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Ab Initio Calculations of Spin−Spin Coupling Constants in Anhydrodeoxythymidines

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For relatively large organic molecules (containing 16 non-hydrogen atoms each), anhydrodeoxythymidines, three- ($^3J_{HH}$) and two-bond ($^2J_{HH}$) $^1H-^1H$ and one-bond $^1H-^{13}C$ ($^1J_{CH}$) spin−spin coupling constants (*J*-couplings) were determined both experimentally and theoretically using NMR spectroscopy and density functional theory (DFT). A very good agreement between DFT-predicted and measured values was obtained for $^3J_{HH}$ (rmsd = 0.4 Hz). $^2J_{HH}$ and $^1J_{CH}$ were underestimated relative to the experiment. For all *J*-couplings investigated, noncontact contributions were negligible or canceled each other out. In general, the level of agreement between DFT and experiment is very promising.

Introduction

High-level ab initio predictions of NMR parameters, i.e., of the nuclear magnetic shielding tensor (chemical shielding) and the indirect nuclear spin−spin coupling constant (*J*-coupling), are becoming increasingly popular.[1] Post-Hartree−Fock approaches[2] were used to evaluate chemical shielding in several sizable systems (for review, see part VIII. D of ref 1). Very recently, we have calculated ^{1}H and ^{13}C chemical shieldings in three relatively large 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) with the inclusion of electron correlation.[3] As an extension of our previous study, the correlated calculations of *J*-couplings in these compounds are described in this communication. To the best of our knowledge, this is the first report where the above-mentioned methodology has been applied to molecular systems containing more than 15 non-hydrogen atoms.

As repeatedly discussed and exemplified in the literature,[4] *J*-couplings obtained at the Hartree−Fock level are in general unreliable due to the triplet instability problem.[1] Highly accurate treatment of spin−spin coupling using methodologies based on, e.g., MCSCF,[5] CC,[6,7] or MPn[8] wave functions is extremely demanding and hence not feasible except for the smallest molecules. A much more efficient approach is to use the finite (Fermi-contact)-field double perturbation theory[9] and combine it with some correlated wave function. The most important applications presented so far include the study of a *J*-coupling occurring across the hydrogen bond in the model of nucleic acid base pairs (B3LYP wave function was applied),[10] and numerous calculations on (models of) flexible carbohydrates by Carmichael et al. (several wave functions were tested).[11] This group, by using scaling of computed values[12] and specially designed basis sets,[13] derived information which is useful in the structural/conformational interpretation of *J*-coupling values in carbohydrate-containing systems.

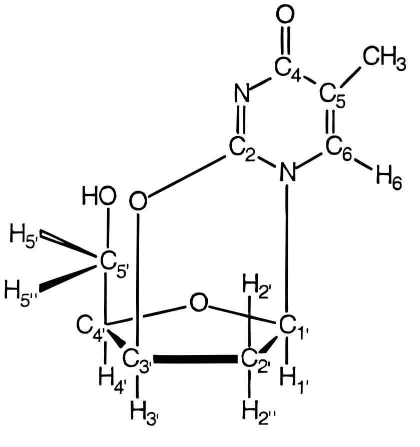

Figure 1. 2,3′-Anhydro-1-(2′-deoxy-*β*-D-xylofuranosyl)thymine.

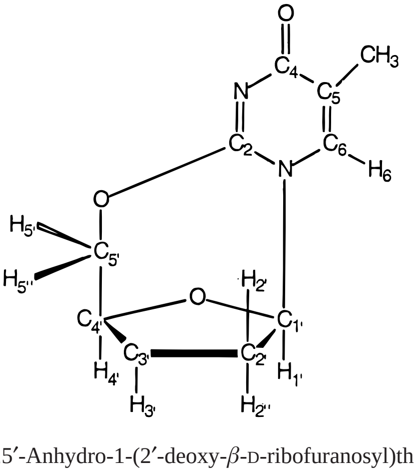

Figure 2. 2,5′-Anhydro-1-(2′-deoxy-*β*-D-ribofuranosyl)thymine.

However, the above-mentioned applications potentially suffer from the neglect of all noncontact contributions to *J*-coupling (vide infra); only the Fermi contact component of investigated coupling constants could be obtained. In an alternative approach,

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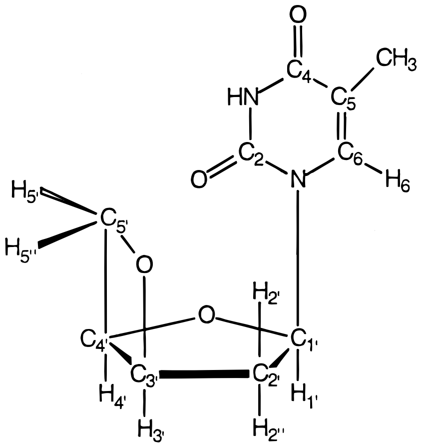

Figure 3. 3′,5′-Anhydro-1-(2′-deoxy-β-D-xylofuranosyl)thymine.

the newly proposed DFT-based methodology[14] also considers the orbital contributions to spin−spin coupling. Recently, this theory has been shown to be capable of reproducing subtle properties of stereoelectronic interactions in diheterocyclohexanes.[15] It has also been successfully applied in studies of flexible hydrocarbons[16] and the monosaccharides.[17] Most recently, this method has been employed to explain some trans-hydrogen nuclear spin−spin couplings in proteins and nucleic acid base pairs.[18] In the present paper, we investigate selected spin−spin scalar interactions in anhydrodeoxythymidines, both on the theoretical and experimental level using DFT methodology. On the basis of the comparison of calculated and experimentally measured values, the following three topics will be primarily addressed: (1) the overall agreement of theory and experiment; (2) the problems specific to $^3J_{HH}$, $^2J_{HH}$, and $^1J_{CH}$ predictions; (3) relative importance of the respective contributions to the J-couplings studied.

Because of the strong geometrical dependence of coupling magnitudes,[19] the population averaging over the calculated values[20] can be indispensable for a fair comparison of ab initio data and measured J-couplings. As mentioned previously,[3] and will be detailed elsewhere,[21] the presence of oxygen bridges in anhydrodeoxythymidines makes them (partially) rigid. Hence, the conformational effects on the reported J-couplings are believed to be negligible. Consequently, the presented data allows us to verify the level of accuracy, which can be obtained with the most progressive ab initio methodology available at present. As with chemical shielding calculations, the limits of J-coupling prediction for large, biologically important fragments are of interest not only to theoreticians, but to NMR spectroscopists as well.

Experimental Section

Samples of 2,3′-anhydrodeoxythymidine **1**, 2,5′-anhydrodeoxythymidine **2**, and 3′,5′-anhydrodeoxythymidine **3** were dissolved in deuterium oxide (99.8% d, Merck) in concentrations of 0.16, 0.11, and 0.10 mol dm^{-3}, respectively. Oxygen was removed by the freeze−pump−thaw procedure (at least three cycles). The samples were flame-sealed (**1** and **2** under low-pressure argon atmosphere) in 5 mm NMR tubes. NMR spectra were measured on Bruker AM 400, AMX 400, and Avance 500 MHz spectrometers at 303 K.

TABLE 1: Contributions to Three-Bond ^{1}H−^{1}H Coupling Constants in 2,3′-Anhydrodeoxythymidine (1), 2,5′-Anhydrodeoxythymidine (2), and 3′,5′-Anhydrodeoxythymidine (3) Together with Total DFT and Experimental Values [Hz][a,b]

bond	compound	FC	PSO	DSO	DFT	experimental
$H_{1'}-H_{2'}$	**1**	0.30	0.37	−0.43	0.2	0.5
	2	1.91	1.16	−1.22	1.9	1.9
	3	2.12	1.14	−1.20	2.1	2.0
$H_{1'}-H_{2''}$	**1**	3.89	−0.20	0.14	3.8	3.9
	2	7.53	−1.27	1.24	7.5	8.1
	3	8.06	−1.42	1.40	8.0	8.3
$H_{2'}-H_{3'}$	**1**	1.39	0.39	−0.46	1.3	1.5
	2	5.69	−1.20	1.16	5.7	6.9
	3	0.11	0.93	−0.99	0.1	0.3
$H_{2''}-H_{3'}$	**1**	2.43	−0.04	−0.01	2.4	2.7
	2	0.62	1.24	−1.31	0.6	1.2
	3	4.72	−0.67	0.63	4.7	5.5
$H_{3'}-H_{4'}$	**1**	1.97	−0.73	0.71	2.0	2.5
	2	0.10	0.75	−0.50	0.4	0.3
	3	2.96	−0.06	0.04	2.9	4.2

[a] Linear relationship between experimentally obtained vs calculated $^3J_{HH}$ couplings: $^3J_{HH}$ (calcd) = 0.921 $^3J_{HH}$ (exptl) − 0.149 ($r^2 = 0.979$), rmsd = 0.382. [b] Calculated data has been obtained at the PP/IGLO−III//RHF/6-31G** level of theory.

TABLE 2: Contributions to Two-Bond ^{1}H−^{1}H Coupling Constants in 2,3′-Anhydrodeoxythymidine (1), 2,5′-Anhydrodeoxythymidine (2), and 3′,5′-Anhydrodeoxythymidine (3) Together with Total DFT and Experimental Values [Hz][a,b]

bond	compound	FC	PSO	DSO	DFT	experimental
$H_{2'}-H_{2''}$	**1**	−10.17	2.04	−1.86	−10.0	−13.5
	2	−13.24	1.69	−1.52	−13.1	−15.8
	3	−13.44	1.81	−1.63	−13.3	−16.5
$H_{5'}-H_{5''}$	**1**	−11.21	1.45	−1.42	−11.2	−11.9
	2	−10.93	1.69	−1.67	−10.9	−13.1
	3	−6.48	2.11	−2.08	−6.5	−8.6

[a] Linear relationship between experimentally obtained vs calculated $^2J_{HH}$ couplings: $^2J_{HH}$ (calcd) = 0.819 * $^2J_{HH}$ (exptl) − 0.001 (r^2 = 0.906), rmsd = 0.952. [b] Calculated data has been obtained at the PP/IGLO−III//RHF/6-31G** level of theory.

TABLE 3: One-Bond ^{13}C−^{1}H Coupling Constants in 2,3‘-Anhydrodeoxythymidine (1), 2,5′-Anhydrodeoxythymidine (2), and 3′,5′-Anhydrodeoxythymidine (3) Obtained at the PP/IGLO−III//RHF/6-31G Level of Theory and from the Experiment[a] [Hz]**

	compound **1**		compound **2**		compound **3**	
	calcd	exptl	calcd	exptl	calcd	exptl
$C_{1'}-H_{1'}$	160.0	181	151.1	173	157.1	174
$C_{2'}-H_{2'}$	129.5	139	127.2	135	128.0	136
$C_{2'}-H_{2''}$	135.6	143	125.5	135	120.8	132
$C_{3'}-H_{3'}$	154.5	172	144.4	154	147.7	166
$C_{5'}-H_{5'}$	133.9	154	137.6	153	143.5	154

[a] Linear relationship between experimentally obtained vs calculated $^1J_{CH}$ couplings: $^1J_{CH}$ (calcd) = 0.734 $^1J_{CH}$ (exptl) + 27.2 ($r^2 = 0.948$), rmsd = 2.96.

The ^{1}H and ^{13}C signals were assigned using standard two-dimensional ^{1}H−^{1}H [22] and ^{1}H−^{13}C [23] correlation spectroscopy. The measured ^{1}H and ^{13}C chemical shifts were reported previously.[3] The CH_2 protons were identified using the proton one-dimensional differential NOE experiment.[24] ^{1}H−^{1}H J-couplings were determined from standard ^{1}H NMR spectra by an interactive fitting procedure using PERCH software.[25] Only selected vicinal $^3J_{HH}$ (Table 1) and geminal $^2J_{HH}$ (Table 2) coupling constants are presented. The values of reported J constants are determined to an accuracy of 0.1 Hz. One-bond, ^{1}H−^{13}C coupling constants ($^1J_{CH}$) were measured for several proton−carbon pairs from proton-coupled ^{13}C NMR spectra (5000 scans, 64 000 data points) to an accuracy of 1.0 Hz (Table 3).

Theory and Computations

The indirect nuclear spin−spin coupling interaction is a tiny effect. Its reliable description poses severe problems regarding the quality and flexibility of a wave function used. As a result, the *J*-coupling calculation presents one of the most demanding tasks of applied quantum chemistry. Nevertheless, the theory needed for the *J*-coupling calculation has been known since the beginning of the 1950s. In the original quantum mechanical treatment of "electron coupled interactions between nuclear spins in molecules" given by Ramsey,[26] two types of contributions to the nuclear spin−spin coupling tensor were presented (see[1] for their detailed discussion): first, the terms originating from the orbital motion of the electrons, i.e., the paramagnetic spin−orbit (PSO) and the diamagnetic spin−orbit (DSO) contributions; second, the terms arising from the spin of the electrons, the Fermi-contact (FC), the spin-dipole (SD), and mixed FC−SD contributions. The DFT-based methodology of Malkin et al.,[14] which has been used in this work, treats the individual terms as follows.[27] The FC and FC−SD terms are evaluated by the finite perturbation theory.[28] The PSO is calculated using the sum-over-states density functional perturbation theory (SOS-DFPT),[27,29] while the DSO is easily obtained by numerical integration.[30] The remaining term, the SD contribution, is neglected (see ref 31 for justification). The cross term of the FC and SD mechanisms does not contribute to the trace of the coupling tensor but affects only the anisotropy of *J*-coupling (see ref 32 for important examples). Consequently, the computed FC−SD values will not be discussed.

Systematic investigation of basis sets requirements and performance of various DFT functionals would be very expensive for anhydrodeoxythymidines. Thus, the previously tested and successful methodology,[15−18] which we will now shortly describe, was employed to study spin−spin coupling networks in molecules **1**−**3**. Calculations were performed with the deMon-NMR code.[14,30,31] The Perdew and Wang[33] semilocal exchange functional and the correlation functional of Perdew[34] were used. The PSO contributions were obtained with the Loc. 1 approximation of SOS-DFPT[27,29] and using a grid of 32 radial points. In the FC calculations, a grid with 64 radial points was applied. In each case, the center of the perturbation of 0.001 was at the position of the selected hydrogen atom. As discussed in detail in refs 27 and 35, due to numerical errors in the FC calculations, the choice of the perturbing center can make a small difference in the computed *J*-coupling. The asymmetries of a few hundredths of hertz have actually been observed in this work. Because of this, the total DFT-predicted values in Tables 1−4 are rounded off to 0.1 Hz. The IGLO-III basis set of Kutzelnigg et al.[36] was employed. IGLO-III is a relatively large basis set, roughly of "quadruple-ζ" quality (the contraction pattern (6)/[3,3*1] with two sets of 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 the application of 712 basis functions for each structure.

Full ab initio optimizations of geometry were carried out on the RHF/6-31G** level with GAUSSIAN94.[37] As the combination of functionals employed in the *J*-couplings calculations (see above) is often denoted as PP, the level of theory used in this work can be referred to as PP/IGLO-III//RHF/6-31G**.

The geometry of 3′,5′-anhydrodeoxythymidine **3** was also fully optimized on the MP2/6-31G** and B3LYP/6-31G** levels using GAUSSIAN94 (see the discussion of $^1J_{CH}$ couplings). RHF, MP2, and B3LYP optimizations started with the same structure preoptimized with Discover.[3]

Results and Discussion

$^3J_{HH}$ Couplings. Because of their sensitivity to variations of internal and dihedral angles,[38] the vicinal $^1H-^1H$ *J*-couplings have a widespread application in stereochemistry.[39] Hence, it is of prime importance to validate the ability of DFT methodology to predict $^3J_{HH}$ couplings. Table 1 summarizes selected experimental and computed $^1H-^1H$ *J*-couplings from the sugar parts of anhydrodeoxythymidines **1**−**3**. The remaining $^3J_{HH}$ could not be unambiguously extracted by the interactive fitting procedure. Consequently, their calculated counterparts are not reported. Below Table 1, the results of the linear correlation of experimental vs theoretical $^3J_{HH}$ values are shown. The value of rmsd (less than 0.4 Hz) shows that the overall agreement of measured and calculated coupling constants is very good. Generally, the latter are underestimated relative to the experiment. This tendency, which is visible already from the illustrative examples of the DFT approach[27] and which was discussed in ref 17 is more pronounced in the case of small (<1 Hz) couplings.

Table 1 also shows the individual contributions to the calculated $^3J_{HH}$. Interestingly, because of (partial) mutual cancellation of orbital terms, the FC component lies within 0.1 Hz of the total DFT value with just one exception (^{3}J ($H_{3'}$−$H_{4'}$) in **2** with the difference of 0.3 Hz). However, the magnitude of PSO and DSO exceeds that of FC in many cases. It is clearly seen in the case of $^3J_{H3'-H4'}$ found in 2,5′-anhydrodeoxythymidine **2** and $^3J_{H2'-H3'}$ in 3′,5′-anhydrodeoxythymidine **3**. The difference in the sugar moiety of compounds **2** (ribofuranosyl derivative) and **1** and **3** (xylofuranosyl) derivatives is reflected in the sign of PSO and DSO (see Table 1). These orbital terms for *J*-couplings of all protons with $H_{3'}$ have opposite signs.

$^2J_{HH}$ Couplings. In comparison with $^3J_{HH}$ couplings, the geminal $^2J_{HH}$ coupling constants are structurally less important.[39] We would like to point out the problems connected with their prediction when the PP/IGLO-III//RHF/6-31G** approach is adopted. Only two types of vicinal interactions are present in the anhydrodeoxythymidines investigated. The calculated and experimental data are reported in Table 2.

In contrary to the smaller systems studied by Malkin et al.,[14,27] all calculated values are systematically underestimated by ca. 20%. The relative order of geminal couplings is correct with the exception of $^2J_{H5'-H5''}$ in 2,3′-anhydrodeoxythymidine **1** and $^2J_{H5'-H5''}$ in 2,5′-anhydrodeoxythymidine **2**. The atypically low $^2J_{HH}$ coupling between $H_{5'}$ and $H_{5''}$ protons in the vicinity of the four-membered ring in 3′,5′-anhydrodeoxythymidine **3** observed experimentally has been successfully reproduced. This *J*-coupling is also interesting from the point of view of the respective contributions to $^2J_{HH}$ values (Table 2). In that case, PSO and DSO values are the largest, both in absolute and relative terms. It is noted, however, that discrepancies between FC term and the total DFT $^2J_{HH}$ couplings are 0.2 Hz at the most. This is due to the compensation of spin−orbit contributions, similarly as in the case of the $^3J_{HH}$ coupling constants. As for the sign of noncontact terms, PSO is positive and DSO negative in each case.

$^1J_{CH}$ Couplings. Important structural information can also be gained from the one-bond $^{13}C-^1H$ coupling interaction.[11] Selected $^1J_{CH}$ coupling constants of the studied compounds are shown in Table 3.

All theoretical values are significantly (up to 21.9 Hz) smaller than the measured data. As noncontact contributions to $^1J_{CH}$ couplings were found to be negligible (less than 1% of the total value; data not given), the error is thus caused by an underestimation of the FC term. This is due to the fact that many

TABLE 4: Calculated[a−c] C−H Bond Lengths (in Å, Upper Values) and Corresponding One-Bond Coupling Constants (in Hertz, Lower Values) in 3′,5′-Anhydrodeoxythymidine (3) with Experimental $^1J_{CH}$ Also Given

	calcd[a]	calcd[b]	calcd[c]	exptl
$C_{1'}-H_{1'}$	1.075	1.086	1.089	174
	157.1	159.6	160.9	
$C_{2'}-H_{2'}$	1.082	1.089	1.094	136
	128.0	128.3	128.6	
$C_{2'}-H_{2''}$	1.084	1.091	1.094	132
	120.8	121.7	122.7	
$C_{3'}-H_{3'}$	1.083	1.091	1.095	154
	147.7	151.1	151.3	

[a] PP/IGLO-III//RHF/6-31G**. [b] PP/IGLO-III//MP2/6-31G**. [c] PP/IGLO-III//B3LYP/6-31G**.

factors may influence the FC value, mainly: (1) the type of exchange-correlation functional employed; (2) the quality of the grid; (3) the basis set incompleteness; (4) the neglect of solvation effects; (5) inaccuracies in the geometry. To (partially) account for the geometrical effects on *J*-coupling values, selected $^1J_{CH}$ couplings in 3′,5′-anhydrodeoxythymidine **3** were also calculated using correlated (B3LYP/6-31G** and MP2/6-31G**) geometries (Table 4).

As expected,[40] these alternative approaches produced more relaxed structures, e.g., longer bond lengths. Although the structures with elongated bonds provided results closer to the experimental values, the remaining discrepancy is still around 10% with respect to the measured $^1J_{CH}$ couplings. Similar inadequacies, of an unidentified origin, in DFT-predicted $^1J_{CH}$ couplings have been described recently.[11,15,17] To quantify the error arising from the basis set incompleteness, the basis set convergence of DFT *J*-coupling calculations in smaller systems is under investigation.[41] Despite the observed discrepancies, Table 3 shows that the computed pattern of $^1J_{CH}$ magnitudes is correct for all anhydrodeoxythymidines.

Conclusions

A reliable description of spin−spin coupling constants in larger molecules is a very delicate problem. This is especially true for the quantitative prediction of *J*-coupling values. Nonetheless, considering the results obtained, some important conclusions can be drawn from the calculations on the systems presented above.

(i) The IGLO-III basis set used in the present study is far from being saturated. However, the calculation of a spin−spin coupling network using a larger basis set would be extremely demanding. For example, JMN-2 (uncontracted IGLO-III with two additional sets of polarization functions) has been shown to significantly improve the agreement between theory and experiment in certain cases.[27] But its use would result in the application of 1121 basis function for each anhydrodeoxythymidine. In this context, the results for $^3J_{HH}$ couplings can be considered as very good. The DFT method is robust and well suited to, for example, ab initio parametrizations of the Karplus-type relationships for biological systems.[42]

(ii) Contrary to $^3J_{HH}$, the computed $^2J_{HH}$ and $^1J_{CH}$ couplings are systematically underestimated. Calculated $^1J_{CH}$ spin−spin coupling constants are in qualitative agreement with their experimental counterparts. Hence, these data can also be useful in gaining insight into the structure−*J*-coupling relationship.

(iii) Both the relative importance and the respective values of noncontact contributions to selected $^1H-^1H$ (^{13}C) spin−spin coupling constants in medium-sized organic molecules are discussed. It can be concluded that for all *J*-couplings investigated, orbital contributions are negligible or canceling each other out. This finding is of utmost interest, as it justifies the comparison of the experimental data in solution solely with the computed FC term, which is the approach adopted in a number of studies.[11]

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