Theoretical Investigation of the Relationship between Proton NMR Chemical Shift and Hydrogen Bond Strength

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Hartree−Fock, Møller−Plesset, and DFT (BLYP, B3LYP) calculations have been carried out using the 6-31+G(d,p) basis set to study the relationship between calculated ^{1}H NMR chemical shifts and calculated hydrogen bond strengths in several model low-barrier hydrogen bond complexes. For both the formic acid-substituted formate anion and enol-substituted enolate anion model systems, we find an excellent linear correlation between calculated hydrogen bond strength and predicted ^{1}H NMR chemical shift, with an average slope of 1.5 kcal/mol per ppm chemical shift.

Introduction

There has been a great deal of interest and debate recently concerning whether low-barrier hydrogen bonds (LBHBs) are important in the chemistry of enzyme catalysis.[1−22] There is considerable evidence that short-strong hydrogen bonds (SSHBs) and possibly LBHBs may be important during the reaction catalyzed by Δ^5-3-ketosteroid isomerase.[1,2b] Additional experimental evidence in favor of the importance of LBHBs during enzyme catalysis has been presented by Gerlt et al. in two very recent reviews.[3] Computational and gas-phase experimental work[4] has also shown that LBHBs (also known as Speakman[5]−Hadzi[6] hydrogen bonds) can readily exist in the gas phase.[4] Condensed-phase work has shown that for the most part LBHBs do not survive in protic or very polar solvents. More recent studies in several aprotic solvents have shown quite convincingly, however, that SSHBs can form in solution, but their stabilities are highly solvent-dependent.[7−10]

It has been suggested by several researchers, most notably Kreevoy,[11] Cleland,[11a,12] and Gerlt,[13] that much of the energy required during a typical enzyme catalytic event can be provided via the formation of one short-strong or possibly low-barrier hydrogen bond involving either the transition state or an energetically similar reactive intermediate.[11−14] The formation of an LBHB can, in principle, supply 10−15 kcal/mol of catalytic energy per enzymatic cycle.[15,16] This is more than enough

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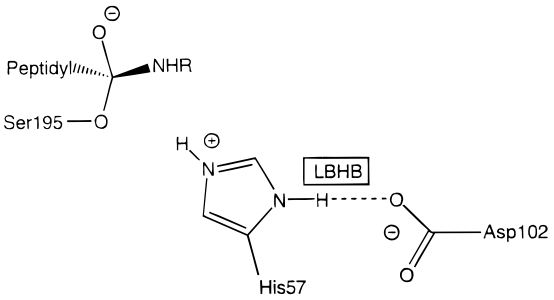
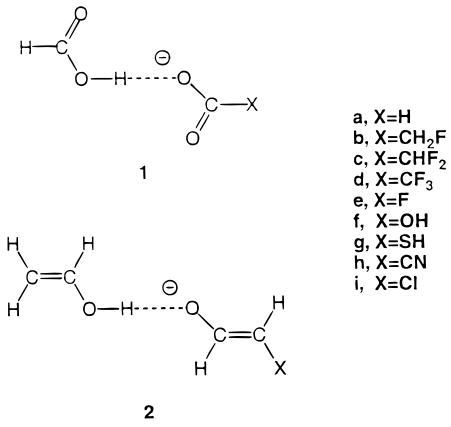
Scheme 1



Scheme 2



energy to account for most of the catalysis observed during many enzymatic processes. This hypothesis has been rebutted by several researchers, including Kluger,[17a] Guthrie,[17] Warshel,[18] and others.[9,10,19]

One of the unique characteristics of an LBHB is an incredibly deshielded proton resonance in NMR spectra. LBHBs with proton chemical shifts as far as 20 ppm (relative to TMS) are not uncommon.[15a] Frey and coworkers, in a series of elegant experiments over the last several years, have used this criteria for characterizing LBHBs as the basis for suggesting a new mechanism for the action of serine proteases.[14] In their mechanism, an LBHB is formed between the His57 and Asp102 residues of the active site as the reaction proceeds to form the tetrahedral intermediate necessary to hydrolyze the peptide bond (Scheme 1). Their experimental evidence includes ^{1}H NMR spectra with resonances in the 18−19 ppm region.[14] They attribute this signal to the proton involved in the purported LBHB between His57 and Asp102. Additional studies of this system with various inhibitors led to a shifting of the LBHB proton signal, sometimes upfield, sometimes downfield. This shifting was interpreted as being a function of the LBHB strength. To our knowledge, however, no one has ever actually determined the relationship between strength of an LBHB and NMR chemical shift. On the other hand, there have been several empirical studies of the relationship between hydrogen bond length (from X-ray crystal studies) and proton NMR chemical shift.[21c]

Over the past several years, we have been interested in the study of SSHBs, using high level ab initio and density functional theory (DFT) calculations.[22] We now extend those studies to the investigation of the relationship between proton NMR chemical shift and SSHB strength. In two very recent papers,[22h,i] we have shown that there is a predictable and determined relationship between the strength of an SSHB and the pK_a's of the hydrogen bond donor and hydrogen bond acceptor. Studies of both the hydrogen biformate[22h] and enol−enolate anion[22i] systems (Scheme 2) have shown that there is a linear dependence between SSHB strength and varying pK_a of the donor/acceptor complex. Thus, not surprisingly, when the pK_a values of the hydrogen bond donor and acceptor are perfectly matched, the LBHB is the strongest possible; on the other hand, as the substituents are altered so as to cause a mismatching (or unbalancing) of the two pK_a's, a weaker SSHB is formed, in a linear, predictable fashion. By calculating NMR chemical shifts for the proton involved in each SSHB of these systems, we can reliably determine the actual relationship between chemical shift and SSHB strength.

Methodology

Geometries for compounds **1a**−**i** and **2a**−**i** were fully optimized using the standard 6-31+G(d,p) basis set.[23] Geometry optimizations were carried out at several levels of theory: Hartree−Fock (HF), Møller−Plesset many-body perturbation truncated at the second order (MP2), and using density functionals (DFT).[24] The density functionals that were chosen for this study were BLYP and B3LYP. BLYP is a gradient-corrected nonlocal functional incorporating the 1988 Becke exchange functional[25] and the correlation functional of Lee−Yang−Parr (LYP).[26] B3LYP is a hybrid functional made up of Becke's exchange functional, the LYP correlation functional, and a Hartree−Fock exchange term.[27] These functionals were used as supplied in the Gaussian 94 suite of programs.[28] These methods have proven reliable in several previous studies of LBHB systems.

NMR chemical shifts were calculated using the gauge-independent atomic orbital method (GIAO),[29] as found in the Gaussian 94 program. The 6-31+G(d,p) basis set was used for all NMR calculations.

Hydrogen bond strength (E_{HB}) is defined as the difference in energy between each complex (**1a**−**i**, **2a**−**i**) and the infinitely separated monomers, as appropriate for each system. For instance, the E_{HB} of complex **1e** is calculated as the difference in calculated internal energy be-

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Table 1. Calculated Hydrogen Bond Distances (Å) for Formic Acid-Substituted Formate Anion (X) Complexes (1a−i) Using the 6-31+G(d,p) Basis Set

	level of theory							
	HF		MP2		BLYP		B3LYP	
X	O···H	O···O	O···H	O···O	O···H	O···O	O···H	O···O
H	1.504	2.521	1.258	2.427	1.230	2.460	1.262	2.434
CH_2F	1.531	2.539	1.379	2.468	1.353	2.483	1.356	2.460
CHF_2	1.578	2.576	1.439	2.501	1.419	2.514	1.412	2.499
CF_3	1.615	2.606	1.485	2.531	1.467	2.542	1.460	2.517
F	1.600	2.593	1.476	2.523	1.452	2.530	1.449	2.509
OH	1.531	2.538	1.376	2.463	1.346	2.477	1.346	2.454
SH	1.618	2.608	1.472	2.521	1.469	2.541	1.466	2.521
CN	1.652	2.637	1.512	2.550	1.500	2.564	1.494	2.541

Table 2. Calculated Hydrogen Bond Distances (Å) for Enol-Substituted Enolate Anion (X) Complexes (2a−i) Using the 6-31+G(d,p) Basis Set

	level of theory							
	HF		MP2		BLYP		B3LYP	
X	O···H	O···O	O···H	O···O	O···H	O···O	O···H	O···O
H	1.523	2.525	1.245	2.413	1.227	2.443	1.247	2.418
CH_2F	1.537	2.535	1.347	2.444	1.317	2.460	1.333	2.441
CHF_2	1.508	2.571	1.466	2.509	1.455	2.524	1.453	2.503
CF_3	1.611	2.593	1.472	2.513	1.458	2.525	1.455	2.504
F	1.530	2.530	1.352	2.456	1.316	2.458	1.331	2.440
SH	1.553	2.547	1.365	2.452	1.348	2.470	1.364	2.454
CN	1.656	2.630	1.506	2.538	1.490	2.545	1.496	2.530
Cl	1.577	2.566	1.398	2.468	1.389	2.487	1.397	2.470

Table 3. Calculated Chemical Shifts (δ, ppm, Relative to TMS) and LBHB Energies (E_{HB}, kcal/mol) for Substituted Formate Anions Hydrogen Bonded to Formic Acid (1a−i), Using the GIAO Method and the 6-31+G(d,p) Basis Set

	HF[a]		BLYP[b]		B3LYP[c]		MP2[d]	
X	δ	E_{HB}	δ	E_{HB}	δ	E_{HB}	δ	E_{HB}
H	17.4	22.2	23.2	26.9	23.0	27.2	23.0	26.9
CH_2F	16.6	21.2	20.9	24.4	21.5	25.2	21.4	25.0
CHF_2	15.5	19.4	19.4	22.6	20.0	23.2	20.0	23.1
CF_3	14.6	17.8	18.3	20.4	18.8	21.1	18.8	21.2
F	14.7	18.2	18.0	19.9	18.7	21.1	18.7	20.7
OH	16.3	21.2	20.6	24.6	21.2	25.4	21.2	25.0
SH	14.0	17.3	17.9	18.4	17.9	19.7	17.9	21.0
CN	13.7	16.3	17.4	19.2	17.9	19.7	17.8	20.2

[a] HF-GIAO/6-31+G(d,p)//HF/6-31+G(d,p). [b] HF-GIAO/6-31+G(d,p)//BLYP/6-31+G(d,p). [c] HF-GIAO/6-31+G(d,p)//B3LYP/6-31+G(d,p). [d] HF-GIAO/6-31+G(d,p)//MP2/6-31+G(d,p).

tween **1e** and the sum of the calculated energy of formic acid and the calculated energy of fluoroformate ($FCOO^-$)

Results

Calculated total energies and optimized geometries for all compounds studied (**1a**−**i**, **2a**−**i**) can be found in Tables S1−S8 of the Supporting Information. Tables 1 and 2 contain the important hydrogen bonding structural information for all compounds at the HF, MP2, BLYP, and B3LYP levels of theory. Tables 3 and 4 contain the results of our NMR studies, showing the calculated NMR chemical shift, relative to TMS, of the proton involved in each SSHB and the calculated SSHB energy. Table 5 reports calculated NMR chemical shifts for other representative compounds, using the same methodology and basis sets as above.

Figure 1 is a plot of calculated SSHB strength (E_{HB}, kcal/mol) versus the heteroatom−heteroatom internuclear distance for the two oxygens involved in the SSHB for the formic acid-substituted formate anion system (**1a**−**i**). Figure 2 is a similar plot for the enol-substituted enolate anion system (**2a**−**i**).

Table 4. Calculated Chemical Shifts (δ, ppm, Relative to TMS) and LBHB Energies (E_{HB}, kcal/mol) for Substituted Enolate Anions Hydrogen-Bonded to Enol (2a−i), Using the GIAO Method and the 6-31+G(d,p) Basis Set

	HF[a]		BLYP[b]		B3LYP[c]		MP2[d]	
X	δ	E_{HB}	δ	E_{HB}	δ	E_{HB}	δ	E_{HB}
H	15.1	25.0	21.6	29.8	21.8	30.0	21.8	30.2
CH_2F	14.6	24.2	20.5	28.4	20.2	28.7	19.8	29.0
CHF_2	12.9	21.4	17.1	23.4	17.1	24.3	16.7	24.5
CF_3	12.7	21.0	17.0	23.2	17.0	24.0	16.5	24.2
F	14.7	24.8	20.3	28.8	20.1	29.2	20.0	29.5
SH	14.0	23.6	19.7	27.1	19.3	27.6	19.3	28.5
CN	11.5	19.0	16.1	22.1	15.8	22.8	15.5	22.8
Cl	13.5	22.7	18.8	26.3	18.5	27.0	18.4	27.6

[a] HF-GIAO/6-31+G(d,p)//HF/6-31+G(d,p). [b] HF-GIAO/6-31+G(d,p)//BLYP/6-31+G(d,p). [c] HF-GIAO/6-31+G(d,p)//B3LYP/6-31+G(d,p). [d] HF-GIAO/6-31+G(d,p)//MP2/6-31+G(d,p).

Table 5. Calculated Chemical Shifts (δ, ppm, Relative to TMS) Using the GIAO Method and the 6-31+G(d,p) Basis Set

	δ (ppm)			
	HF[a]	BLYP[b]	B3LYP[c]	MP2[d]
HCOO*H*	5.7	6.6	6.4	6.6
CH_3COOH	5.5	6.3	6.2	6.3
CF_3COOH	6.2	7.4	6.6	7.1
$H_2C{=}CHOH$	2.8	3.4	3.3	3.4
$CF_3CH{=}CHOH$	3.4	4.1	4.1	4.0
$(HCOOH)_2$	10.5	14.4	14.0	13.0
$HCOOH{\cdots}NH_3$	11.4	15.2	14.9	14.6
$HCOOH{\cdots}^-OOCH$	17.4	23.2	23.0	23.0
H-maleate	17.5	23.6	23.2	23.4
$F{-}H{-}F^-$	19.3	19.1	19.2	19.3
*H*F	3.0	4.0	3.8	3.8

[a] HF-GIAO/6-31+G(d,p)//HF/6-31+G(d,p). [b] HF-GIAO/6-31+G(d,p)//BLYP/6-31+G(d,p). [c] HF-GIAO/6-31+G(d,p)//B3LYP/6-31+G(d,p). [d] HF-GIAO/6-31+G(d,p)//MP2/6-31+G(d,p).

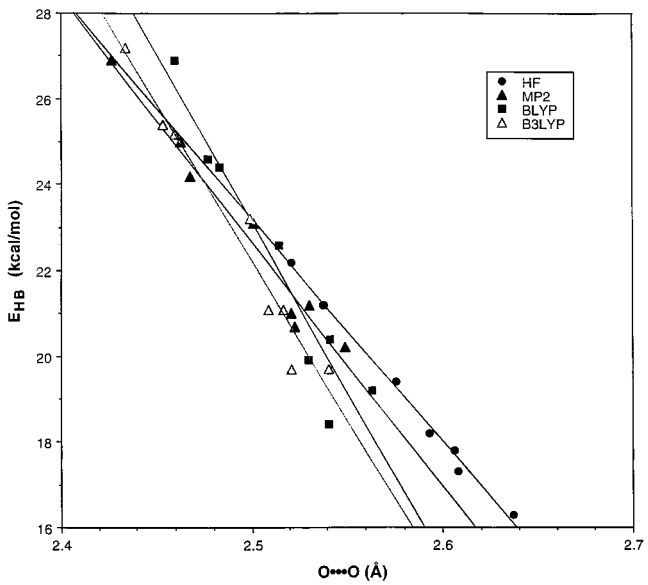

Figure 1. Plot of calculated interaction energies, E_{HB} (kcal/mol), versus calculated oxygen−oxygen distances (Å) for the formic acid-substituted formate anion (**1a**−**i**) hydrogen-bonded complexes using 4 levels of theory (HF, MP2, BLYP, and B3LYP).

Figure 3 is a plot of calculated E_{HB} versus ^1H NMR chemical shift (δ) for the hydrogen involved in the SSHB

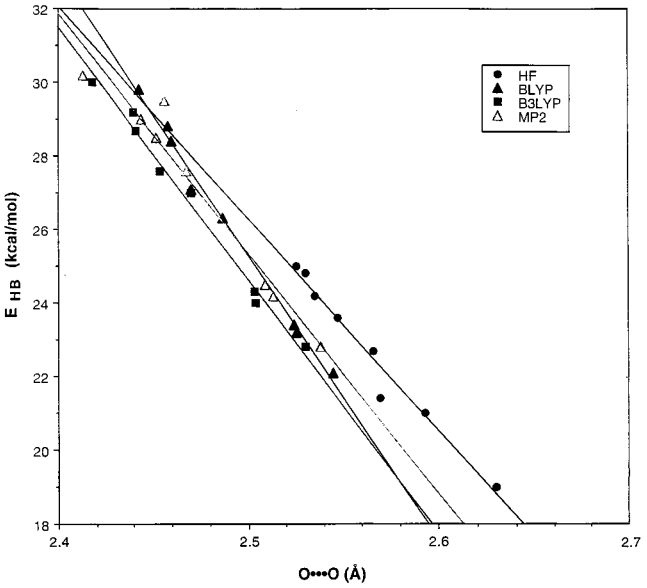

Figure 2. Plot of calculated interaction energies, E_{HB} (kcal/mol), versus calculated oxygen−oxygen distances (Å) for the enol-substituted enolate anion (**2a**−**i**) hydrogen-bonded complexes using 4 levels of theory (HF, MP2, BLYP, and B3LYP).

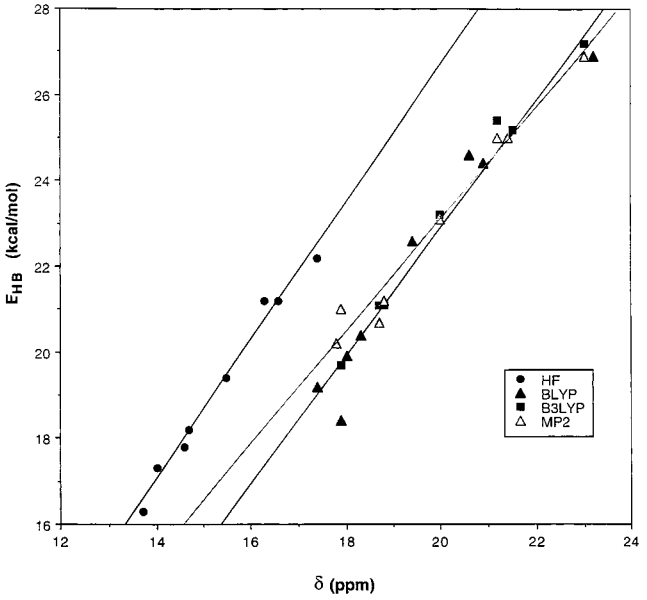

Figure 3. Plot of calculated interaction energies, E_{HB} (kcal/mol), versus calculated (HF-GIAO) ^{1}H NMR chemical shift (δ, ppm) for the formic acid-substituted formate anion (**1a**−**i**) hydrogen-bonded complexes using geometries optimized at four levels of theory (HF, MP2, BLYP, and B3LYP).

of the formic acid-substituted formate anion system. Figure 4 is a similar plot for the enol−enolate anion system. In each case, calculations from the four levels of theory (HF, MP2, BLYP, and B3LYP) employed in this study are presented.

Discussion

The data in Tables 1 and 2 and the linear correlations of Figures 1 and 2 clearly show the close relationship between hydrogen bond length and hydrogen bond strength in SSHBs. This is not surprising and has been elaborated upon in much more detail elsewhere.[22h,i] However, this relationship is important when considering

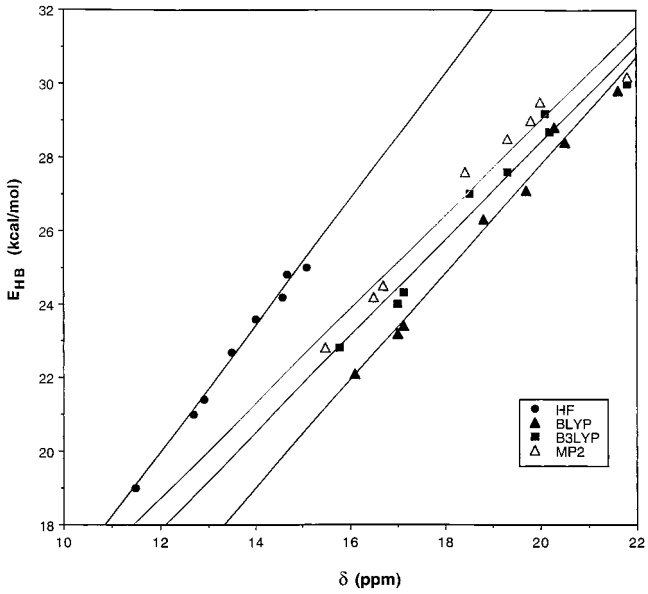

Figure 4. Plot of calculated interaction energies, E_{HB} (kcal/mol), versus calculated (HF-GIAO) ^{1}H NMR chemical shift (δ, ppm) for the enol-substituted enolate anion (**2a**−**i**) hydrogen-bonded complexes using geometries optimized at four levels of theory (HF, MP2, BLYP, and B3LYP).

the effect of SSHB strength on calculated NMR chemical shifts and thus is presented here for the sake of completeness. In Figure 1 the linear least-squares fit had a correlation of $r = 0.997$, 0.984, 0.957, and 0.980 for the HF, MP2, BLYP, and B3LYP calculated energies and geometries. In Figure 2 this correlation is $r = 985$, 0.996, 0.994, and 0.977 for the HF, BLYP, B3LYP, and MP2 optimized structures, respectively. These excellent correlations certainly bear witness to the inherent close relationship between SSHB length and SSHB strength.

The results in Tables 3 and 4 (and Figures 3 and 4) also suggest that there is a linear relationship between SSHB strength and SSHB NMR chemical shift. The correlations in Figure 3 (formic acid-substituted formate anion system, **1a**−**i**) are $r = 0.992$, 0.973, 0.9995, and 0.987 for calculations at the HF, BLYP, B3LYP, and MP2 levels of theory, respectively. Similarly, from Figure 4 (enol-substituted enolate anion system, **2a**−**i**), the correlations are $r = 0.995$, 0.994, 0.983, and 0.977 for calculations at the HF, BLYP, B3LYP, and MP2 levels of theory, respectively. The average slope from Figure 3 is 1.55 kcal/mol per ppm, and the average slope from Figure 4 is 1.45 kcal/mol per ppm. Thus, one can conclude that within any family of similar substrates, a ^{1}H NMR chemical shift of 1 unit downfield implies an approximately 1.5 kcal/mol stronger SSHB. Similarly, if the NMR resonance shifts upfield, this can be interpreted as a decrease in SSHB strength, by the same 1.5 kcal/mol per ppm.

Care must be taken, however, when comparing chemical shifts in structurally unrelated compounds. For instance, although this study uses a common set of substituents for the study of both the formic acid−formate anion and enol−enolate anion systems, the range of both hydrogen bond energy and calculated chemical shifts are somewhat different. Thus, while the correlation between hydrogen bond strength and chemical shift remains strong, the absolute values of calculated ^{1}H chemical shifts are different for the different systems.

To illustrate this point, one can look at Table 3 and find a calculated ^{1}H NMR chemical shift for **1c** (X = CHF_2) of 20.0 at the B3LYP level of theory and compare this to compound **2e** (X = F) in Table 4, which shows a δ of 20.1 at the B3LYP level of theory. These calculated NMR shifts are practically identical at the same level of theory, yet **1c** (which is part of the formic acid−formate anion series) has a calculated hydrogen bond energy of 23.2 kcal/mol, whereas **2e** (part of the enol−enolate anion system) has an E_{HB} of 29.2 kcal/mol at the same level of theory. Clearly, the SSHB chemical shift is sensitive to more than just the strength of the hydrogen bond itself. Other local factors such as charge delocalization and polarization are presumably quite important in determining the exact chemical shift resonance. Hence, it is apparent that one cannot easily use NMR chemical shifts to garner *absolute* bond strengths directly, but *relative* hydrogen bond strengths are readily obtained from the derived correlation of Figures 3 and 4 (1.5 kcal/mol per ppm chemical shift) presented here.

Table 5 presents some interesting comparisons between the calculated ^{1}H NMR chemical shift of various isolated hydrogens, hydrogens involved in a neutral H-bond, and hydrogens involved in an ionic (short, strong) H-bond. Using HF-GIAO/6-31+G(d,p) calculated NMR chemical shifts from B3LYP/6-31+G(d,p) optimized geometries (Table 5), an isolated formic acid molecule is predicted to have a δ (HCOO*H*) of 6.4 ppm. Dimerization of formic acid (as occurs experimentally) leads to a shifting of the proton resonance in (HCOO*H*)$_2$ to 14.0 ppm. Similarly, hydrogen bonding formic acid to an ammonia molecule has a similar though larger effect on chemical shift, leading to a δ of 14.9 ppm. Clearly, an external hydrogen bond to a proton tends to move the NMR resonance downfield. This is further exemplified by the ionic complexes of hydrogen biformate, hydrogen maleate, and hydrogen bifluoride, which exhibit calculated proton NMR shifts of 23.0, 23.2, and 19.2 ppm, respectively, for the hydrogen-bonded proton in each complex. Comparison to experimental NMR values is possible for both the hydrogen maleate and hydrogen bifluoride systems. Experimentally these chemical shifts are 20.5 and 16.4, respectively.[15a] Although the calculated numbers here are slightly larger than those found experimentally (due to the effect of solvent), they are certainly close, and more importantly, the relative shifts match experiment perfectly. Even though the *absolute* values of δ for both hydrogen maleate and hydrogen bifluoride are too high, they are too high by exactly the same amount, suggesting again that *relative* differences in calculated NMR chemical shifts are very accurate.

Finally, it is important to note that there is a difference between an LBHB and an SSHB, though we have largely ignored that point here (for a more detailed discussion please see ref 22f). Specifically, true LBHBs are only formed in systems where the pK_a's of the proton donor and proton acceptor are very closely matched. For the systems in this study, that criteria is only satisfied for the symmetrically substituted parent systems (**1a**, **2a**). Thus, **1a** and **2a** exhibit true LBHB behavior: a double-minimum potential energy surface with a very small energy barrier for transfer of the proton from one minimum to another (less than the zero-point vibrational energy of the molecule). However, notice that these compounds lie perfectly on the slopes depicted in Figures 1−4. Thus, there is a smooth transition from SSHB to LBHB, with no special stability associated with the formation of a proper LBHB except to say that it has a unique potential energy surface. Thus, whether enzymes use LBHBs specifically or SSHBs in general is largely immaterial to the question of catalysis. The fact that short-strong ionic hydrogen bonds may form in regions of low dielectric within the enzyme active site could result in significant transition-state stabilization and, hence, catalysis.

Conclusions

Hartree−Fock, Møller−Plesset, and DFT calculations have been employed to investigate the relationship between the strength of a low-barrier hydrogen bond and the ^{1}H NMR chemical shift of the central hydrogen in such a structure. We have studied a series of substituted formic acid−formate anion (**1a**−**i**) and enol−enolate anion (**2a**−**i**) complexes. The calculated hydrogen bond energies in these complexes were found to vary from a low of 16.3 kcal/mol to a high of 30.2 kcal/mol, and the range in calculated proton NMR chemical shifts was from 11.5 to 23.2 ppm. We find that in general there is an excellent linear relationship between the strength of an SSHB and the associated proton NMR chemical shift. Thus, within a family of closely related structures, one can readily interpret changes in NMR chemical shift as being due to a strengthening or weakening of the SSHB interaction. Stronger SSHBs have more delocalized structures, which in turn lead to downfield NMR chemical shifts. A weakening of any SSHB will lead to a more localized structure and an upfield shifting of the associated NMR resonance. Furthermore, these changes are predictable via the linear relationship between SSHB strength and NMR chemical shift, as determined in this study. Thus, we find that on average a 1 ppm shifting of the ^{1}H resonance of an LBHB (or SSHB, in general) is due to a weakening (or strengthening, if the shift is downfield) of the SSHB by approximately 1.5 kcal/mol. Care must be taken, however, when attempting to compare SSHB proton NMR resonances between different classes of compounds. This analysis should prove useful in the future study of enzyme mechanisms by providing a direct link between NMR chemical shift *changes* and H-bond strengths.

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Supporting Information Available: Tables S1−S4 containing calculated total energies and Tables S5−S8 containing complete optimized geometries of all compounds studied (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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