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Scalar Coupling Across the Hydrogen Bond in 1,3- and 1,4-Diols

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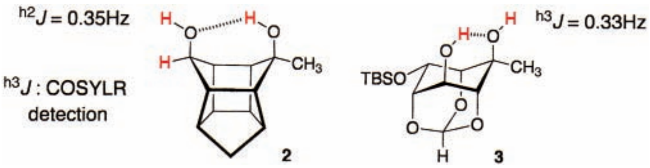
ABSTRACT



Scalar coupling between hydroxyl groups sharing a 1,4- or 1,3-intramolecular hydrogen bond can be readily detected using standard 2D NMR techniques. Analyses of isotopically perturbed 2D *J*-resolved spectra have revealed ^{h2}J to be on the order of 0.3 Hz in systems such as diols 2 and 3. A standard 2D COSY experiment, modified to detect small coupling constants, is shown to be a convenient method for detecting ^{h2}J in these systems. Couplings derived from density functional finite perturbation theory (DFT/FPT) are found to be in general agreement with experimental data.

The hydrogen bond plays an essential role in maintaining the three-dimensional structure of proteins, nucleic acids, and carbohydrates.[1] Accordingly, hydrogen bond detection in systems such as these remains an area of active research. Recently, several groups reported that the hydrogen bond is capable of transmitting scalar couplings[2] in peptide and nucleic acid systems.[3,4] Intermolecular couplings have also been observed in the HF−lutidine complex[5] as well as in $(HF)_n$ clusters.[6] The implication of this work, in addition to providing new and reliable NMR structural constraints, is that it provides information on the nature of the hydrogen bond.[7]

Intramolecular "through space" scalar coupling was described by Anet and co-workers in a 1965 study of hexachloro half-cage **1**.[8] This compound exhibited a 1.1 Hz coupling between the hydroxyl proton and the transannular C−H hydrogen. The origin of this relatively large coupling

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(1) Jeffrey, G. A.; Sanger, W. *Hydrogen Bonding in Biological Structures*; Springer: New York, 1991.

(2) The convention for describing these couplings is ^{hx}J, where x designates the number of bonds separating the coupling nuclei.

(3) Peptides: (a) Blake, P. R.; Park, J. B.; Adams, M. W. W.; Summers, M. F. *J. Am. Chem. Soc.* **1992**, *114*, 4931−4933. (b) Cordier, F.; Grzesiek, S. *J. Am. Chem. Soc.* **1999**, *121*, 1601−1602. (c) Cornilescu, G.; Hu, J.-S.; Bax, A. *J. Am. Chem. Soc.* **1999**, *121*, 2949−2950.

(4) Nucleic acids: (a) Dingley, A. J.; Grzesiek, S. *J. Am. Chem. Soc.* **1998**, *120*, 8293−8297. (b) Pervushin, K.; Ono, A.; Fernandez, C.; Szyperski, T.; Kainosho, M.; Wuthrich, K. *Proc. Natl. Acad. Sci U.S.A.* **1998**, *95*, 14147−14151. (c) Dingley, A. J.; Masse, J. E.; Peterson, R. D.; Barfield, M.; Feigon, J.; Grzesiek, S. *J. Am. Chem. Soc.* **1999**, *121*, 6019−6027.

(5) Golubev, N. S.; Shenderovich, I. G.; Smirnov, S. N.; Denisov, G. S.; Limbach, H.-H. *Chem. Eur. J.* **1999**, *5*, 492−497.

(6) Shenderovich, I. G.; Smirnov, S. N.; Denisov, G. S.; Gindin, V. A.; Golubev, N. S.; Dunger, A.; Reibke, R.; Kirpekar, S.; Malkina, O. L.; Limbach, H.-H. *Ber. Bunsen.-Ges. Phys. Chem.* **1998**, *102*, 422−428.

(7) For a recent study of hydrogen bonding in the water dimer and ice, see: Ghanty, T. K.; Staroverov, V. N.; Koren, P. R.; Davidson, E. R. *J. Am. Chem. Soc.* **2000**, *122*, 1210−1214.

(8) Anet, F. A. L.; Bourn, A. J. R.; Carter, P.; Winstein, S. *J. Am. Chem. Soc.* **1965**, *87*, 5249−5250.

(9) Platzer, N.; Buisson, J.-P.; Demerseman, P. *J. Heterocycl. Chem.* **1992**, *29*, 1149−1153.

(10) The synthesis of diol **2** will be described in a separate paper.

(11) Two conformers, differing in the orientation of the secondary hydroxyl group, occupy the unit cell (Table 1). The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre.

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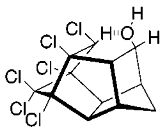
was traced to the proximity of the C−H to the hydroxyl oxygen lone pair. Intramolecular hydrogen bond-mediated scalar couplings have also been observed between peri OH/CHO groups in certain rigid aromatic systems.[9]



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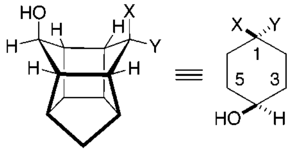

2: X = OH, Y = CH_3
5: X = H, Y = OH

The measurement of hydrogen bond-mediated scalar couplings has provided new structural constraints for conformational studies of proteins and nucleic acids. We became interested in extending the detection of ^{h}J to carbohydrates and hydroxyl-containing natural products. To this end, we have employed model compounds containing rigidly held 1,3- and 1,4-diols (**2**−**6**). We have discovered that scalar couplings across such OH/OH hydrogen bonds are readily observable using routine NMR techniques, and the magnitudes of the observed coupling constants are in general agreement with computed values.

Our initial evidence for these couplings came in a study of methyl cage compound **2**.[10] The structure of this compound was confirmed by X-ray diffraction analysis[11] and is shown in Figure 1.

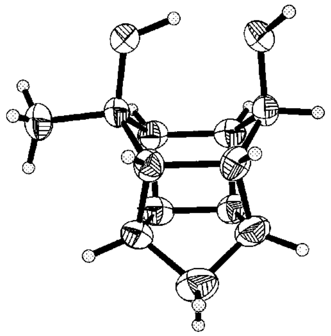

Figure 1. X-ray structure of diol **2** (unit cell structure a).

When this compound is dissolved in DMSO-d_6 containing a trace amount of exchangeable deuterium (CD_3OD), separate chemical shifts are observed for the OH/OH and OH/OD isotopomers (Figure 2A). In the case of diol **2**, an upfield isotope shift is observed upon partial deuteration. The isotope shifts are sufficiently large (+18.5 ppb for OH-4; +25.5 ppb for OH-1) so as to enable a direct comparison of line widths for a hydroxyl group bearing a proximal OH vs a proximal OD.

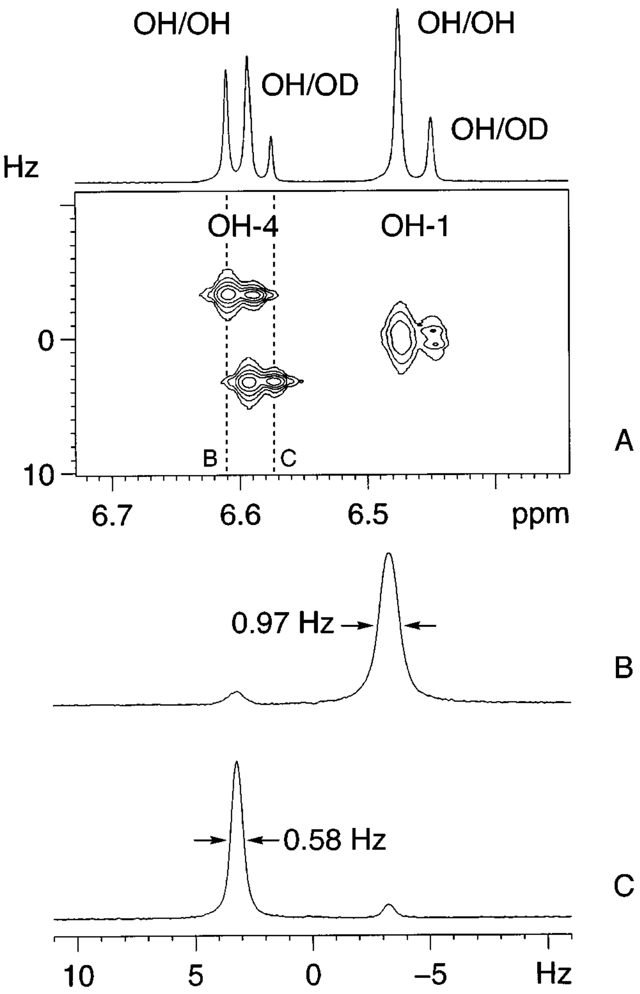

Figure 2. (A) 400 MHz ^{1}H 2D *J*-resolved data[12] for OH-4 and OH-1 chemical shifts for diol **2** dissolved in DMSO-d_6. Upper trace shows peak assignments for the OH/OH and OH/OD isotopomers for each hydroxyl group. (B) F_1 slice through the low-field portion of the OH-4 doublet corresponding to the OH/OH isotopomer; the measured line width at half-height is 0.97 Hz. (C) F_1 slice through the high-field portion of the OH-4 doublet corresponding to the OH/OD isotopomer; the measured line width at half-height is 0.58 Hz.

The 2D *J*-resolved experiment[13] was employed in order to examine the intrinsic multiplet line widths, i.e., in the absence of contributions from magnetic field inhomogeneity. As is evident from the *J*-resolved contours (Figure 2A), the multiplets associated with the OH/OD isotopomers are narrower than those associated with the OH/OH isotopomers. Analysis of F_1 slices associated with OH-4 revealed a line width of 0.97 Hz for the OH/OH isotopomer and 0.58 Hz for the OH/OD isotopomer. The increased line width (0.39 Hz) of the OH/OH isotopomer is attributed to scalar H−H coupling mediated by the hydrogen bond. This coupling should be reduced by the factor γ_D/γ_H (the ratio of gyromagnetic ratios) in the OH/OD isotopomer.[14] A spectral

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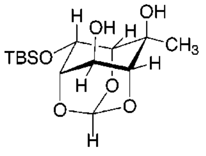
(12) Acquisition parameters used with a Bruker Avance 400 MHz spectrometer using the jres pulse program: F_2 sweep width, 2997 Hz; F_1 sweep width, 40 Hz. Digital resolution (F_2/F_1): 1.46/0.04 Hz/pt, 256 FIDs recorded, each consisting of 8 scans and 2048 data points. Processing parameters: unshifted sinusoidal apodization was applied in both dimensions prior to the Fourier transform. Zero-filling was employed to achieve 0.02 Hz/pt digital resolution in F_1. Experiment time: 190 min.

(13) Bax, A. *Two-Dimensional Nuclear Magnetic Resonance in Liquids*; Delft University Press: Delft, 1982.

simulation of slices B and C in Figure 2 revealed ^{h2}J to be on the order of 0.35 Hz.

Scalar couplings of this magnitude can be detected using a 2D COSY experiment modified with a delay to allow evolution of small or long-range couplings (2D COSYLR).[15] We have found it useful to run experiments with delays of 100, 200, and 400 ms in order to gain a qualitative sense of long-range couplings.[16] In cage diol **2**, for example, a distinct correlation between OH-1 and OH-4 was observed in all three experiments. An additional weak correlation between OH-1 and H-4 was observed in experiments using 200 and 400 ms delays; this coupling (^{h3}J) is very likely less than 0.2 Hz and likely transmitted via the hydrogen bond.



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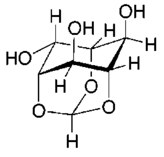

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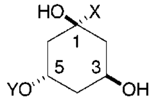


3: X=CH$_3$, Y=TBS
4: X=H, Y=H

Inositol derivative **3** was examined for similar effects. This compound was previously reported to exhibit downfield isotope shifts upon partial deuteration.[17] Using a comparison of 2D *J*-resolved line widths, we determined ^{h2}J to be 0.33 Hz (data not shown). A 2D COSYLR experiment using a 400 ms delay was used to study scalar coupling pathways in this 1,3-diaxial diol system (Figure 3). A correlation between OH-1 and OH-3 is clearly evident in these data (Figure 3, inset). All of the other hydroxyl-derived cross-peaks are due to four-bond couplings to ring hydrogens and the C-1 methyl group. In contrast with diol **2**, no correlation is observed between OH-1 and ring proton H-3.

We also performed 2D *J*-resolved and a series of COSYLR experiments on two control systems, *myo*-inositol monoorthoformate (**4**) and axial/equatorial 1,4-diol **5**.[19] Scalar coupling between the diaxial OH groups in **4** should not be observable due to the chemical shift degeneracy of these symmetry-related groups. Equivalent line widths (OH/OH vs OH/OD) were observed in isotopically perturbed 2D *J*-resolved experiments employing triol **4** in DMSO-d_6. Scalar couplings between the axial and equatorial OH groups (through six and seven bonds) were not observed in 2D COSYLR experiments with either triol **4** or diol **5**.

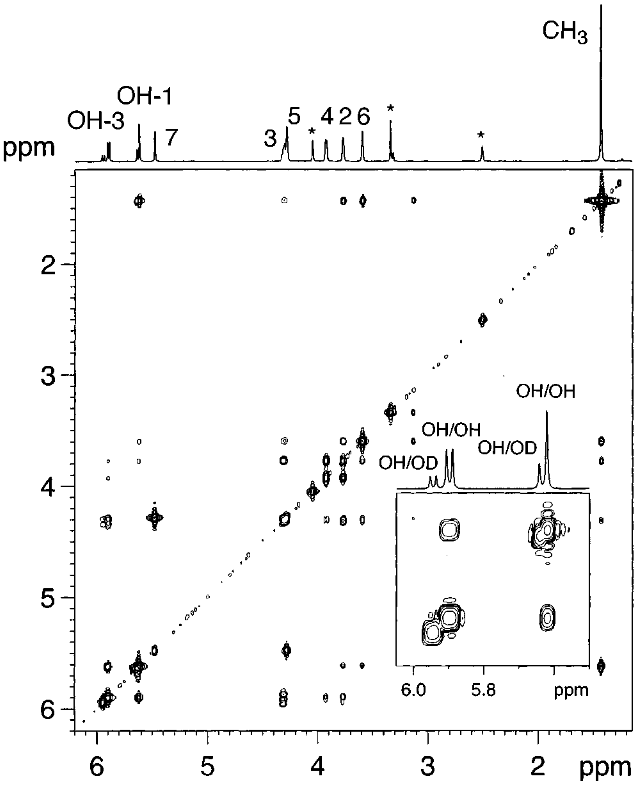
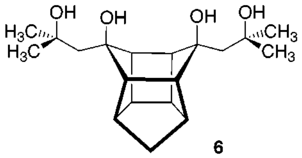


Figure 3. 400 MHz ^{1}H 2D COSYLR data[18] (400 ms delay) for inositol diol **3** in DMSO-d_6 (TBS resonances not shown). Asterisks denote ^{1}H signals arising from methanol, water, and dimethyl sulfoxide solvents (low to high field, respectively). Inset: expansion of hydroxyl resonances.

Using the COSYLR experiment, we have also observed scalar coupling between hydroxyl groups in an acyclic system (a correlation is observed between the inner and outer OH groups of tetrol **6** dissolved in DMSO-d_6, data not shown).



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To gain an understanding of the relative sign and magnitude of scalar couplings in systems such as these, we have used ab initio techniques to compute coupling constants for several geometries of the methyl cage diol (Table 1).[20,21] For diol **2**, ^{h2}J was computed for (i) the two unique unit cell conformers using the X-ray coordinates (hydrogen atoms located by Fourier difference mapping), (ii) a hybrid X-ray/

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(14) Given the viscosity of DMSO-d_6 and molecular weight of diol **2**, it is very likely that the deuterium spin states are sufficiently short-lived so as to provide spontaneous deuterium decoupling.

(15) Bax, A.; Freeman, R. *J. Magn. Reson.* **1981**, *44*, 542−561.

(16) COSYLR cross-peaks develop as a function of *J* and the spin−spin relaxation time T_2. See ref 15.

(17) For a discussion of the origin of these equilibrium isotope shifts, see: Craig, B. N.; Janssen, M. U.; Wickersham, B. M.; Rabb, D. M.; Chang, P. S.; O'Leary, D. J. *J. Org. Chem.* **1996**, *61*, 9610−9613.

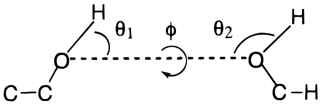
(18) Acquisition parameters used with a Bruker Avance 400 MHz spectrometer using the cosylr pulse program: F$_2$ and F$_1$ sweep widths, 2759 Hz. Digital resolution (F$_2$ and F$_1$): 2.69 Hz/pt, 256 FIDs recorded, each consisting of 8 scans and 1024 data points. Processing parameters: unshifted sinusoidal apodization was applied in both dimensions prior to the Fourier transform. Experiment time: 70 min.

(19) Diol **5** was synthesized according to an established procedure: Cookson, R. C.; Crundwell, E.; Hill, R. R.; Hudec, J. *J. Chem. Soc.* **1964**, 3062−3075.

(20) Structures were optimized at the MP2/6-31G* level of theory using Gaussian 94/98.

(21) The Fermi contact contributions to the scalar coupling constants were based on finite perturbation theory and were obtained from Gaussian 94 via the FIELD option. All coupling constants were computed by using the unrestricted DFT UB3PW91/6-311G** triple-split level with polarization functions on hydrogens and heavier elements. See: Onak, T.; Jaballas, J.; Barfield, M. *J. Am. Chem. Soc.* **1999**, *121*, 2850−.

Table 1. Structural Parameters and Computed OH/OH Coupling Constants for Cage Diol **2**. Note: Two Conformers, Differing in the Orientation of the Secondary Hydroxyl Group, Occupy the Unit Cell. Ab Initio Geometry Optimizations Are Reported for Two Structures Derived from Unit Cell Structure b



structure	r_{O-O} (Å)	θ_1	θ_2	ϕ	$\angle_{H-O-C-H}$	$\angle_{H-O-C-C}$	^{h2}J (Hz)
2, X-ray unit cell structure a	2.545	20.8	118.4	55.1	−51.1	−176.2	−0.1
2, X-ray unit cell structure b	2.542	19.2	124.3	−35.8	45.4	−175.4	−0.3
2, H only opt, MP2/6-31G*	2.542	11.4	111.6	−94.8	65.7	173.9	0.1
2, full opt, MP2/6-31G*	2.666	13.0	109.7	−87.3	67.3	175.3	0.2

ab initio structure computed by a hydrogen atom-only MP2/6-31G* optimization using the heavy atom X-ray coordinates for unit cell structure b, and (iii) unit cell structure b fully optimized at the MP2/6-31G* level of theory. The computed coupling constants were found to range from −0.3 to +0.2 Hz. Like other two-bond scalar couplings, it appears that OH/OH couplings can be either negative or positive.

Preliminary DFT/FPT calculations are consistent with the expectation that the coupling is dominated by the direct interactions between the OH bond pairs rather than an indirect interaction involving the lone pairs on oxygen.[22] Coupling between two bond pairs is characterized by the two internal angles θ_1 and θ_2, the dihedral angle ϕ, and the oxygen−oxygen interatomic distance r_{O-O}.[23,24] Differences in the computed ^{h2}J in Table 1 appear to correlate with the substantially different values of the dihedral angle ϕ inferred from X-ray versus ab initio results. Although the experimental and theoretical values reported here are indeed small in magnitude, calculations in model compounds derived from diol **2** give a calculated ^{h2}J value of −2.7 Hz if $\angle_{H-O-C-H}$ is decreased to 0°, which corresponds to $\phi = 0°$. It is worthwhile noting, in light of these theoretical results, that conformational averaging is likely to play a strong role in determining the sign and magnitude of hydrogen-bond mediated couplings in carbohydrate derivatives.

In conclusion, we have found that hydrogen bond-mediated scalar couplings can be used to detect intramolecular hydrogen bonds in 1,4- and 1,3-diols. Although small in magnitude, these couplings can be readily observed using standard 2D NMR techniques. Scalar couplings such as these can provide additional conformational constraints and assist in assignments of relative stereochemistry in carbohydrates and natural products. Current studies are directed at correlating theoretical and experimental scalar couplings and equilibrium NMR isotope shifts with hydrogen bond geometry. An account of this work will be reported in due course.

Acknowledgment. Work at Pomona College was supported by the National Science Foundation and the Camille and Henry Dreyfus Foundation.

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(22) Barfield, M.; Karplus, M. *J. Am. Chem. Soc.* **1969**, *91*, 1−10.
(23) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870−2871.
(24) Barfield, M.; Smith, W. B. *J. Am. Chem. Soc.* **1992**, *114*, 1574−1581.