b] Linear relationships between experimentally obtained vs calculated chemical shifts: $\delta(\text{IGLO}) = 0.9248\delta(\text{exp}) + 0.393$ ($r^2 = 0.996$), rmsd = 0.170; $\delta(\text{DFT}) = 0.8865\delta(\text{exp}) - 0.460$ ($r^2 = 0.990$), rmsd = 0.249; $\delta(\text{CPHF}) = 0.9016\delta(\text{exp}) + 0.165$ ($r^2 = 0.983$), rmsd = 0.332.

TABLE 4: ^{13}C NMR Chemical Shifts of 2,3′-Anhydrothymidine 1 [ppm] Obtained by IGLO and GIAO Calculations Using RHF/6-31G Geometry[a,b]**

	SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO	δ(exp)
CH_3	17.6 (+1.4)	16.2 (0.0)	14.1 (−2.1)	16.2
$C_{2'}$	37.4 (+0.3)	32.1 (−5.0)	32.7 (−4.4)	37.1
$C_{5'}$	69.3 (+5.3)	63.3 (−0.7)	59.1 (−4.9)	64.0
$C_{3'}$	80.3 (−3.9)	70.1 (−13.6)	68.8 (−14.9)	83.7
$C_{4'}$	94.7 (+5.6)	87.5 (−1.6)	80.3 (−8.8)	89.1
$C_{1'}$	93.1 (+1.5)	82.4 (−9.2)	79.4 (−12.2)	91.6
C_5	128.8 (+6.9)	122.8 (+0.9)	124.3 (+2.4)	121.9
C_6	134.3 (−9.9)	134.5 (−9.7)	139.3 (−4.9)	144.2
C_2	151.4 (−8.2)	149.7 (−9.9)	160.4 (+0.8)	159.6
C_4	167.0 (−12.3)	166.8 (−12.5)	173.5 (−5.8)	179.3

[a] The differences from experimental data (exp) are given in parentheses. [b] Linear relationships between experimentally obtained vs calculated chemical shifts: $\delta(\text{IGLO}) = 0.9154\delta(\text{exp}) + 7.06$ ($r^2 = 0.995$), rmsd = 5.53; $\delta(\text{DFT}) = 0.9433\delta(\text{exp}) - 0.539$ ($r^2 = 0.996$), rmsd = 4.88; $\delta(\text{CPHF}) = 1.017\delta(\text{exp}) - 7.14$ ($r^2 = 0.995$), rmsd = 5.62.

TABLE 5: ^{1}H NMR Chemical Shifts of 2,3′-Anhydrothymidine 1 [ppm] Obtained by IGLO and GIAO Calculations Using RHF/6-31G Geometry[a,b]**

	SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO	δ(exp)
H_6	6.74 (−0.84)	7.18 (−0.40)	6.66 (−0.92)	7.58
$H_{1'}$	5.24 (−0.70)	5.09 (−0.85)	4.63 (−1.31)	5.94
$H_{3'}$	4.94 (−0.52)	4.43 (−1.03)	4.38 (−1.08)	5.46
$H_{4'}$	4.18 (−0.29)	3.74 (−0.73)	3.70 (−0.77)	4.47
$H_{5'}$	3.75 (−0.12)	3.53 (−0.34)	3.37 (−0.50)	3.87
$H_{5''}$	3.78 (0.00)	3.78 (0.00)	3.44 (−0.34)	3.78
$H_{2''}$	2.27 (−0.42)	2.20 (−0.49)	1.97 (−0.72)	2.69
$H_{2'}$	2.19 (−0.46)	2.00 (−0.65)	1.88 (−0.77)	2.65
CH_3	1.75 (−0.07)	1.93 (+0.11)	1.82 (0.00)	1.82

[a] The differences from experimental data (exp) are given in parentheses. [b] Linear relationships between experimentally obtained vs calculated chemical shifts: $\delta(\text{IGLO}) = 0.8854\delta(\text{exp}) + 0.107$ ($r^2 = 0.993$), rmsd = 0.209; $\delta(\text{DFT}) = 0.9063\delta(\text{exp}) - 0.088$ ($r^2 = 0.980$), rmsd = 0.359; $\delta(\text{CPHF}) = 0.8488\delta(\text{exp}) - 0.0692$ ($r^2 = 0.984$), rmsd = 0.298.

TABLE 6: ^{13}C NMR Chemical Shifts of 2,5′-Anhydrothymidine 2 [ppm] Obtained by IGLO and GIAO Calculations Using MM/NMR Geometry[a,b]

	SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO	δ(exp)
CH_3	19.6 (+4.3)	17.3 (+2.0)	14.6 (−0.7)	15.3
$C_{2'}$	53.5 (+8.6)	52.0 (+7.1)	45.4 (+0.5)	44.9
$C_{3'}$	85.7 (+10.9)	82.7 (+7.9)	71.0 (−3.8)	74.8
$C_{5'}$	83.7 (+5.4)	81.3 (+3.0)	72.8 (−5.5)	78.3
$C_{4'}$	102.2 (+13.0)	99.3 (+10.1)	85.6 (−3.6)	89.2
$C_{1'}$	107.8 (+10.3)	104.6 (+7.1)	90.1 (−7.4)	97.5
C_5	139.1 (+17.5)	139.7 (+18.1)	134.2 (+12.6)	121.6
C_6	148.3 (+4.0)	150.2 (+5.9)	153.6 (+9.3)	144.3
C_2	168.6 (+7.6)	172.7 (+11.7)	178.0 (+17.0)	161.0
C_4	175.9 (−1.8)	179.3 (+1.6)	184.7 (+7.0)	177.7

[a] The differences from experimental data (exp) are given in parentheses. [b] Linear relationships between experimentally obtained vs calculated chemical shifts: $\delta(\text{IGLO}) = 0.9766\delta(\text{exp}) + 10.3$ ($r^2 = 0.995$), rmsd = 5.58; $\delta(\text{DFT}) = 1.021\delta(\text{exp}) + 5.31$ ($r^2 = 0.996$), rmsd = 5.18; $\delta(\text{CPHF}) = 1.108\delta(\text{exp}) - 8.34$ ($r^2 = 0.994$), rmsd = 6.66.

TABLE 7: ^{1}H NMR Chemical Shifts of 2,5′-Anhydrothymidine 2 [ppm] Obtained by IGLO and GIAO Calculations Using MM/NMR Geometry[a,b]

	SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO	δ(exp)
H_6	7.62 (−0.18)	7.45 (−0.35)	7.46 (−0.34)	7.80
$H_{1'}$	6.05 (−0.07)	5.77 (−0.35)	5.26 (−0.86)	6.12
$H_{3'}$	4.85 (+0.03)	4.75 (−0.07)	4.42 (−0.40)	4.82
$H_{4'}$	4.28 (−0.41)	4.30 (−0.39)	4.16 (−0.53)	4.69
$H_{5'}$	4.59 (−0.07)	4.40 (−0.26)	4.02 (−0.64)	4.66
$H_{5''}$	4.52 (+0.22)	4.42 (+0.12)	4.18 (−0.12)	4.30
$H_{2'}$	2.98 (+0.53)	2.95 (+0.22)	2.67 (−0.06)	2.73
$H_{2''}$	2.51 (−0.03)	2.50 (−0.04)	2.37 (−0.17)	2.54
CH_3	2.10 (+0.16)	2.16 (+0.22)	2.18 (+0.24)	1.94

[a] The differences from experimental data (exp) are given in parentheses. [b] Linear relationships between experimentally obtained vs calculated chemical shifts: $\delta(\text{IGLO}) = 0.9398\delta(\text{exp}) + 0.254$ ($r^2 = 0.995$), rmsd = 0.189; $\delta(\text{DFT}) = 0.8951\delta(\text{exp}) + 0.362$ ($r^2 = 0.996$), rmsd = 0.166; $\delta(\text{CPHF}) = 0.8790\delta(\text{exp}) + 0.212$ (r^2 =0.989), rmsd = 0.265.

or MM/NMR geometries. Below the tables, the results of the linear correlation of experimental vs theoretical shifts are shown.

2,3′-Anhydrodeoxythymidine. As will be detailed elsewhere,[15] due to an oxygen bridge connecting the sugar ring with the thymine part, 2,3′-anhydrodeoxythymidine **1** is a rather rigid molecule. The overall agreement of measured and calculated shifts is good for both geometries. Average root-mean-square deviations (rmsd) are 5.96 and 5.34 ppm for ^{13}C shifts in MM/NMR and ab initio geometries, respectively. For proton shifts, the results are 0.251 and 0.287 ppm, respectively. As far as the prediction of relative shifts is concerned, the results are perfect only in the case of ^{13}C shifts in MM/NMR geometry. In ab initio geometry, all methods interchanged the relative position of $C_{4'}$ and $C_{1'}$ in the spectrum which is tolerable because of a small experimental difference of chemical shifts ($\delta(C_{4'})-\delta(C_{1'}) = -2.5$ ppm, about one-half of rmsd). Similarly, the positions of $H_{5''}$ and $H_{5'}$ for ab initio the geometry were inverted (the experimental difference is 0.09 ppm only). The least satisfactory results were obtained for proton shielding in MM/NMR geometry. The difference between measured shifts of $H_{4'}$ and $H_{5'}$ is +0.60, but SOS-DFPT-IGLO predicted +0.10, DFT-GIAO interchanged them (the difference −0.02), and CPHF-GIAO gave practically the same values (0.00).

TABLE 8: ^{13}C NMR Chemical Shifts of 2,5′-Anhydrothymidine 2 [ppm] Obtained by IGLO and GIAO Calculations Using RHF/6-31G Geometry[a,b]**

	SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO	δ(exp)
CH_3	17.8 (+2.5)	15.9 (+0.6)	14.1 (−1.2)	15.3
$C_{2'}$	49.2 (+4.3)	47.9 (+3.0)	42.1 (−2.8)	44.9
$C_{3'}$	82.1(+7.3)	79.6 (+4.8)	68.9 (−5.9)	74.8
$C_{5'}$	76.7 (−1.6)	74.5 (−3.8)	67.1 (−11.2)	78.3
$C_{4'}$	95.0 (+5.8)	92.4 (+3.2)	80.6 (−8.6)	89.2
$C_{1'}$	99.6 (+2.1)	96.9 (−0.6)	84.4 (−13.1)	97.5
C_5	129.4 (+7.8)	129.1 (+7.5)	123.2 (+1.6)	121.6
C_6	136.8 (−7.5)	137.9 (−6.4)	142.3 (−2.0)	144.3
C_2	156.0 (−5.0)	158.5 (−2.5)	163.9 (+2.9)	161.0
C_4	168.2 (−9.5)	170.0 (−7.7)	174.6 (−3.1)	177.7

[a] The differences from experimental data (exp) are given in parentheses. [b] Linear relationships between experimentally obtained vs calculated chemical shifts: $\delta(\mathrm{IGLO}) = 0.9206\delta(\mathrm{exp}) + 8.60$ ($r^2 = 0.995$), rmsd = 4.98; $\delta(\mathrm{DFT}) = 0.9509\delta(\mathrm{exp}) + 4.74$ ($r^2 = 0.996$), rmsd = 4.51; $\delta(\mathrm{CPHF}) = 1.029\delta(\mathrm{exp}) - 7.21$ ($r^2 = 0.995$), rmsd = 5.39.

TABLE 9: ^{1}H NMR Chemical Shifts of 2,5′-Anhydrothymidine 2 [ppm] Obtained by IGLO and GIAO Calculations Using RHF/6-31G Geometry[a,b]**

	SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO	δ(exp)
H_6	7.00 (−0.80)	6.80 (−1.00)	6.80 (−1.00)	7.80
$H_{1'}$	5.54 (−0.58)	5.25 (−0.89)	4.74 (−1.38)	6.12
$H_{3'}$	4.63 (−0.19)	4.47 (−0.35)	4.10 (−0.72)	4.82
$H_{4'}$	3.73 (−0.96)	3.73 (−0.96)	3.60 (−1.09)	4.69
$H_{5'}$	4.20 (−0.46)	3.99 (−0.67)	3.67 (−0.99)	4.66
$H_{5''}$	4.26 (−0.04)	4.12 (−0.18)	3.84 (−0.46)	4.30
$H_{2'}$	2.70 (−0.03)	2.66 (−0.07)	2.38 (−0.35)	2.73
$H_{2''}$	2.20 (−0.34)	2.18 (−0.36)	2.07 (−0.47)	2.54
CH_3	1.77 (−0.17)	1.81 (−0.13)	1.84 (−0.10)	1.94

[a] The differences from experimental data (exp) are given in parentheses. [b] Linear relationships between experimentally obtained vs calculated chemical shifts: $\delta(\mathrm{IGLO}) = 0.8862\delta(\mathrm{exp}) + 0.104$ ($r^2 = 0.988$), rmsd = 0.274; $\delta(\mathrm{DFT}) = 0.8390\delta(\mathrm{exp}) + 0.198$ ($r^2 = 0.990$), rmsd = 0.236; $\delta(\mathrm{CPHF}) = 0.8196\delta(\mathrm{exp}) + 0.065$ ($r^2 = 0.987$), rmsd = 0.265.

TABLE 10: ^{13}C NMR Chemical Shifts of 3′,5′-Anhydrothymidine 3 [ppm] Obtained by IGLO and GIAO Calculations Using MM (Discover) Geometry[a,b]

	SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO	δ(exp)
CH_3	17.9 (+3.5)	15.7 (+1.3)	13.4 (−1.0)	14.4
$C_{2'}$	50.3 (+10.8)	48.5 (+9.0)	41.9 (+2.4)	39.5
$C_{5'}$	82.4 (+3.3)	80.1 (+1.0)	71.6 (−7.5)	79.1
$C_{4'}$	83.5 (−0.1)	81.0 (−2.6)	71.2 (−12.4)	83.6
$C_{3'}$	92.0 (+0.9)	89.7 (−1.4)	77.9 (−13.2)	91.1
$C_{1'}$	103.2 (+10.9)	100.1 (+7.8)	86.6 (−5.7)	92.3
C_5	135.4 (+21.2)	136.4 (+22.2)	131.5 (+17.3)	114.2
C_6	147.2 (+6.2)	149.0 (+8.0)	153.4 (+12.4)	141.0
C_2	155.3 (−0.2)	158.7 (+3.2)	167.0 (+11.5)	155.5
C_4	168.6 (−0.8)	171.9 (+2.5)	179.2 (+9.8)	169.4

[a] The differences from experimental data (exp) are given in parentheses. [b] Linear relationships between experimentally obtained vs calculated chemical shifts: $\delta(\mathrm{IGLO}) = 0.9762\delta(\mathrm{exp}) + 7.90$ ($r^2 = 0.990$), rmsd = 7.29; $\delta(\mathrm{DFT}) = 1.019\delta(\mathrm{exp}) + 3.22$ ($r^2 = 0.990$), rmsd = 7.57; $\delta(\mathrm{CPHF}) = 1.119\delta(\mathrm{exp}) - 10.3$ ($r^2 = 0.986$), rmsd = 9.89.

TABLE 11: ^{1}H NMR Chemical Shifts of 3′,5′-Anhydrothymidine [ppm] Obtained by IGLO and GIAO Calculations Using MM (Discover) Geometry[a,b]

	SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO	δ(exp)
H_6	8.00 (−0.14)	7.90 (−0.24)	7.98 (−0.16)	8.14
$H_{1'}$	6.73 (+0.15)	6.59 (+0.01)	6.07 (−0.51)	6.58
$H_{3'}$	5.48 (−0.22)	5.38 (−0.32)	4.93 (−0.77)	5.70
$H_{4'}$	5.12 (+0.04)	4.97 (−0.11)	4.58 (−0.50)	5.08
$H_{5''}$	4.98 (+0.75)	4.98 (+0.75)	4.63 (+0.40)	4.90
$H_{5'}$	4.74 (−0.16)	4.75 (−0.15)	4.46 (−0.44)	4.23
$H_{2'}$	3.04 (+0.31)	2.99 (+0.26)	2.77 (+0.04)	2.73
$H_{2''}$	2.26 (−0.35)	2.29 (−0.32)	2.24 (−0.37)	2.61
CH_3	2.18 (+0.26)	2.27 (+0.35)	2.31 (+0.39)	1.92

[a] The differences from experimental data (exp) are given in parentheses. [b] Linear relationships between experimentally obtained vs calculated chemical shifts: $\delta(\mathrm{IGLO}) = 0.9633\delta(\mathrm{exp}) + 0.242$ ($r^2 = 0.991$), rmsd = 0.282; $\delta(\mathrm{DFT}) = 0.9327\delta(\mathrm{exp}) + 0.339$ ($r^2 = 0.990$), rmsd = 0.290; $\delta(\mathrm{CPHF}) = 0.9050\delta(\mathrm{exp}) + 0.229$ ($r^2 = 0.985$), rmsd = 0.347.

TABLE 12: ^{13}C NMR Chemical Shifts of 3′,5′-Anhydrothymidine 3 [ppm] Obtained by IGLO and GIAO Calculations Using RHF/6-31G Geometry[a,b]**

	SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO	δ(exp)
CH_3	16.1 (+1.7)	14.3 (−0.1)	12.8 (−1.6)	14.4
$C_{2'}$	43.7 (+4.2)	42.2 (+2.7)	36.8 (−2.7)	39.5
$C_{5'}$	78.5 (−0.6)	76.7 (−2.4)	69.6 (−9.5)	79.1
$C_{4'}$	87.5 (+3.7)	85.1 (+1.5)	75.3 (−8.3)	83.6
$C_{3'}$	92.4 (+1.3)	90.6 (−0.5)	79.9 (−11.2)	91.1
$C_{1'}$	95.0 (+2.7)	88.1 (−4.2)	80.5 (−11.8)	92.3
C_5	120.6 (+6.4)	119.8 (+5.6)	113.4 (−0.8)	114.2
C_6	138.1 (−2.9)	139.9 (−1.1)	146.5 (+5.5)	141.0
C_2	150.1 (−5.4)	152.4 (−3.1)	158.6 (+3.1)	155.5
C_4	161.3 (−8.1)	163.4 (−6.0)	169.4 (0.0)	169.4

[a] The differences from experimental data (exp) are given in parentheses. [b] Linear relationships between experimentally obtained vs calculated chemical shifts: $\delta(\mathrm{IGLO}) = 0.9366\delta(\mathrm{exp}) + 6.53$ ($r^2 = 0.997$), rmsd = 3.56; $\delta(\mathrm{DFT}) = 0.9693\delta(\mathrm{exp}) + 2.25$ ($r^2 = 0.998$), rmsd = 3.27; $\delta(\mathrm{CPHF}) = 1.053\delta(\mathrm{exp}) - 8.90$ ($r^2 = 0.994$), rmsd = 5.87.

TABLE 13: ^{1}H NMR Chemical Shifts of 3′,5′-Anhydrothymidine 3 [ppm] Obtained by IGLO and GIAO Calculations Using RHF/6-31G Geometry[a,b]**

	SOS-DFPT-IGLO	DFT-GIAO	CPHF-GIAO	δ(exp)
H_6	7.57 (−0.57)	7.74 (−0.40)	8.78 (+0.64)	8.14
$H_{1'}$	6.63 (−0.05)	6.14 (−0.44)	7.91 (+1.33)	6.58
$H_{3'}$	5.01 (−0.69)	4.62 (−1.08)	6.23 (+0.53)	5.70
$H_{4'}$	4.34 (−0.74)	3.98 (−1.10)	5.72 (+0.64)	5.08
$H_{5''}$	4.24 (+0.01)	4.06 (−0.17)	5.42 (+1.19)	4.90
$H_{5'}$	3.64 (−1.26)	3.60 (−1.30)	4.77 (−0.13)	4.23
$H_{2'}$	1.85 (−0.76)	1.79 (+0.18)	3.06 (+0.45)	2.73
$H_{2''}$	1.64 (−1.09)	1.63 (−1.10)	2.84 (+0.11)	2.61
CH_3	1.43 (−0.49)	1.58 (−0.34)	2.53 (+0.61)	1.92

[a] The differences from experimental data (exp) are given in parentheses. [b] Linear relationships between experimentally obtained vs calculated chemical shifts: $\delta(\mathrm{IGLO}) = 1.067\delta(\mathrm{exp}) - 0.925$ ($r^2 = 0.994$), rmsd = 0.277; $\delta(\mathrm{DFT}) = 1.029\delta(\mathrm{exp}) - 0.887$ ($r^2 = 0.990$), rmsd = 0.317; $\delta(\mathrm{CPHF}) = 1.083\delta(\mathrm{exp}) + 0.207$ ($r^2 = 0.993$), rmsd = 0.275.

2,5′-Anhydrodeoxythymidine. The absolute carbon shielding of 2,5′-anhydrodeoxythymidine **2** is reproduced with a rmsd of 5.81 and 4.96 ppm for MM/NMR and ab initio geometries, respectively. As in the previous case, theoretical methods failed to correctly predict the relative ^{13}C shifts when the experimental difference was rather small ($C_{3'}$ and $C_{5'}$). In terms of rmsd and slopes of correlations between measured and calculated values, slightly better results were obtained for ^{13}C shifts in the ab initio than in the MM/NMR geometry. On the contrary, the reversed result was obtained for proton shielding with rmsd of 0.207 and 0.259 ppm for MM/NMR and ab initio geometries, respectively. The slopes for ab initio geometry are all less than 0.9, the lowest ones found in the present work. Both in the MM/NMR and ab initio geometries, the relative shifts of $H_{4'}$, $H_{5'}$, and $H_{5''}$ are predicted incorrectly, which is not too surprising considering the very small difference in the measured values ($\delta(H_{4'})-\delta(H_{5'}) = 0.03$ ppm).

3′,5′-Anhydrodeoxythymidine. The influence of geometry on the quality of calculated shifts is clearly manifested in the case of 3′,5′-anhydrodeoxythymidine **3**, which is the most flexible molecule among the nucleosides investigated in this study. The average chemical shift rmsd for the "experimental" structure obtained from Discover was 8.25 and 0.306 ppm for carbons and hydrogens, respectively. This is substantially more than for the ab initio structure (4.23 and 0.289 ppm, respectively). The ab initio and MM geometries differ significantly both in the relative orientation of the thymine part (different values of the glycosidic angle) and in the sugar pucker.[15] However, the relative positions of ^{13}C shifts are reproduced correctly with just one exception for each geometry ($C_{4'}$ and $C_{5'}$ in CPHF-GIAO for MM, and $C_{1'}$ and $C_{3'}$ in DFT-GIAO for ab initio geometry). As far as proton shielding is concerned, the DFT-GIAO approach reversed the relative positions of $H_{4'}$ and $H_{5''}$ shifts in comparison to the experimental spectrum. All methods predicted the difference between the chemical shifts of $H_{2'}/H_{2''}$ and the methyl group with an error exceeding 0.5 ppm.

Conclusions

Considering the results obtained, the topics formulated in the Introduction can be addressed as follows.

(1) The overall agreement of theoretically predicted and experimentally measured chemical shifts is fairly good. The quantum chemical methods provide a reliable estimate of where to expect proton and carbon chemical shifts in the experimental spectrum. Since saturated basis sets were used in calculations, the differences between theory and experiment resulted mainly from the fact that the intermolecular forces had been completely neglected. In addition, inaccuracy of referencing of the absolute isotropic shielding and the treatment of molecules as rigid structures contributed as well. The theoretical results could also be influenced by electron correlation effects. Currently, it is not feasible to treat the investigated systems on the MBPT(2)[28] (nor any higher[29]) level with a reasonably large basis set. However, the effects of electron correlation are implicitly included in DFT schemes. Comparison of the average rmsd shows some improvement for DFT-based approaches over the CPHF method (see below), but the discrepancies between theoretical and experimental data are still significant and are probably induced by factors mentioned earlier.

(2) The quality of the results obtained by various methods varied as follows. The slopes of experimental vs theoretical chemical shift were close to unity for DFT-GIAO in the case of carbon shielding and for SOS-DFPT-IGLO when protons were considered. The average rmsd values for SOS-DFPT-IGLO, DFT-GIAO, and CPHF-GIAO calculations were 5.5, 5.2, and 6.6 ppm for ^{13}C and 0.233, 0.269, and 0.297 ppm for ^{1}H, respectively. These values concur with the results obtained recently for ^{13}C shielding in aromatic systems.[30]

(3) The maximum absolute errors are up to 22.2 ppm for ^{13}C and up to 1.38 ppm for ^{1}H shifts which represent roughly 10% of the respective shielding scales. Also, the rmsd for both nuclei are relatively comparable, considering their chemical shift ranges. Nonetheless, the number of wrong relative positions on the chemical shift scale is much higher for protons than for carbons. In addition, from slopes of linear correlations between the calculated and measured chemical shifts, it follows that proton values are more difficult to predict accurately.

(4) The ab initio geometry of 3′,5′-anhydrodeoxythymidine **3** brought a much more reliable description of shielding than structure obtained by minimization using Discover. In the case of compounds **1** and **2**, the fact that MM/NMR geometries gave a smaller number of wrong relative orders of chemical shifts compared to ab initio geometry is rather surprising. However, in terms of slopes and rmsd of experimental vs theoretical correlations, the ab initio geometry gave better results in the majority of cases.

(5) The typical CPU time requirements for each molecule in a given geometry were roughly 10, 50, and 40 h using SOS-DFPT-IGLO, DFT-GIAO, and CPHF-GIAO approaches, respectively. The SOS-DFPT-IGLO method, despite employing the largest basis set, produced results of the quality comparable with that achieved using DFT-GIAO for ^{13}C shifts and of even higher quality for ^{1}H, with substantial time savings. Time requirements are very important from a practical point of view, considering possible applications to nucleic acid fragments. Based on our work and results of others,[31] SOS-DFPT-IGLO represents the present method of choice for studies of larger organic systems.

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References and Notes

(1) de Dios, A. C. *Prog. NMR Spectrosc.* **1996**, *29*, 229.
(2) Wolinski, K.; Hinton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251.
(3) Häser, M.; Ahlrichs, R.; Baron, H. P.; Weis, P.; Horn, H. *Theor. Chim. Acta* **1992**, *83*, 455.
(4) Cheeseman, J. R.; Trucks, G. W.; Keith, T. A.; Frish, M. J. *J. Chem. Phys.* **1996**, *104*, 5497.
(5) Kutzelnigg, W. *Israel J. Chem.* **1980**, *19*, 193.
(6) Schindler, M.; Kutzelnigg, W. *J. Chem. Phys.* **1982**, *76*, 1919.
(7) Hansen, A. E.; Bouman, T. D. *J. Chem. Phys.* **1985**, *82*, 5035.
(8) Bouman, T. D.; Hansen, Aa. E. *Chem. Phys. Lett.* **1988**, *82*, 510.
(9) Malkin, V. G.; Malkina, O. L.; Eriksson, L. A.; Salahub, D. R. In *Theoretical and Computational Chemistry*; Seminario, J. M., Politzer, P., Eds.; Elsevier: Amsterdam, 1995; Vol. 2, p 273.
(10) Malkin, V. G.; Malkina, O. L.; Casida, M. E.; Salahub, D. R. *J. Am. Chem. Soc.* **1994**, *116*, 5898.
(11) Hu, J. Z.; Facelli, J. C.; Alderman, D. W.; Pugmire, R. J.; Grant, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 9863.
(12) Sitkoff, D.; Case, D. A. *Prog. NMR Spectrosc.* **1998**, *32*, 165.
(13) Dejaegere, A.; Case, D. A. *J. Phys. Chem. A* **1998**, *102*, 5280.
(14) Stahl, M.; Schopfer, U.; Frenking, G.; Hoffmann, R. W. *Mol. Phys.* **1997**, *92*, 569.
(15) Lang, J.; Czernek, J.; Sklenář, V. Manuscript in preparation.
(16) Malkin, V. G.; Malkina, O. L.; Salahub, D. R. *MASTER-CS Program*; Universite de Montreal: Montreal, Quebec, 1994.
(17) Kutzelnigg, W.; Fleischer, U.; Schindler, M. *NMR Basic Principles and Progress*; Springer-Verlag: Berlin, Heidelberg, 1990; Vol. 23.
(18) Perdew, J. P.; Wang, Y. *Phys. Rev.* **1992**, *B45*, 13244.
(19) Perdew, J. P.; Chevary, J. A.; Vosko, S. H.; Jackson, K. A.; Pederson, M. R.; Singh, D. J.; Fiolhais, C. *Phys. Rev.* **1992**, *B46*, 6671.
(20) Frish, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replongle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzales, C.; Pople, J. A. *Gaussian 94*, Revision C.2; Gaussian, Inc.: Pittsburgh, PA, 1995.
(21) Ditchfield, R. *Mol. Phys.* **1974**, *27*.
(22) Dunning, T. H.; Hay, P. J. In *Methods of Electronic Structure Theory*; Plenum Press: New York, 1977; Vol. 3, p 1.
(23) Thakkar, A. J.; Koga, T.; Saito, M.; Hoffmeyer, R. E. *Int. J. Quantum Chem.* **1993**, *27*, 343.
(24) Schäfer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571.
(25) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(26) *Discover 96.0 User Guide*, version 4.0.0; Molecular Simulations: San Diego, 1996.
(27) Raynes, W. T. *Nucl. Magn. Reson.* **1978**, *7*, 1.
(28) Gauss, J. *Chem. Phys. Lett.* **1992**, *191*, 614.
(29) Chesnut D. B. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, B. D., Eds.; VCH Publishers: New York, 1996; Vol. 8., p 245.
(30) Iuliucci, R. J.; Phung, C. G.; Facelli, J. C.; Grant, D. M. *J. Am. Chem. Soc.* **1996**, *118*, 4880 and references therein.
(31) Case, D. A. *J. Biomol. NMR* **1995**, *6*, 341.