Theoretical Prediction of Hydrogen Bond Strength for Use in Molecular Modeling

Monika Nocker,*,†,‡ Sandra Handschuh,‡ Christofer Tautermann,‡ and Klaus R. Liedl†

Theoretical Chemistry, Center of Molecular Biosciences, Faculty of Chemistry and Pharmacy, University of Innsbruck, Innrain52a, A-6020 Innsbruck, Austria, and Department of Lead Discovery, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Strasse 65, D-88397 Biberach/Riss, Germany

Received April 28, 2009

Hybrid density functional theory calculations are used to investigate the strength of hydrogen bonds of structurally different molecules in complex with a standard donor and acceptor in vacuo. B3LYP/aug-cc-pVDZ calculations with one angle constraint lead to excellent correlations with experimental data ($R^2 = 0.94$, $s_y = 0.45$ for acceptors and $R^2 = 0.77$, $s_y = 0.88$ for donors). Substitutions of aromatic systems by electron donating and -withdrawing groups show a reinforcement of the interaction when substituting an acceptor with electron donating groups and weakening by substitution with electron withdrawing groups. For donor systems the opposite effect can be observed. Drug design of novel ligands will be able to profit from the predictive power of the method established, as hydrogen bonds between receptor and drug molecules are an important criterion for binding affinities.

1. INTRODUCTION

Hydrogen bonds are of immense importance in biological systems.[1−3] Existence of protein's secondary structure,[4] DNA and RNA are due to this kind of force. H-bonds also play an important role for the ligand-protein binding process: They are responsible for direction and recognition of substrates and modifying the affinity to their binding partners.[5]

The development of new drugs is a very time-consuming process requiring a huge financial investment[6] and aiming for a high affinity and selectivity of the ligand's binding to its target.[7] To achieve high drug binding affinities either binding enthalpy and binding entropy must contribute favorable to binding since from a thermodynamic point of view the binding constant K_a is defined as

$$K_a = e^{-\Delta G/RT} \tag{1}$$

where T is the absolute temperature, R is the gas constant, and ΔG is the change in Gibbs free energy that in its turn is given by the equation

$$\Delta G = \Delta H - T\Delta S \tag{2}$$

Here ΔH and ΔS are the changes in binding enthalpy and binding entropy, respectively. Related to formula 2 it is clear that strong binding affinities can be reached either by a more negative ΔH, a more positive ΔS, or a combination of both.[8] At physiological conditions a change of 1.4 kcal/mol in Gibbs free energy ΔG leads to a 10-fold higher or lower equilibrium constant K_a as a result of the exponential relationship between these two thermodynamical properties[9] (see eq 1). The binding enthalpy itself depends on the interaction forces (van der Waals, hydrogen bonds, etc.) between the ligand and the target protein, while the binding entropy is made up of two main contributions: changes in solvation and conformational entropy. This is evidence of the fact that drug affinity is related not only to structural behavior (enthalpy) but also the dynamics (entropy) of the interacting species.[10] The simultaneous optimization of the enthalpy and entropy term is though a difficult goal to achieve, because it implies the overcoming of the so-called 'enthalpy/entropy compensation' phenomenon. This effect consists in an entropy loss contemporary to an enthalpy gain that can be understood when a ligand binds to its protein by establishing favorable interactions like hydrogen bonds but losing conformational freedom. Further the optimization of the binding enthalpy depending on various forces is very difficult, while the same optimization process for the binding entropy is easier to obtain because of its primary dependence on the hydrophobic effect. One strategy in drug design is therefore the generation of hydrophobic and conformationally constrained ligands.[11] Their binding affinity is entropically dominated, but binding enthalpy often shows an unfavorable contribution. Those ligands being constrained in their conformation cannot easily respond to binding site geometry changes, and so they are highly susceptible to drug resistance mutations or genetic polymorphism naturally occurring.[11] Also such compounds with entropically dominated binding show a significant improvement in binding affinity when an unfavorable binding enthalpy is eliminated. The importance of optimizing binding enthalpy during drug design is consequently clear. In this context hydrogen bonds play a key role in the gain of enthalpy. They are also crucial to improve selectivity as they are determined by strict geometric and distance constraints.[12]

An aim in drug design is therefore to modify the hydrogen-bonds strength between a ligand and a protein in order to achieve higher binding affinities but without any negative influence on other interactions contributing positively to binding established.[13]

* Corresponding author e-mail: m.nocker@uni-wuerzburg.de.
† University of Innsbruck.
‡ Boehringer Ingelheim Pharma GmbH & Co. KG.

10.1021/ci9001469 CCC: $40.75
Published on Web 08/31/2009

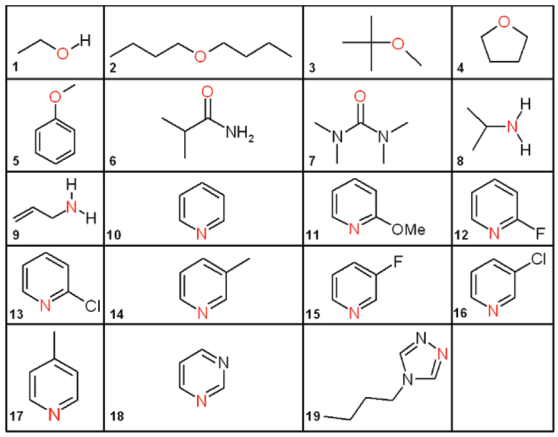

Figure 1. Structurally different acceptors studied in this work.

One way to accomplish this intention is to alter the chemical properties in the neighborhood of an existing H-bond by adding functional groups or to modify existing groups.[14,15]

These additions or modifications ideally are solvent exposed in the complex thereby ensuring minimal changes both in binding entropy and in the rest of the interactions of the drug and the protein, thus allowing to consider the binding energy instead of the binding free energy that would be strongly influenced by binding entropy changes due to chemical differences. Previous studies also dealt with the influence of chemically different substituents on the hydrogen bonds strength. Reynisson et al.[9] investigated the change in energy between p-substituted phenol and aniline as both hydrogen bond donor and acceptor toward two different H-bond donors (methanol and protonated methylamine) and H-bond acceptors (formaldehyde and acetate). Substituents chosen showed electron-donating and -withdrawing behavior evaluated by experimentally derived σ-Hammett constants. Correlations between these constants and calculated quantum-mechanical hydrogen bond energies (B3LYP/6-311+G (2df,2dp) with ZPE and BSSE correction) demonstrate excellent results.

Hao et al.[16] studied BSSE-corrected hydrogen bond strengths calculated with density functional theory B3LYP/6-31++G** in correlation with experimental hydrogen-bonding constants from isotherm titration calorimetry.[17] The method consists in fixing the nucleus position of three donor and three acceptor atoms (not part of the H-bond) during geometry optimization in order to avoid secondary interactions and gave a linear correlation with an R^2-value of 0.94.

In contrast to these supermolecular approach calculating optimized energies and interaction energies there also exist models trying to predict the H-bond strength directly from molecular structure. In these studies either just one descriptor $V_\alpha(r)$ at a distance r, defined as the electrostatic potential, is introduced as effective hydrogen bond acidity predictor[18] or various contributions to the hydrogen bond energy like electrostatic (Coulomb) contribution, polarizability, charge transfer component, dispersion energy, short-range exchange repulsion (due to donor and acceptor electron clouds overlap), and higher-order contributions associated with the donor−acceptor coupling[19] are analyzed. There exist such studies for both donor and acceptor molecules showing both very good predictability[19,20] handling with *ab initio* and density functional theory levels HF/6-31 g** and B3LYP/6-31G**.

In this work hydrogen bonds are calculated by development of a more general method avoiding lots of restraints basing on the supermolecular approach and use of Density Functional Theory (DFT), a well established method when dealing with this type of interactions[21−27] that in comparison with force-field derived hydrogen bond energies points out an underestimation of those in all studied force fields.[28] DFT expresses the electronic energy of a system in terms of its density[29] instead of using the many-electronic wave function and depends on the knowledge of the exchange correlation

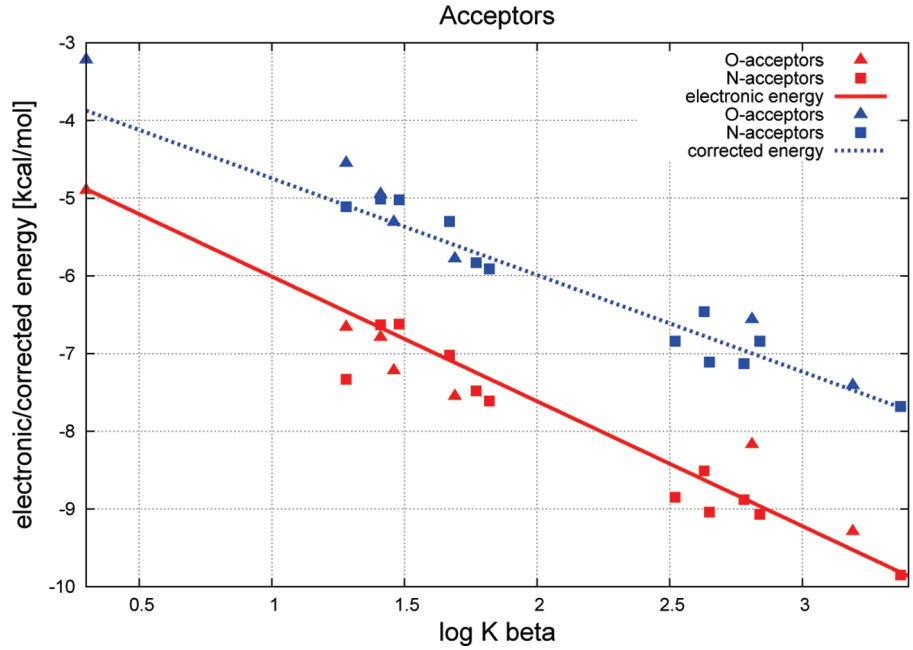

Figure 2. Correlation of the B3LYP/aug-cc-pVDZ calculated hydrogen bond energies for various acceptors in complex with the standard donor phenol. The upper line (blue dots, $R^2 = 0.94$) shows the correlation of the electronic energy with the experimental log K_β constants. The lower line (red dots, $R^2 = 0.95$) shows the correlation of the ZPE and BSSE corrected energy with the experimental log K_β constants.

Table 1. R^2-Values for Correlating B3LYP/aug-cc-pVDZ Calculated Hydrogen Bond Electronic and ZPE and BSSE Corrected Energy with Experimental Log K_β Constants for Acceptors in Complex with Standard Donor Phenol

R^2-values	ΔE_{HB}(electronic)	ΔE_{HB}(corrected)
all acceptors	0.94	0.95
O-compounds	0.94	0.96
N-compounds	0.93	0.95

Table 2. Energy Values for m- and p-Substituted Pyridine in Comparison with Unsubstituted Pyridine[a]

pyridine	ΔE_{HB}(uncorrected) [kcal/mol]
unsubstituted	−8.58
p-CH_3	−8.88
m-OCH_3	−8.66
m-NH_2	−9.13
p-NH_2	−9.66
m-Cl	−7.48
p-Cl	−7.81
m-F	−7.61
m-F	−7.94
m-NO_2	−6.44
p-NO_2	−6.63
m-CF_3	−7.11
p-CF_3	−7.23

[a] In kcal/mol. The horizontal line divides activating from deactivating groups.

energy functional for which different approximations can be used.[30] Interaction energies between structurally different acceptors and a common hydrogen bond donor as well as between different donors and a chosen hydrogen bond acceptor were examined by the use of the hybrid functional B3LYP and basis set aug-cc-pVDZ. Further calculations for investigating possible outliers were performed with the smaller 6-31+g* basis set and B3LYP as well as MPW1PW91 procedure. For comparison multilevel G3MP2B3 calculations with a high accuracy were performed.

Experimental data were obtained from Abraham et al.[17] Note that obtained thermodynamic constants of complex formation are free energies, while quantum-mechanical studies lead to enthalpies. A linear correlation of the two quantities implies that entropy changes are constant on hydrogen bond formation or are at least linearly depending on its strenghts.

Influence of electron-withdrawing and -accepting substituents on the aromatic systems phenol as H-bond donor and pyridine as H-bond acceptor is also elucidated using correlation with σ-Hammett constants.

2. METHODS

Quantum chemical calculations were carried out with the program package Gaussian03.[31] Theoretical determination of hydrogen bond energies is achieved by

$$\Delta E_{HB}(\text{uncorrected}) = E_{AD} - (E_D + E_A) \quad (3)$$

$$\Delta E_{HB}(\text{corrected}) = E_{AD} - (E_D + E_A) + \text{ZPE} + \text{BSSE} \quad (4)$$

where ΔE_{HB} is the interaction energy of bonding, E_{AD} is the energy of the geometry optimized complex, and E_D as well as E_A is the energy of the individual geometry optimized hydrogen bond donor and acceptor. In quantum chemical calculations correction of the Zero Point Energy (ZPE) and Basis Set Superposition Error (BSSE) is thought to be needed.[32]

The Zero Point Energy (ZPE) summarizes the electronic ground state energy for each nucleus' vibration considering them as harmonic oscillator.

The Basis Set Superposition Error (BSSE) is a systematic error when dealing with complexes formed by fragments.[33] It can be estimated with the so-called Counterpoise correction by Boys and Bernardi[34,35] that eliminates the error that arises from calculating complex and fragments with different basis sets.

The majority of the calculations in this study is executed with the Density Functional Theory using the hybrid functional B3LYP and the correlation-consistent basis set

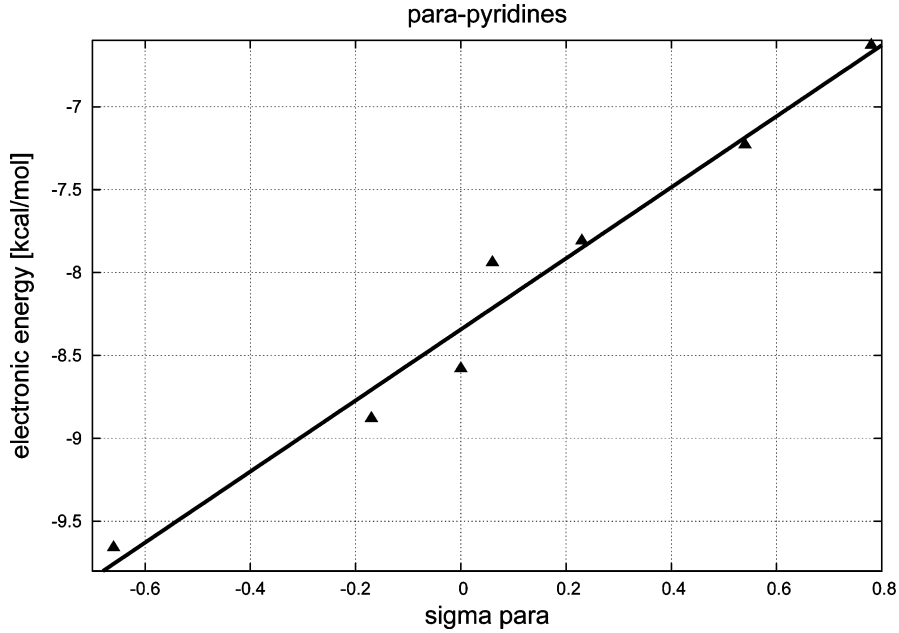

Figure 3. Correlation between the B3LYP/aug-cc-pVDZ calculated hydrogen bond electronic energy and σ_{para}-Hammett constants for p-substituted pyridine in complex with phenol, $R^2 = 0.96$.

Table 3. R^2-Values for Correlating Hydrogen Bond B3PLYP/aug-cc-pVDZ Energy and σ-Hammett Constants When Substituting Pyridine

substituted pyridine	m-substitution	p-substitution	m- and p-substitution
R^2-value	0.99	0.96	0.95

aug-cc-pVDZ. The geometries of all fragments and complexes have been preoptimized with the force field MMFF94s in MOE.[36]

Further calculations of hydrogen bond O-donors were performed with the smaller and therefore less CPU-time demanding 6-31+g* basis set. Additionally a series of O-donors was calculated using the modified Perdew−Wang functional MPW1PW91[37,38] and the smaller basis 6-31+g* in order to exclude the three parameter B3LYP functional as a reason for outliers and to narrow down possible experimental deficiencies.

For the same intention also high level-calculations (G3MP2B3)[39] were performed for a number of selected compounds including two outliers.

During the geometry optimization of the complex only one constraint, the fixing of one single angle, was applied. Due to this simple fixing method the number of imaginary frequencies was minimized. Therefore the hydrogen bond angle itself or an angle that includes an atom by one bond farther was fixed. The hydrogen bond angle for the calculated examples was nearly linear at about 175°. The hydrogen bond donor and acceptor themselves were energy minimized separately.

Experimental data to evaluate the prediction of hydrogen bond strength were taken from a publication by Abraham et al.[17] In the cited study Abraham measured the thermodynamic constant K_β and K_α of the hydrogen bond complex formation for 91 structurally different acceptors and 67 donors by isothermic titration calorimetry using a common

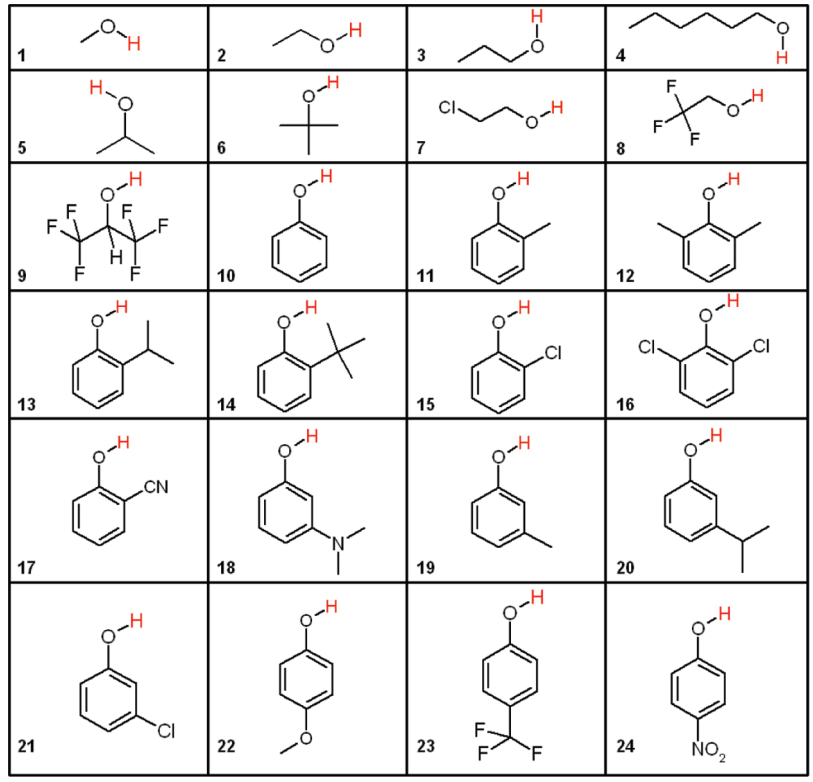

Figure 4. Structurally different O-donors studied in this work.

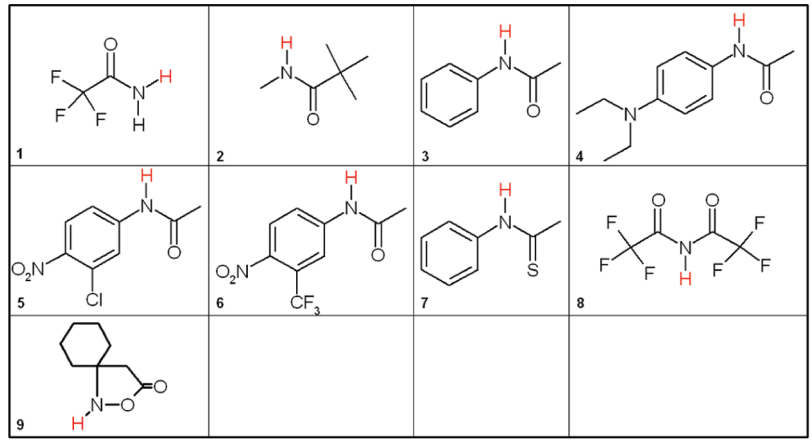

Figure 5. Structurally different N-donors studied in this work.

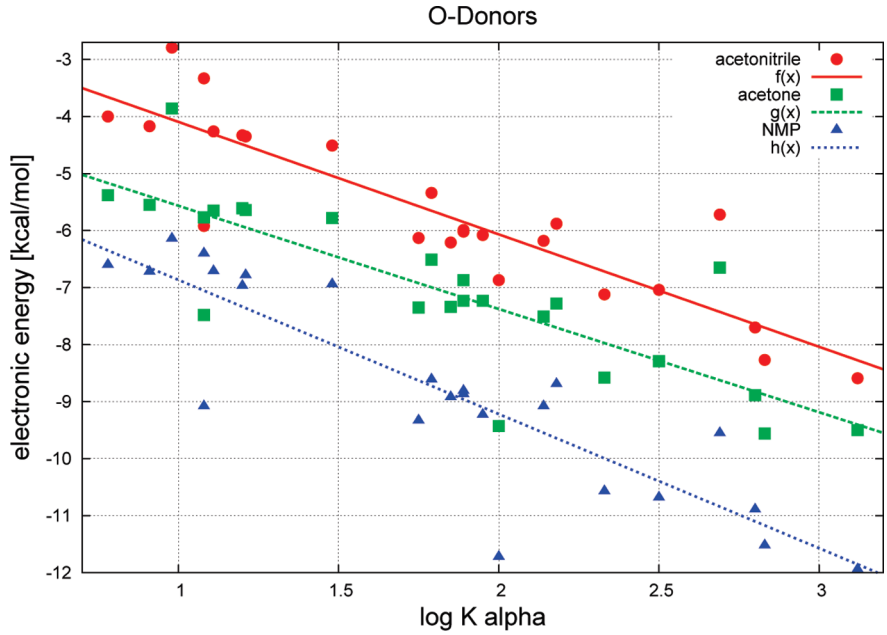

Figure 6. Correlation of the B3LYP/aug-cc-pVDZ calculated hydrogen bond electronic complex energies with the experimental log K_α constants for O-donors in complex with the standard acceptor NMP ($R^2 = 0.77$), acetone ($R^2 = 0.68$), and acetonitrile ($R^2 = 0.79$).

Table 4. R^2-Values for Correlating the B3LYP/aug-cc-pVDZ Calculated Hydrogen Bond Electronic and ZPE and BSSE Corrected Complex Energies with the Experimental Log K_α Constants for O-Donors in Complex with the Three Different Acceptors NMP, Acetone, and Acetonitrile

R^2-values	ΔE_{HB}(uncorrected)	ΔE_{HB}(corrected)
NMP	0.77	0.70
acetone	0.68	0.69
acetonitrile	0.79	0.78

hydrogen bond donor for measuring acceptors and a common acceptor for hydrogen bond donors. p-Nitrophenol was chosen as a standard H-bond donor, and N-methylpyrrolidinone was chosen as a standard H-bond acceptor. 1,1,1-Trichloroethane was used as solvent for the experiments. The dielectricity constant of 1,1,1-trichloroethane is 7.53 and is so a good model for real biological systems; it shows good solvent properties and above all chemical inertness with no tendency for hydrogen bond complex formations.

3. RESULTS AND DISCUSSION

3.1. Acceptors. As mentioned earlier hydrogen bond strengths were calculated for both H-bond donors and acceptors. First we will discuss the results obtained when dealing with H-acceptors. Figure 1 shows the structurally diverse acceptors examined in this study.

The calculated complex energies that have been corrected by BSSE and ZPE correlate with a R^2 of 0.95 with the experimental log K_β values. The uncorrected energies correlate with a nearly identically R^2 of 0.94. The calculated energies are provided in the Supporting Information. Figure 2 shows the resulting regression for the electronic and BSSE and ZPE corrected energy. Structurally similar compounds are marked by the same symbols.

Triangular symbols represent O-compounds (with an oxygen atom as H-bond acceptor atom like in ethers, alcohols, and carbonyl groups), while quadratic symbols are representing data from N-compounds (with a nitrogen atom as H-bond acceptor atom like in amines, pyridines, pyrimidine, and triazole). Data from one substance class spread over the four visible data clusters, and so each of them is not attributed to only one family of compounds.

Additionally the influence of different substituents on an aromatic acceptor system was examined in this study. Pyridine was chosen as hydrogen bond acceptor. The aromatic system was substituted in the meta and para positions by groups that belong to the known three different types of substituents from the theory of electrophile aromatic substitution: o-, p-directing activating (-CH_3, -OCH_3, and -NH_2), o-, p-directing deactivating (-Cl and -F)), and m-directing deactivating (-NO_2 and $-CF_3$). For the ortho position sterical hindrance is expected, and therefore ortho-substituted systems were excluded from the analysis. Also in these calculations phenol was chosen as the standard donor. B3LYP/aug-cc-pVDZ electronic energies were calculated because of previous results showing no improvement in R^2 for corrected energy and extreme CPU time saving, because no additional frequency calculations have to be performed.Table 2 shows the difference in hydrogen bond electronic energy between the substituted and the unsubstituted system. There is evidence for weakening of the H-bond strength by deactivating groups like halogens, -NO_2, and -CF_3 in relation to unsubstituted pyridine, while activating groups like -CH_3, -OCH_3, and -NH_2 are strengthening H-bond strength. The table also demonstrates either if the meta or para position is preferred when substituting with one type of group. It can be seen that o-, p-directing groups (-CH_3, -OCH_3, -NH_2, -Cl, and -F) lead to stronger H-bonds in the para position due to a higher electron density that causes strong acceptor behavior in this position. For m-directing groups (-NO_2 and -CF_3) a privileged meta position is expected but not obtained for a small value of energy (0.19 and 0.12 kcal/mol respectively). In the other substituent cases the difference between the m- and p-position's energy lies between 0.33 and 0.53 kcal/mol and is therefore higher.

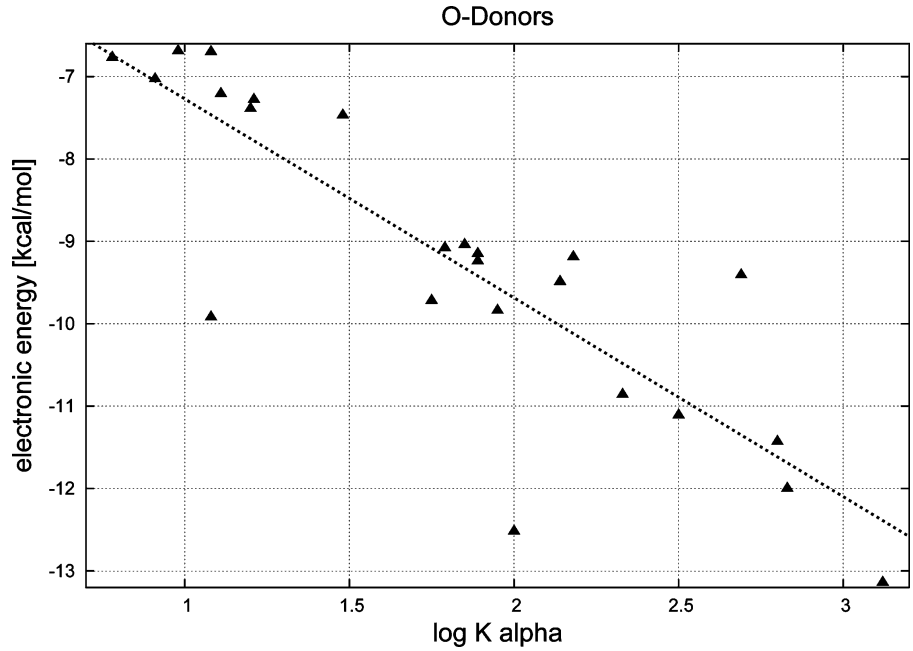

Figure 7. Correlation of the B3LYP/6-31+g* calculated hydrogen bond uncorrected complex energies with the experimental log K_α constants, $R^2 = 0.73$.

Electronic effects of substituents are characterized by the σ-Hammett constants.[40] These constants originate from experimental studies on benzoic acid. Nevertheless we tried to use these values for correlations with theoretically predicted hydrogen bond strength. As σ-values rank substituents due to their electron-donating and -withdrawing properties, respectively, it should be possible to bring them in relation with the effect that varying substituents provoke on hydrogen bond energies. Figure 3 shows the resulting plot when correlating hydrogen bond energy for para substituted pyridine and the σ_{para}-values. A linear correlation is evident ($R^2 = 0.96$). Table 3 completes the study on the substituent effects by listing R^2-values for meta-, para- and meta- and para-substitution.

The plot in Figure 3 shows a positive gradient that reveals electron-withdrawing groups (by definition with positive σ-Hammett constant) to lower hydrogen bond strength. Electron-donating groups cause the opposite in agreement with chemical intuition.

3.2. Donors. Hydrogen bond donors were divided right from the start into a group of substances involving an oxygen atom in the H-bond (these are O-donors comprising aromatic and aliphatic alcohols) and a group involving a nitrogen atom (these are N-donors comprising amides). The following schemes (see Figures 4 and 5) illustrate the structural diversity of the O- and N-donors.

The complexes were calculated using each donor and N-methylpyrrolidinone as standard acceptor. The method to obtain the complex energies was again B3LYP/aug-cc-pVDZ.

The comparison to the experimental values is shown in Figure 6. The resulting R^2-value is 0.77 when plotting the calculated data for the electronic energy against the experimental data and is therefore worse than for the acceptor case ($R^2 = 0.94$).

To rule out the steric influence of our chosen standard acceptor NMP containing a methyl group in the direct neighborhood of the acceptor carbonyl-group, O-donors were again calculated in complex with two further acceptors demonstrating less sterical hindrance than the cyclic amide.

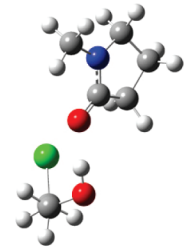

Figure 8. Gauche-conformer of chlorethanol in complex with the acceptor NMP.

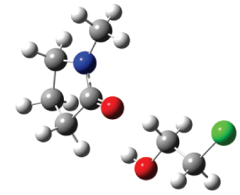

Figure 9. Trans-conformer of chlorethanol in complex with the acceptor NMP.

For this analysis the simple acceptor acetone and the structurally linear acceptor acetonitrile were consulted. Distribution of data points reveal no significant change for these complexes. In Figure 6 the electronic energy for all three calculated series of O-donors are plotted in one graph to demonstrate their similar behavior. R^2-values for the uncorrected and corrected energies are listed in Table 4. Again no improvement employing ZPE and BSSE corrections can be seen. All calulated energies are provided in the Supporting Information.

In addition, calculations for the uncorrected complex energies were carried out with the smaller and therefore time-saving basis set 6-31+g* for the hydrogen-bonded complexes with the standard acceptor NMP. The obtained results (shown in Figure 7) were comparable to the results obtained when

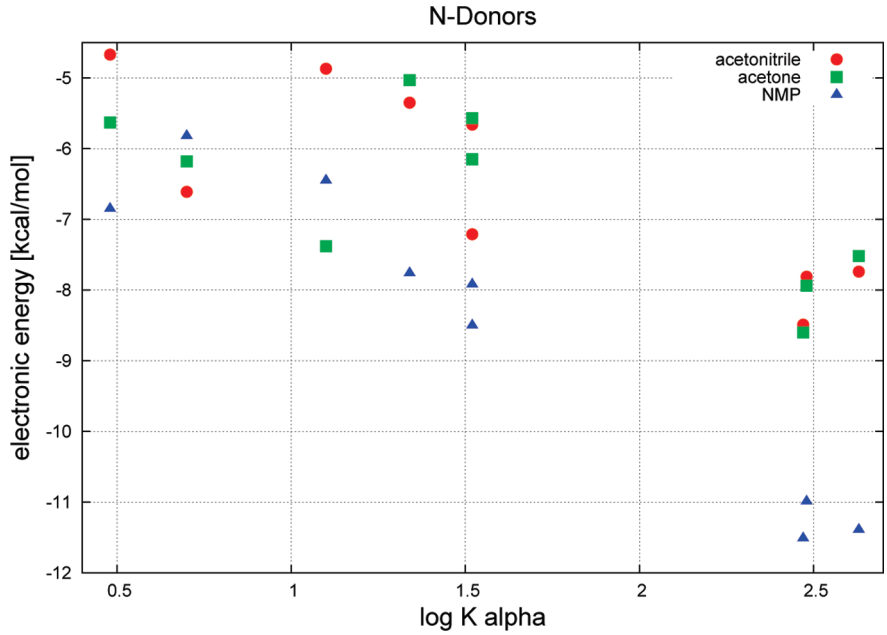

Figure 10. Correlation of the B3LYP/aug-cc-pVDZ calculated hydrogen bond uncorrected complex energies with the experimental log K_α constants for N-donors in complex with the standard acceptor NMP ($R^2 = 0.92$), acetone ($R^2 = 0.50$), and acetonitrile ($R^2 = 0.67$).

using the correlation-consistent basis set aug-cc-pVDZ. The correlation coefficient is 0.73.

Mainly two outliers have to be mentioned. These are aliphatic halogen-substituted alcohols (chlorethanol and trifluorethanol) with a log K_α of 1.08 and 2.00, respectively.

To exclude the hybrid functional B3LYP used so far in this study as the culprit for these outliers uncorrected 6-31+g* energy calculations for O-donors in complex with NMP were studied by the application of the modified Perdew−Wang functional MPW1PW91. The resulting regression line shows an R^2-value of 0.76. The result looks very similar to the correlation obtained with the B3LYP functional, and again the two aliphatic halogen-substituted alcohols are strong outliers.

Finally high level calculations were also performed for selected O-donors (methanol, ethanol, propan-1-ol, propan-2-ol, hexan-1-ol, phenol, 2-methylphenol, and 3-chlorophenol), and the two most evident outliers, chlorethanol and trifluorethanol, using the G3MP2B3 method. Even when using this accurate extrapolation method the resulting plot does not change its appearance, and the aliphatic halogen-substituted alcohols lie still far away from the resulting regression line. For understanding the outlying value of chlorethanol's energy another attempt was to change the complex starting conformation. While the calculations so far dealt with the gauche-conformer (see Figure 8) of this aliphatic alcohol leading to a mismatching energy, B3LYP/6-31+g* calculations for the trans-conformer (see Figure 9) resulted in a weaker and therefore better fitting complex energy. Therefore it is assumed that the experimental value was measured for the trans-form.

Analogous calculations with B3LYP/aug-cc-pVDZ for the trans-conformer produced smaller changes in the energy but again resulted in a better fit to the overall regression line. Therefore it it worth mentioning that for the calculated aliphatic molecules different local energy-minima can exist that affect the results.

For the 9 different N-donors the same approach as for the O-donors was applied. Figure 10 demonstrates the calculated series for the uncorrected complex energy of amides in complex with NMP, acetone, and acetonitrile. In this case a good correlation for the donors in complex with NMP can be seen ($R^2 = 0.92$) but not for complexes with acetone ($R^2 = 0.60$) or acetonitrile ($R^2 = 0.67$). The R^2 values are shown in Table 5.

Table 5. R^2-Values for Correlating B3LYP/aug-cc-pVDZ Calculated Hydrogen Bond Electronic and ZPE and BSSE Corrected Complex Energies with the Experimental Log K_α Constants for N-Donors in Complex with Three Different Acceptors NMP, Acetone, and Acetonitrile

R^2-values	ΔE_{HB}(uncorrected)	ΔE_{HB}(corrected)
NMP	0.92	0.91
acetone	0.50	0.62
acetonitrile	0.67	0.50

We assume that the worse correlation for the acetone and acetonitrile series is due to the fact that the experimental data are obtained for complexes with NMP, although series with O-donors gave even good results for these two standard acceptors. It could be argued that the established method works fine for O-donors but has to be optimized for N-donors.

Substituent effects on an aromatic donor system were studied using the same method as explained above for the acceptor system. Phenol was chosen as hydrogen bond donor, and substitutions in the meta and para positions by the groups $-NH_2$, $-CH_3$, $-OCH_3$, -Cl, -F, $-CF_3$, and $-NO_2$ were performed. Table 6 shows the difference in hydrogen bond energy between the substituted systems and the unsubstituted case. In line with chemical intuition and in contrast to the presented acceptor system in the previous subsection, activating groups in the meta and para positions on the phenol system decrease the hydrogen bond energy, whereas deactivating groups increase energy with respect to the unsubstituted system. The analysis of the preferred positions demonstrate for o-, p-directing substituents an energetically favored H-bond in the meta position due to a higher polarization of the phenol −OH

Table 6. Energy Values for m- and p-Substituted Phenol in Comparison with Unsubstituted Phenol[a]

phenol	$\Delta E_{(HB)}$electronic [kcal/mol]
unsubstituted	–9.08
m-CH_3	–8.92
p-CH_3	–8.84
m-OCH_3	–8.83
p-OCH_3	–8.71
m-NH_2	–8.82
p-NH_2	–8.44
m-Cl	–10.48
p-Cl	–9.73
m-F	–10.68
m-F	–10.60
m-NO_2	–11.54
p-NO_2	–11.94
m-CF_3	–10.39
p-CF_3	–10.89

[a] In kcal/mol. The horizontal line divides activating from deactivating groups.

Table 7. R^2-Values for Correlating Hydrogen Bond Energy and σ-Hammett Constants for a Substituted Phenol Ring

substituted phenol	m-substitution	p-substitution	m- and p-substitution
R^2-value	0.91	0.91	0.87

group in this position, while m-directing substituents lead to a stronger interaction in the para position.

When plotting theoretically calculated hydrogen bond energies against the σ-Hammett constants a very good correlation can be seen independently of the position of substitution. The data are shown in Table 7. Figure 11 shows the linear regression line for para-substituted phenol.

The plot in Figure 11 shows a negative slope and is consistent with chemical knowledge on hydrogen bond properties. Electron donating substituents lead to a decrease of the hydrogen bond donor strength of the OH-group, while electron-withdrawing groups increase the interaction energy. This can be explained by the reverse effect on the polarization of the OH group.

4. DISCUSSION

The results achieved clearly demonstrate the possibility of predicting hydrogen bond strengths as shown by the excellent correlations obtained when plotting theoretically determined hydrogen bond strengths against experimental data. ZPE and BSSE corrections do not change the quality of the correlations considerably so there is no need for frequency calculations or Counterpoise Correction.[41,42] Therefore calculations can be performed faster.

We only fixed one angle, preferably the hydrogen bond angle. No atom positions were frozen. This single angle constraint does not lead to a loss of 3N-6 internal degrees of freedom that would be the consequence of fixing N atom positions.

Comparing O-acceptors and O-donors the correlation for the latter is lower than for the former due to the existence of two aliphatic halogen-substituted alcohols (chlorethanol and trifluoroethanol) as outliers. Analysis with another DFT functional (MPW1PW91) and high level calculations (G3MP2B3) shows the same behavior for those outlying alcohols. Therefore, we assume that the reason for the discrepancy is not founded in the method employed. We rather surmise that the reason can be found in the experimental setup.

Interestingly in the NMP series of N-donors, both investigated aliphatic halogen substituted amides (see Figure 5 donors 1 and 8 with log K_α 1.52 and 2.63, respectively) show a good fitting and are not identified as outliers. Also a third aliphatic halogen substituted alcohol (bis-(trifluormethyl)-methanol) with log K_α 2.83 is situated on the regression line.

For chlorethanol calculations were done with both possible conformers, the gauche form and the trans form. Data inserted in Figure 6 belong to the gauche conformer and

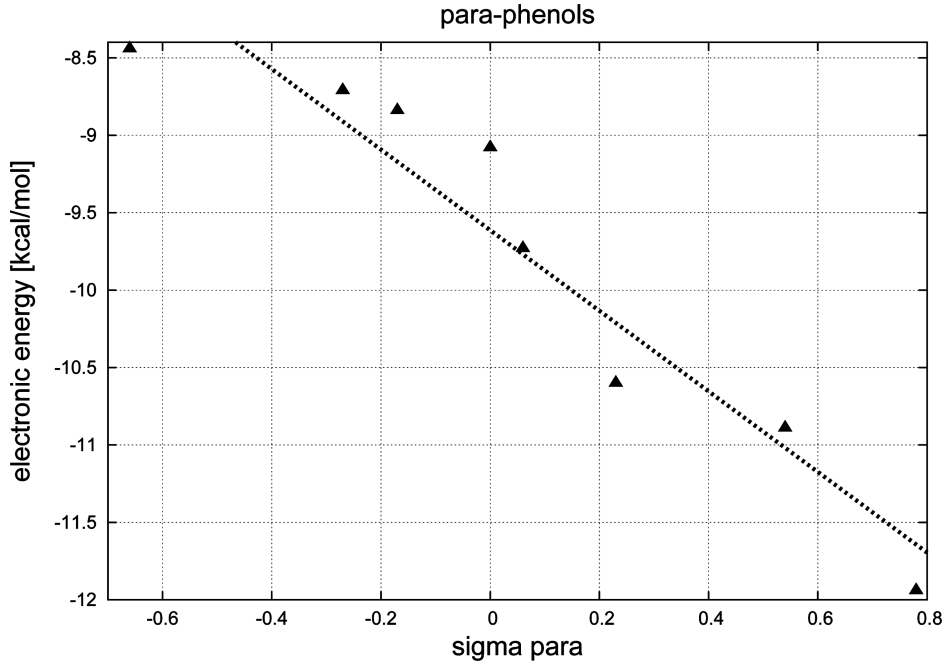

Figure 11. Correlation between the B3LYP/aug-cc-pVDZ calculated hydrogen bond electronic energy and σ_{para}-Hammett constants for p-substituted phenol in complex with NMP, $R^2 = 0.91$.

demonstrate an energy value far away from the regression line. The energy seems to be overestimated.

When dealing with the trans-conformer B3LYP/6-31+g* calculated energy in Figure 7, the value rises from −9.92 to −7.54 kcal/mol and gives a better fit. Calculations with aug-cc-pVDZ for the trans-form in complex with the three different acceptors NMP, acetone, and acetonitrile resulted in a weaker hydrogen bond in the case of acetone by 2.22 kcal/mol (from −7.48 to −5.26 kcal/mol) but without matching into the linear regression perfectly. For the NMP and acetonitrile case the energy rises by 0.73 and 0.23 kcal/mol, respectively. But in all three series energy is less negative and leads to a better fit.

In addition it should be mentioned that enthalpy values are correlated with free energy in this study. Hence entropic effects could disturb the correlation.

The correlations for the B3LYP/aug-cc-pVDZ uncorrected complex energies with the empirically established and substituent characterizing σ-values demonstrate good correlation coefficients for both the acceptor and the donor system case.

The possibility of hydrogen bonds strength predicition could be of paramount importance in ligand optimization for drug design. Insertion of different substituents on aromatic systems could be one way of modulating hydrogen bonds energies and in consequence the binding affinities between a protein and possible drug molecules.

5. CONCLUSION

In this study we have clearly demonstrated that prediction of hydrogen bond energies is possible. The method evolved is simple and consists in fixing of one single angle, but it has to be mentioned that the calculations are performed for a vacuum situation and not for realistic settings in structure-based drug design where surroundings can have a crucial influence on results.

In contrast to other studies on hydrogen bond strength this study is a supermolecular approach considering therefore also the interaction partner and probably being complicated by basis set superposition error (BSSE). Though it could be shown that BSSE correction is not necessary, making the method even more convenient. Nevertheless the method consists in a supermolecular approach using the B3LYP level of theory it was demonstrated that also computationally less expensive basis sets (6-31+g* compared to aug-cc-pVDZ) lead to good correlations with experimental data. The CPU time for the system methanol-NMP is 2 h 34 min 25.5 s and 18 h 24 min 54.7 s for the 6-31+g* and aug-cc-pVDZ calculations on a SGI Cluster machine, respectively.

ACKNOWLEDGMENT

The authors are grateful to Gudrun Spitzer for her mentoring of M.N. during her time in Innsbruck, for her support concerning the preoptimization of complexes, and for her help with literature search. The authors want to thank Thomas Fox for his comments on this study and Christoph A. Sotriffer for his thorough reading of the paper.

Supporting Information Available: Tables of theoretical and experimental values for hydrogen bond strength of the analyzed molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES AND NOTES

(1) Pauling, L. *The Nature of the Chemical Bond*; Cornell Univ. Press: Ithaca, NY, 1939.
(2) Martin, T. W.; Derewenda, Z. W. The name is bond - H-bond. *Nat. Struct. Biol.* **1999**, *6*, 403–406.
(3) Huggins, M. L. 50 Years of Hydrogen Bond Thoery. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 147–208.
(4) Pauling, L.; Corey, R. B.; Branson, H. R. The Structure of Proteins: Two Hydrogen-bonded Helical Configurations of the Polypeptide. *Proc. Natl. Acad. Sci. U.S.A.* **1951**, *37*, 205–211.
(5) Kubinyi, H. Hydrogen Bonding: The Last Mystery in Drug Design? In *Pharmacokinetic optimization in drug research: biological, physicochemical, and computational strategies*, 1st ed; Testa, B., van de Waterbeemd, H., Folkers, G., Guy, R. Helvetica Chimica Acta: Zürich, Switzerland, 2001; pp 513−524.
(6) Ladbury, J. E. Isothermal titration calorimetry: application to structure-based drug design. *Thermochim. Acta* **2001**, *380*, 209–215.
(7) Freire, E. Do enthalpy and entropy distinguish first in class from best in class. *Drug Disovery Today* **2008**, *13*, 869–874.
(8) Velazquez-Campoy, A.; Freire, E. Incorporating Target Heterogeneity in Drug Design. *J. Cell. Biochem. Suppl.* **2001**, *37*, 82–88.
(9) Reynisson, J.; McDonald, E. Tuning of hydrogen bond strength using substituents on phenol and aniline: A possible ligand design strategy. *Journal of Comput.-Aided Mol. Des.* **2004**, *18*, 421–431.
(10) Homans, S. W. Water, water everywhere where it matters. *Drug Discovery Today* **2007**, *12*, 534–539.
(11) Teague, S. J. Implications of Protein Flexibility for Drug Discovery. *Nature Reviews* **2003**, *2*, 527–541.
(12) Davis, A. M.; Teague, S. J. Hydrogen Bonding, Hydrophobic Interactions, and Failure of the Rigid Receptor Hypothesis. *Angew. Chem., Int. Ed. Engl.* **1999**, *28*, 736–749.
(13) Böhm, H.-J.; Klebe, G. What Can We Learn from Molecular Recognition in Protein- Ligand Complexes for the Design of New Drugs. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2588–2614.
(14) Ahn, D.-S.; Park, S.-W.; Lee, S.; Kim, B. Effects of Substituting Group on the Hydrogen Bonding in Phenol-H2O Complexes: Ab Initio Study. *J. Phys. Chem. A* **2003**, *107*, 131–139.
(15) Bryantsev, V. S.; Hay, B. P. Influence of Substituents on the Strength of Aryl C-H. .Anion Hydrogen Bonds. *Org. Lett.* **2005**, *2005*, 5031–5034.
(16) Hao, M. H. Theoretical Calculation of Hydrogen-Bonding Strength for Drug Molecules. *J. Chem. Theory Comput.* **2006**, *2*, 863–872.
(17) Abraham, M. H.; Duce, P. P.; Prior, D. V. Solute Proton Donor and Proton Acceptor Scales for Use in Drug Design. *J. Chem. Soc., Perkin Trans. II* **1989**, 1355–1375.
(18) Kenny, P. W. Hydrogen Bonding, Electrostatic Potential, and Molecular Design. *J. Chem. Inf. Model.* **2009**, *49*, 1234–1244.
(19) Schwöbel, J.; Ebert, R.-U.; Kühne, R.; Schuurmann, G. Modeling the H Bond Donor Strength of -OH, -NH, and -CH Sites by Local Molecular Parameters. *J. Comput. Chem.* **2008**, *30*, 1454–1464.
(20) Schwöbel, J.; Ebert, R.-U.; Kühne, R.; Schüürmann, G. Prediction of the Intrinsic Hydrogen Bond Acceptor Strength of Organic Compounds by Local Molecular Parameters. *J. Chem. Inf. Model.* **2009**, *49*, 956–962.
(21) Reynisson, J.; Steenken, S. DFT studies on the pairing abilities of the one-electron reduced or oxidized adenine-thymine base pair. *Phys. Chem. Chem. Phys.* **2002**, *4*, 5353–5358.
(22) Koch, W.; Holthausen, M. C. Hydrogen Bonds and Weakly Bound Systems In *A chemist's guide to Density Functional Theory*, 2nd ed; Wiley-VCH: 2001; pp 217−236.
(23) Guerra, C. F.; Bickelhaupt, F. M.; Snijders, J. G.; Baerends, E. J. Hydrogen Bonding in DNA Base Pairs: Reconciliation of Theory and Experiment. *J. Am. Chem. Soc.* **2000**, *122*, 4117–4128.
(24) Konè, M.; Illien, B.; Graton, J.; Laurence, C. B3LYP and MP2 Calculations of the Enthalpies of Hydrogen-Bonded Complexes of Methanol with Neutral Bases and Anions: Comparison with Experimental Data. *J. Phys. Chem. A* **2005**, *109*, 11907–11913.
(25) Garza, J.; Ramı´rez, J.-Z.; Vargas, R. Role of Hartree-Fock and Kohn-Sham Orbitals in the basis Set Superposition Error for Systems Linked by Hydrogen Bonds. *J. Phys. Chem. A* **2005**, *109*, 643–651.
(26) Daza, M. C.; Dobado, J. A.; Molina Molina, J.; Salvador, P.; Duran, M.; Villaveces, J. L. Basis set superposition error-couterpoise corrected potential energy surfaces. Application to hydrogen peroxide---X ($X=F^-$, Cl^-, Br^-, Li^+, Na^+) complexes. *J. Chem. Phys.* **1999**, *110*, 11807–11813.
(27) Smallwood, C. J.; McAllister, M. A. Characterization of Low-Barrier Hydrogen Bonds. 7. Relationship between Strength and Geometry of Short-Strong Hydrogen Bonds. The Formic Acid-Formate Anion

Model System. An ab initio and DFT Investigation. *J. Am. Chem. Soc.* **1997**, *119*, 11277–11281.
(28) Paton, R. S.; Goodman, J. M. Hydrogen Bonding and Π-Stacking: How Reliable are Force Fields? A Critical Evaluation of Force Field Descriptions of Nonbonded Interactions. *J. Chem. Inf. Model.* **2009**, *49*, 944–955.
(29) Ziegler, T. Approximate Density Functional Theory as a Practical Tool in Molecular Energetics and Dynamics. *Chem. Rev.* **1991**, *91*, 651–667.
(30) Kohn, W.; Becke, A. D.; Parr, R. G. Density Functional Theory of Electronic Structure. *J. Phys. Chem.* **1996**, *100*, 12974–12980.
(31) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian, Inc.: Wallingford, CT, 2004.
(32) Senent, M. L.; Wilson, S. Intramolecular Basis Set Superpostition Errors. *Int. J. Quantum Chem.* **2001**, *82*, 282–292.
(33) Jensen, F. Basis Set Superposition Errors In *Introduction to Computational Chemistry*, 1st ed.; John Wiley & Sons: Chichester, England, 1999; pp 150−176.
(34) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553.
(35) Senent, M. L.; Wilson, S. Accuracy of the Boys and Bernardi fuction counterpoise method. *J. Chem. Phys.* **1993**, *98*, 4728–4737.
(36) *MOE Molecular Operating Environment, Version 2006.08*; Chemical Computing Group: Montreal, Canada, 2006.
(37) Liao, M.-S.; Lu, Y.; Scheiner, S. Performance Assessment of Density Functional Methods for Study of Charge-Transfer Complexes. *J. Comput. Chem.* **2003**, *24*, 623–631.
(38) Adamo, C.; Barone, V. Hybrid Meta Density Functional Theory Methods for Thermochemistry, Thermochemical Kinetics, and Noncovalent Interactions: The MPW1B95 and MPWB1K Models and Comparative Assessments for Hydrogen Bonding and van der Waals Interactions. *J. Chem. Phys.* **1998**, *108*, 664–675.
(39) Leach, A. R. Advanced ab initio Methods, Density Functional Theora nad Solid-state Quantum Machanics In *Molecular Modelling Principles and Applications*, 2nd ed.; Pearson Prentice Hall: Edinburgh, England, 2001; pp 108−164.
(40) Hansch, C.; Leo, A. In *Exploring QSAR; Fundamentals and Applications in Chemistry and Biology*, 1st ed.; ACS Professional Reference Book: Washington, DC, 1995; Vol. 1, p 7.
(41) Liedl, K. R. Dangers of counterpoise corrected hypersurfaces. Advantages of basis set superposition improvement. *J. Chem. Phys.* **1998**, *108*, 3199–3204.
(42) Liedl, K. R.; Kroemer, R. T. Highly Accurate Estimation of Hydrogen Bond Energies Relying on Basis Set Convergence Patterns. *J. Phys. Chem. A* **1998**, *102*, 1832–1836.

CI9001469