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Analysis of NMR *J* Couplings in Partially Protected Galactopyranosides

E. Andreas Larsson,[†] Jozef Ulicny,[‡,§] Aatto Laaksonen,[‡] and Göran Widmalm*,[†]

Department of Organic Chemistry and Division of Physical Chemistry,
Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden

gw@organ.su.se

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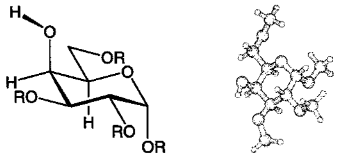
ABSTRACT



Hydrogen bond mediated NMR *J* couplings offer additional structural information. The interpretation of these usually small ^{h}J couplings are, however, not necessarily straightforward. In the present case of a carbohydrate system, a four-bond classical *W* coupling, $^{4}J_{HO4,H5}$, is more reasonable on the basis of, in particular, density functional theory calculations of spin–spin coupling constants at the UB3LYP/6-311G level of theory.**

The presence of hydrogen bond mediated NMR *J* couplings[1] in biomolecules has recently attracted substantial interest.[2] The ^{h}J couplings are usually small, but extremely valuable in the refinement of protein and nucleic acid structures.[3−6] However, the interpretation of spin−spin couplings may not be straightforward and it is not always necessary to invoke a complex *J* mediated pathway, as is shown below for a carbohydrate system.

The synthesis of complex oligosaccharides makes it possible to obtain probes for the study of glycobiology related interactions and mechanisms.[7] Of special interest in oligosaccharide synthesis is the formation of the glycosidic linkage, which should be performed with high stereoselectivity. Some recent studies have addressed this issue in residues with a galacto configuration, i.e., those having an axial group at C4 of the sugar.[8−10] A free hydroxyl group at this position in glycosyl donors can have a directing effect.[8] In galactosyl acceptors, different reactivity was observed depending on their anomeric configuration.[10] An interaction between the hydroxyl proton and the ring oxygen was judged to be important in product formation in both cases.[8,10]

The above studies prompted us to further investigate the importance of the hydroxyl proton. In their excellent synthetic work, Kwon and Danishefsky[8] observed a cross-peak between HO4 and H5 in $^{1}H-^{1}H$ COSY NMR spectra of several compounds. We selected two model substances, viz., ethyl 2,3,6-tri-*O*-benzyl-1-thio-*β*-D-galactopyranoside (**1**) and methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**2**) (Figure 1). We were able to confirm the presence of a cross-peak between HO4 and H5 in $^{1}H-^{1}H$ COSY spectra for our two model substances in $CDCl_3$ solution. For instance, the

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* Corresponding author. Phone: + 46 8 16 37 42. Fax: +46 8 15 49 08.

[†] Department of Organic Chemistry.

[‡] Division of Physical Chemistry.

[§] Permanent address: Department of Biophysics, Safárik University, SK 04154 Kosice, Slovakia.

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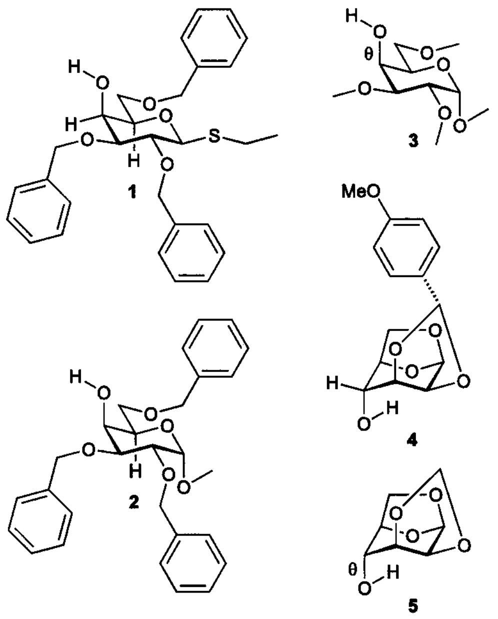

Figure 1. Schematic of the molecular structures investigated. The torsion angle θ = HO4−O4−C4−H4. Syntheses of **1**[21] and **2**[22] have been described previously.

^{1}H NMR resonance of the hydroxyl proton in **1** was a dd with $J_{\mathrm{H4,HO4}} = 2.6$ Hz and $J_{\mathrm{HO4,H5}} = 1.0$ Hz (Figures 2 and S1) and H5 was a dddd with, in addition, $J_{\mathrm{H4,H5}} = 1.0$ Hz, $J_{\mathrm{H5,H6a}} = 5.7$ Hz, and $J_{\mathrm{H5,H6b}} = 6.0$ Hz.

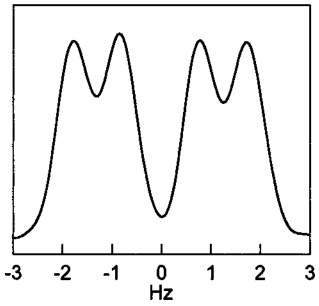

Figure 2. Part of the ^{1}H NMR spectrum at 600 MHz of **1** in $CDCl_3$ at 25 °C showing the HO4 resonance, δ 2.50, with $J_{\mathrm{H4,HO4}} = 2.6$ Hz and $J_{\mathrm{HO4,H5}} = 1.0$ Hz.

As a means to study the interaction of the hydroxyl proton and the ring oxygen (as a pathway for mediation of the *J* coupling between HO4 and H5), we performed Density Functional Theory (DFT) calculations at the B3LYP/6-31G* level of theory on methyl 2,3,6-tri-*O*-methyl-α-D-galactopyranoside (**3**) as our model compound. A structure with the hydroxyl proton pointing toward the ring oxygen was optimized (Figure 3a) and selected data for this structure **3t** (where **t** refers to a "trans" conformation of the torsion angle θ = HO4−O4−C4−H4) are given in Table 1. However, when the contact between the hydrogen and the ring oxygen was investigated using the Atoms in Molecules analysis,[11,12] no significant interaction could be found in terms of the electron density at the bond critical point.[13] The lack of

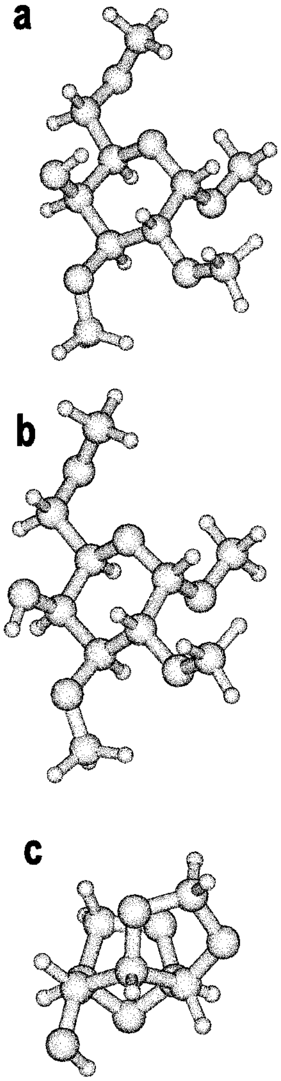

Figure 3. Structure **3t** (a), **3g**$^+$ (b), and **5t** (c). Geometry optimization and electron density analysis were performed with the Gaussian 98 ab initio package[23] at the B3LYP/6-31G* level of theory. Initial guesses of the geometries were obtained from molecular mechanics structures; intermediate optimization was made using the HF/3-21G level of theory. Optimizations were always terminated using default convergence criteria of Gaussian 98. The character of the stationary point as a local minimum was confirmed by normal-mode analysis with the Hessian evaluated analytically, allowing us to obtain also the corresponding normal modes and IR frequencies at the same level of theory. Energetics refer to differences in local minimum energies with correction for zero-point vibrational energy applied. Atoms in Molecules analysis was done using the AIMPAC software package[24] with the electronic density exported from Gaussian 98.

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Table 1. Selected Data for Optimized Structures Using DFT Calculations

structure	ΔE (kcal/mol)[a]	θ (deg)	$\Delta\nu$ (cm^{-1})[b]
3t	3.5	−163	−37
3g$^+$	0	74	−44
5t	0	165	−47
5g$^+$	2.5	75	0
5g$^-$	2.5	−56	−5

[a] Lowest energy conformation of each compound is used for comparison of relative energy differences. [b] $\Delta\nu = \nu - \nu_{\mathbf{5g}+}$, i.e., the highest wavenumber is used for comparison of frequency differences in IR spectra.

significant interactions is also corroborated by the large equilibrium interatomic distance, $r_{\mathrm{HO4,O5}} = 2.315$ Å, unfavorable for a strong hydrogen bond interaction. Thus, the experimentally observed J coupling between HO4 and H5 is not supported to be mediated via O5. In contrast, scalar coupling across the hydrogen bond in 1,3- and 1,4-diols was shown to exist as determined by ^{1}H NMR spectroscopy.[14] In particular, the presence of the experimentally observed $^{\mathrm{h}}J$ couplings was supported by density functional finite perturbation theory calculations.

A conformation with the θ torsion angle as gauche$^+$ was optimized (Figure 3b) as above. Interestingly, the relative energy of this structure (**3g**$^+$) was 3.5 kcal/mol lower (Table 1) than **3t**, due to energetically more favorable hydrogen bonding of the hydroxyl proton, suggesting it to be a favored conformation also in solution. In addition, a **3g**$^-$ conformation was also subjected to optimization. However, several starting conformations converged to the **3g**$^+$ conformer, having $r_{\mathrm{HO4,O3}} = 2.112$ Å.

The $J_{\mathrm{H4,HO4}}$ coupling may be interpreted via a Karplus-type relationship[15] where a staggered gauche conformation has a J value of ∼2 Hz, similar to that observed in **1**. If there is no preference for the θ torsion angle, i.e., equal populations throughout the torsional rotation, the averaged value is ∼5 Hz. On the basis of this Karplus relationship, structure **3t** has $J \approx 11$ Hz. Thus, the low experimental value of this coupling suggests that a gauche conformation is preferred and that a structure similar to **3t** is not predominant in solution.

In **4**, the value of $J_{\mathrm{HO4,H4}}$ equals ∼9 Hz,[16] which strongly indicates a trans conformation of θ. The above computational approach was carried out for the model compound **5**, and the results are also given in Table 1. Clearly, the experimentally suggested conformation is supported by the calculations, since neither of the gauche conformers are to be populated to any great extent.

The O4−C4−C5−H5 torsion angle in **1**−**3** is close to antiperiplanar. Therefore, a conformation with θ as gauche$^+$ will lead to a typical W arrangement of HO4−O4−C4−C5−H5. Spin−spin couplings over four bonds in saturated compounds may not be of a negligible magnitude, such as in α-bromocyclohexanone where these interactions show $^4J = 1.1$ Hz.[17] Therefore, a classical W arrangement[18,19] is a highly reasonable explanation for the mediation of the $J_{\mathrm{HO4,H5}}$ coupling.

IR spectra were recorded for **1** (Figure 4) and **2**, which both showed a distinct O−H stretching band at 3565 cm^{-1} in CH_2Cl_2 at ambient temperature, indicating a cis five-membered ring. Small differences of a few wavenumbers depending on whether the hydroxyl donor is axial or equatorial are anticipated.[20] A shoulder at ∼3500 cm^{-1} is indicative of some presence of a six-membered ring.[19] However, from $J_{\mathrm{H5,H6}}$ (vide supra), the population of a gg conformation of ω (O5−C5−C6−O6), required for a six-membered ring, is low. The conclusions drawn from the experimental position of the O−H stretching band are also well supported by the trends observed in the ab initio calculated IR spectra for different conformers of **3** and **5**. A comparison of relative frequencies (Table 1) was made, and the magnitude of the red shifts, i.e., a lowering of the O−H stretching frequency, is indicative of a traditional hydrogen bond (electrostatic) type of interaction. Although this does not differentiate **3g**$^+$ from **3t**, it shows in particular for the three conformers of **5** the predictive power of the calculations.

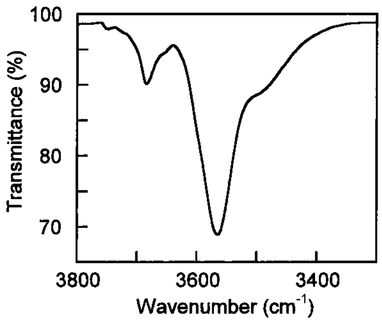

Figure 4. Part of the IR spectrum of **1** in CH_2Cl_2 at ambient temperature.

In addition, spin−spin coupling constants were calculated for **3g**$^+$ and **3t** at the UB3LYP/6-311G** level of theory. The results are compiled in Table 2 together with the corresponding experimental data of **1**. Excellent agreement is observed for $J_{\mathrm{H4,H5}}$ as well as for the postulated large value of $J_{\mathrm{H4,HO4}}$ in **3t** (vide supra). It is shown that $J_{\mathrm{HO4,H5}}$ is significant in **3g**$^+$ but only marginal in **3t**, thereby supporting the line of argument described herein. Since only static

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Table 2. Experimental (**1**) and Calculated[a] (**3**) Spin−Spin Coupling Constants (Hz)

structure	$^{3}J_{H4,HO4}$	$^{4}J_{HO4,H5}$	$^{3}J_{H4,H5}$
1	2.6	1.0	1.0
3g^{+}	0.04	1.8	1.6
3t	12.2	−0.4	0.7

[a] Computations were performed with Gaussian 98.[23] Fermi contact terms were evaluated using density functional theory/finite perturbation theory (DFT/FPT) at the UB3LYP/6-311G** level with the equilibrium geometry obtained at the B3LYP/6-31G* level. The perturbation size was 0.01 au placed at the pertinent hydrogen.

conformers are evaluated, i.e., no conformational averaging is accounted for, the agreement between simulation and experiment is quite satisfactory.

In conclusion, we do not find it necessary to invoke a “virtual” bond and strong hydrogen bonding via the ring oxygen as proposed by Kwon and Danishefsky[8] to account for the experimentally observed $J_{HO4,H5}$ coupling. Instead, a straightforward interpretation is preferred on the basis of the following: (i) no support for electron density at the bond critical point as deduced by ab initio calculations, (ii) relative energies between conformations, (iii) the magnitude of $^{3}J_{HO4,H4}$, (iv) the feasibility of significant ^{4}J couplings when *W* arrangements are present, also in saturated systems, and (v) the calculated *J* couplings, in particular $^{4}J_{HO4,H5}$. However, the axially oriented substituent at C4 in sugars with the galacto configuration is *certainly of great importance in glycosylation-related reactions* as previously demonstrated[8,10,25] and a detailed understanding of the behavior of the hydroxyl proton as a function of the reaction path is of fundamental interest.

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Supporting Information Available: ^{1}H NMR spectrum of **1** and Cartesian coordinates of the energy minimized structures described in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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