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$^1J_{CH}$ Correlates with Alcohol Hydrogen Bond Strength

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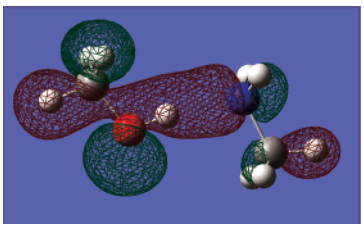
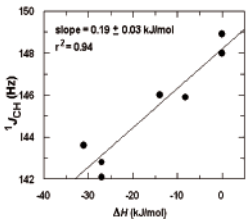


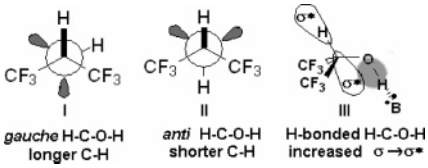


The strength of the H-bond donation by alcohols is reflected in the carbon−hydrogen bond of the H−C−O−H functional group. The one-bond $^{13}C-^{1}H$ spin−spin coupling constant of hexafluoroisopropanol (HFIP) correlates with the strength of the H-bond in various HFIP−amine complexes with a slope of ~ -0.2 Hz in $^1J_{CH}$ per $\sim$1 kJ mol^{-1} increase in the H-bond enthalpy. The decrease in $^1J_{CH}$ is attributed to an increased overlap of the H-bonding σ orbital with the antibonding σ^* orbitals of the vicinal C−H bonds.

Characterizing the contribution of H-bonding to intermolecular and intramolecular interactions is an important aspect of macromolecular chemistry and structural biology. Dissecting the contributions of O−H•• acceptor H-bonds is particularly difficult because of the absence of well-characterized spectroscopic probes that can be correlated with the strength of these interactions. Using hexafluoroisopropanol (HFIP) as the alcohol H-bond donor, we observe that the one-bond $^{13}C-^{1}H$ spin−spin coupling constant, $^1J_{CH}$, decreases $\sim$0.2 Hz per kJ of H-bond strength.

The effects of molecular structure on $^1J_{CH}$ have been grouped into five different contributions, the most prominent being negative hyperconjugation from lone electron pairs on heteroatoms α to the C−H bond (n → σ^*),[1] commonly manifested in $^1J_{CH}$ differences between aldopyranosyl ring anomers.[2] Experimental and computational work on 1,3-dioxanes indicate that a single antiperiplanar lone-pair on oxygen will result in a decreased $^1J_{CH}$ of $\sim$5 Hz.[3] The attribution of this effect to lone pair negative hyperconjugation has been challenged recently.[4]

CHART 1. Definition of Gauche (I) and Anti (II) H−C−O−H Torsions and a Simplified MO Representation of the Effect of H-Bonding on the C−H Bond Length Caused by Negative Hyperconjugation (III)



Negative hyperconjugation has been invoked to explain other stereoelectronic effects on H−C−O(N)−H bonds. This interaction is reflected in the vibrational spectra of conformationally defined amines[5] and in D−C−O−H functionalities that display two separate C−D stretching frequencies (ν_{CD})[6] arising from the gauche and anti conformations (Chart 1, **I** and **II**). Negative hyperconjugation decreases ν_{CD} of the gauche C−D bond. The decrease in ν_{CD} is correlated with a decrease in C−D bond strength and an increase in bond length in the gauche conformer.

Previous characterizations of ν_{CD} in (D)H−C_α−O−H systems by Raman spectroscopy and computational chemistry have shown that H-bond donation by primary and secondary alcohols will result in a decrease in $\nu_{CD(H)}$ for the anti and gauche conformers while both C_α−D(H) bond lengths increase. This effect was envisioned as arising from an increase in negative hyperconjugation from the delocalization of the electrons in the O−H bond (Chart 1, **III**). This increased negative hyperconjugation should be reflected in the bond length and $^1J_{CH}$ of C−H bonds α to hydroxyl groups serving as H-bond donors. We show that this phenomenon exists and can be substantial in the case of HFIP complexed with amines of varying basicity, permitting changes in $^1J_{CH}$ to be correlated with H-bond strength.

DFT calculations of $^1J_{CH}$ using the B3LYP functional[7] confirmed the potential of using $^1J_{CH}$ as a reporter for H-bonding. For methanol, these calculations reproduced the $^1J_{CH}$ Perlin effect[8] of 5 Hz in the absence of H-bonding. This effect increased to 6.0 Hz with quinuclidine as a H-bond acceptor (Figure 1), because $^1J_{CH}$ of the gauche and anti C−H bonds decreased by 3.3 and 2.3 Hz, respectively, relative to the couplings observed in methanol.

HFIP was chosen as an experimental system to examine the effect of H-bonding on $^1J_{CH}$ as a result of the presence of a single C−H bond and the previous success at determining a

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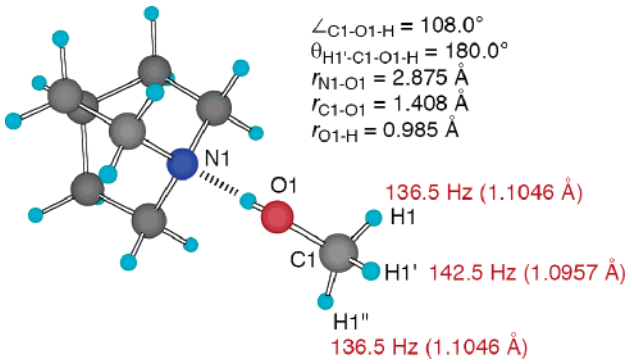

FIGURE 1. Ball-and-stick model of the DFT-optimized methanol−quinuclidine H-bonded complex. The increased C−H bond lengths and decreased $^1J_{CH}$ values of the methanol C−H bonds are shown in red, while structural parameters are shown beside the complex. Calculations were performed at the B3LYP/[5s2p1d,3s1p]//B3LYP/6-31G* level.[10]

TABLE 1. $^1J_{CH}$, ν_{CD}, and ΔH for HFIP−Amine H-Bonded Complexes

solvent	$^1J_{CH}$ (±0.1 Hz)	pK_a[a]	ν_{CD} (±1 cm^{-1})	ΔH[b] (± 2 kJ/mol)
toluene	148.0			
chloroform	148.9		2195	
dimethylaniline	145.9	5.1	2192	−8.2
N-methylmorpholine	146.0	7.4	2172	−14
N,*N*-diisopropyl-ethylamine	142.1	10.7	2174	−27
triethylamine	142.8	10.8	2164	−27
quinuclidine	143.6	11.0	2168	−31

[a] pK_a of conjugate acid in aqueous solution, obtained from ref 14. [b] Enthalpy of H-bond formation measured by isothermal titration calorimetry.

correlation between H-bond strength and ν_{CD} in [2-D]HFIP.[9] $^1J_{CH}$ was measured under conditions where HFIP was complexed to tertiary amines of varying basicity by dissolution in the amine as solvent. The 140−150 Hz coupling constants could be determined accurately from ^{1}H-coupled ^{13}C NMR spectra (Figure S1).

Table 1 reports the decrease in $^1J_{CH}$ as a function of the amine acceptor. These values are correlated with the enthalpy of H-bond formation determined by isothermal titration calorimetry and the decrease in the C−D stretching frequency for the anti C−D in the analogous [2-D]HFIP−amine complex.[9] The decrease in $^1J_{CH}$ is strongly correlated with the enthalpy of formation (Figure 2), where the slope of the correlation is a 0.2 Hz decrease for each kJ/mol increase in the negative enthalpy of H-bond formation.

The variation in $^1J_{CH}$ of ∼7 Hz is comparable to other perturbations of $^1J_{CH}$ arising from lone electron pairs on vicinal heteroatoms or other conformational effects.[1a,3a,10,11] However, the observed effect cannot be attributed solely to changes in the C−O rotamer populations of HFIP. The relative intensities of the Raman gauche and anti ν_{CD} bands of [2-D]HFIP in the same H-bonded complexes suggests that the gauche form is favored in all of the complexes,[9] which limits the potential contribution arising from changes in conformer population to less than 2.5 Hz.

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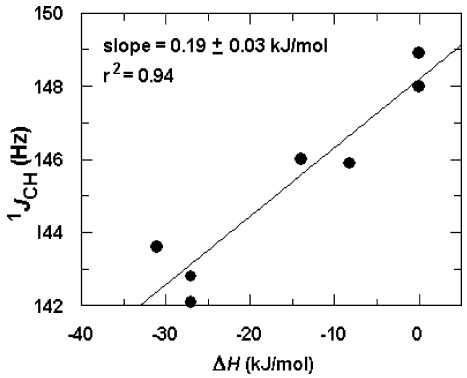

FIGURE 2. Variation of $^1J_{CH}$ with H-bond strength in HFIP−amine complexes determined by isothermal titration calorimetry.

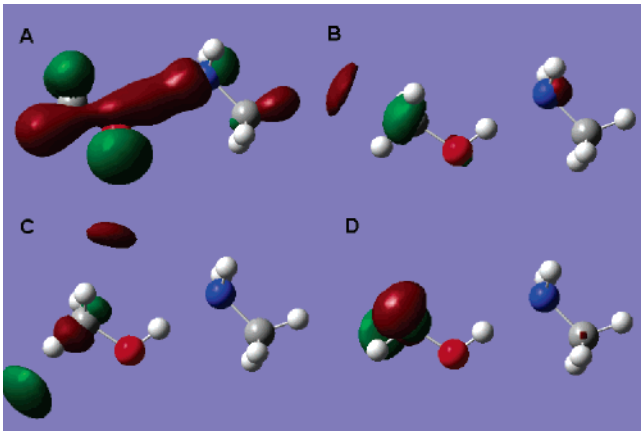

FIGURE 3. Molecular orbitals of a methanol−methylamine H-bonded complex contoured at 0.045 au generated by Gaussview 3.09. (A) The H-bonding orbital is identified by the continuous electron density encompassing the O−H−N bond axis. (B) The symmetric σ^* C−H antibonding orbital and the methanol LUMO. (C) The anti σ^* orbital. (D) The gauche σ^* orbital. A visual superposition of the bonding orbital with the σ^* orbitals suggests that this overlap accounts for the increased length of the C−H bonds and the accompanying changes in spectroscopic properties that accompany H-bond formation.

Both the decrease in ν_{CD} for the gauche rotamer in the H-bonded complexes and the calculated decrease in $^1J_{CH}$ for C−H bonds both gauche and anti to the H-bond suggest that there are electronic contributions besides the negative hyperconjugation with the anti C−H bond suggested in Chart 1 (**III**). H-bond formation can be viewed as a donation of electron density from the lone pair of the H-bond acceptor into the LUMO of the H-bond donor. The bonding orbital encompassing the O−H−N axis of a methanol−methylamine complex is shown in Figure 3A. This electron density overlaps with the three C−H σ^* orbitals (Figure 3B−D) calculated at the B3LYP/6-31+G(*d*,*p*) level in *Gaussian* 03.[12] This overlap results in a decrease in the bond order reflected in the spectroscopic and structural properties of the H-bond donor. Increasing H-bond strength results in greater electron density in the bonding orbital and, hence, in the overlap, producing the correlation between H-bond enthalpy and $^1J_{CH}$.

Recognizing that the strength of H-bond donation affects $^1J_{CH}$ may contribute to the characterization of molecular interactions and conformational analysis of sugars, nucleotides, and other oxygen nucleophiles present in macromolecular complexes.

Multidimensional NMR methods are available to permit the precise measurement of $^1J_{CH}$ in ^{13}C-labeled macromolecules.[13]

Both C−O bond conformation and H-bonding contribute to observed $^1J_{CH}$ values, and, thus, if one contribution is known, the other may be estimated. In cases where the conformation of a $^1H-^{13}C-O-H$ fragment is known from crystallographic data or other NMR parameters, the determination of $^1J_{CH}$ should provide insight into the strength of the H-bonds formed by the alcohol.

Experimental Section

Determination of $^1J_{CH}$. HFIP solutions (1 M) in the tertiary amine solvents or an equimolar HFIP/amine solution in $CHCl_3$ were prepared, and proton-coupled ^{13}C NMR spectra were acquired at 150.861 MHz. Data were recorded using a 40 000 Hz sweep width, 4.2 ms acquisition time, and a 4.3 s interpulse delay. D_2O in a sealed capillary was used as the lock standard. Typical spectra are presented in Supporting Information as Figure S1.

Isothermal Titration Calorimetry. The enthalpy of H-bond formation was measured at 24 °C by the addition of HFIP in $CHCl_3$ to solutions of the amines in $CHCl_3$ in an isothermal titration calorimeter. Experimental details were reported previously.[9]

Computational Methods. H-bonded complexes were optimized at the B3LYP/6-31G(*d*) level and the *J*-couplings were calculated using *Gaussian* 03[12] and an extended basis set [5*s*2*p*1*d*|3*s*1*p*].[11]

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Supporting Information Available: ^{13}C NMR spectra of HFIP in toluene and trimethylamine and Cartesian coordinates for MeOH−base H-bonded complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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