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Predicted NMR Coupling Constants Across Hydrogen Bonds: A Fingerprint for Specifying Hydrogen Bond Type?

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Much has been written about the hypothesis of the formation of “low-barrier” hydrogen bonds and their role in enzymic catalysis.[1−7] However, experimental tests of this hypothesis are limited, although some hope exists for NMR coupling constants providing characteristic fingerprints for such hydrogen bonds.[8] Until recently, there were no sufficiently accurate methods available to predict quantum chemically what values would be anticipated for X−Y (heavy atom) coupling constants across X−H−Y hydrogen bonds, and whether coupling constant values could discriminate among the different types of hydrogen bonds. In the past few years we have developed coupled-cluster methods (EOM-CCSD) for NMR coupling constants which appear to be accurate to within a few percent by calibration with known examples,[9−13] and demonstrated reliability by reproducing the experimental FH and FF couplings in $[F(HF)_n]^-$ ($n = 1-4$) clusters, in contrast to the results of DFT calculations.[14] In this communication, we present predictions for coupling constants for the different prototype hydrogen bonds (traditional, proton-shared, and ion-pair) that can occur between the biochemically important nitrogen and oxygen atoms as a function of distance and H-bond types. This demonstrates that NMR fingerprints exist for different types of hydrogen bonds.

Traditional X−H···Y hydrogen bonds have normal (as opposed to short) intermolecular X−Y distances, an X−H distance slightly elongated relative to the X−H distance in the monomer, and a Y−H distance that is much longer than a normal covalent bond distance. Ion-pair $Y{-}H^+\cdots X^-$ hydrogen bonds are formed after proton transfer from X to Y. These have X−Y distances that are comparable to X−Y distances in traditional hydrogen bonds, long X−H distances, and Y−H distances slightly elongated relative to the Y−H distance in the corresponding cation. Intermediate between these two is the proton-shared X···H···Y hydrogen bond. This type is characterized by a short X−Y distance, and X−H and Y−H distances which are longer than the X−H distance in a traditional hydrogen bond, and the Y−H distance in a hydrogen-bonded ion pair, respectively. A special proton-shared hydrogen bond is the symmetric (or quasisymmetric) hydrogen bond in which the proton is equally shared between X and Y, which makes the forces on the proton from X and Y equal.[15,16] A study of coupling constants as a function of the ionic character in a bond will be presented elsewhere.[17]

Table 1. NMR Total and Fermi-Contact Coupling Constants (Hz) for Hydrogen-Bonded Atoms X and Y in X−H−Y Hydrogen Bonds[a]

complex	H-bond type[b]	R(X−Y), Å	total	Fermi-contact
$O_2H_5^+$	PS	2.38	39.54	39.92
$O_2H_3^-$	PS	2.44	16.28	17.96
O_2H_4	T	2.91	1.29	1.47
$^+H_2OH{:}NCH$	PS	2.47	34.12	34.07
HOH:NC$^-$	T	2.82	6.55	6.62
CNH:OH_2	T	2.84	8.51	8.57
HOH:NCH	T	3.13	1.16	1.14
$^+$HCNH:NCH	PS	2.52	32.52	32.46
CNH:NC$^-$	PS	2.58	21.52	21.47
CNH:NCH	T	3.00	5.62	5.60

[a] Coupling constants for ^{17}O and ^{15}N. [b] PS = proton-shared; T = traditional.

In this study we report EOM-CCSD NMR coupling constants[9,10] using a (qzp,qz2p) basis set[18] appropriate for chemical shifts[19] and coupling constants, calibrated for the latter.[10] These provide spin−spin coupling constants for hydrogen-bonded $^{17}O-^{17}O$, $^{15}N-^{15}N$, and $^{15}N-^{17}O$ atoms in 10 model complexes. These include examples of neutral, cationic, and anionic complexes, stabilized by either traditional or proton-shared hydrogen bonds. The complexes and their symmetries are shown in Table 1. No $^{17}O-^{17}O$ coupling constants have been measured experimentally because the O atom has a quadrupole moment. Quite recently an experimental observation of $^{15}N-^{15}N$ couplings has been reported for nucleic acid base pairs.[20]

The geometries of all complexes are optimized at second-order many-body perturbation theory [MBPT(2)][21,22] with a 6-31+G(d,p) basis set,[23−26] except for $O_2H_3^-$, in which case C_2 symmetry is imposed. The equilibrium structure of $O_2H_3^-$ has C_1 symmetry, but is only 0.2 kcal/mol more stable than the C_2 structure. Using the ACES II[27] program, the CI-like approximation[9] is employed to compute all of the terms (paramagnetic spin−orbit, diamagnetic spin−orbit, Fermi-contact, and spin-dipole) which contribute to the spin−spin coupling constant (J) as a function of the intermolecular X−Y distance in an X−H−Y hydrogen bond. For these calculations, all other coordinates were frozen, and the symmetry of the equilibrium structure was

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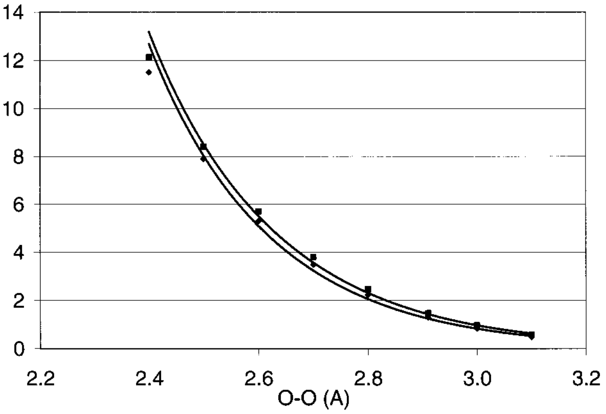

Figure 1. The distance dependence of the Fermi-contact contribution to the O−O spin−spin coupling constant in $O_2H_5^{+1}$ (▲), O_2H_4 (◆), and $O_2H_3^{-1}$ (■).

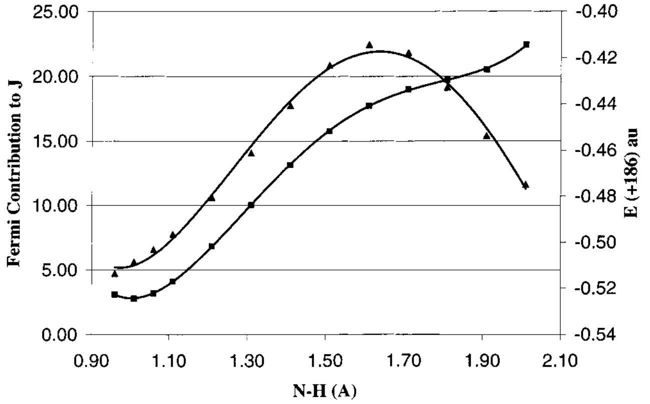

Figure 2. The total energy (■) and the Fermi-contact contribution to the N−N spin−spin coupling constant (▲) in CN_aH:N_bCH plotted against the N_a−H distance.

maintained. We have also examined the $^{15}N-^{15}N$ coupling constant in CN_aH:N_bCH as a function of the N_a−H distance, while keeping all other coordinates frozen at their equilibrium values.

Table 1 reports the hydrogen bond type, the equilibrium intermolecular distance, the total coupling constant (*J*), and the Fermi-contact contribution to *J* for all complexes considered. It is apparent that the Fermi-contact term dominates *J*, independent of the charge on the complex and the heavy-atom separation. Moreover, the dominance of the Fermi-contact term evident in the equilibrium structures is observed at all intermolecular distances for each of the 10 model complexes. (This is not the case for HF and FF couplings in $[F(HF)_n]^-$ ($n = 1-4$) clusters.) Figure 1 shows the variation of the Fermi-contact term as a function of the O−O distance in $O_2H_5^+$, O_2H_4, and $O_2H_3^-$. Note the computed O−O distance in the $O_2H_3^-$ model is in excellent agreement with the crystal structure.[28] The dominance of the strongly distance-dependent Fermi-contact term in determining the total X−Y spin−spin coupling constant across a hydrogen bond has implications for structure determination by NMR. The variation of *J* with the charge on the complex can be seen from Table 1. The X−Y coupling constant is largest in the cationic complexes, being largest for O−O coupling in $O_2H_5^+$, the complex with the shortest intermolecular distance. The N−N coupling in $^+$HCNH:NCH, the cationic complex with the longest intermolecular distance, has the smallest coupling constant. All three of these complexes are stabilized by symmetric or quasisymmetric proton-shared hydrogen bonds that are characterized by very short intermolecular distances and low electron densities on the hydrogen-bonded proton.

The anionic species $O_2H_3^-$ and CNH:NC^- have moderate spin−spin coupling constants. These two complexes are also stabilized by proton-shared hydrogen bonds, and have short intermolecular O−O and N−N distances. The Fermi-contact term and total *J* for N−O coupling in HOH:NC^- are small relative to the other two anionic complexes. In this complex, the hydrogen bond is traditional with a relatively long intermolecular distance of 2.82 Å. All of the neutral complexes are stabilized by traditional hydrogen bonds with rather small X−Y coupling.

Figure 2 shows two plots for CNH:NCH, a complex with an equilibrium structure stabilized by a traditional $N_a-H\cdots N_b$ hydrogen bond. As the proton moves away from its equilibrium position near N_a toward N_b with the N−N distance held constant, the hydrogen bond changes from traditional to proton-shared to ion-pair. In Figure 2 the Fermi-contact contribution to the $^{15}N-^{15}N$ coupling constant is plotted against the N_a−H distance. As the proton moves from its position in the equilibrium structure through the region of the proton-shared hydrogen bond to the hydrogen-bonded ion pair, the Fermi-contact term increases to a maximum in the proton-shared region, then decreases as the ion-pair structure is approached. Note this behavior does not correlate with the stability of the complex, also plotted in Figure 2. Mulliken population analyses computed along this same coordinate indicate that the electron population on the hydrogen-bonded proton is at a minimum in the proton-shared region.

The data reported in this communication demonstrate that the spin−spin coupling constant across the hydrogen bond provides a "fingerprint" for hydrogen bond type. Moreover, at $R(NN) = 2.9$ Å, the computed $^{15}N-^{15}N$ coupling across the $N-H\cdots N$ hydrogen bond is 7.2 Hz, in excellent agreement with the observed NN couplings across $N-H\cdots N$ hydrogen bonds in adenine-uracil and guanine-cytosine base pairs,[20] suggesting that the distance between the atoms is the dominant factor in determining the value of the coupling constant. For the O−H−O systems, all values are predictive in the absence of experiment. Regarding the detailed role of the proton, for $O_2H_5^+$ if the proton is removed from the hydrogen bond, the O−O coupling constant decreases from 39.9 to 25 Hz, still quite large even for a through space interaction.

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