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Hydrogen Bond Detection

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In this Article we extend the idea of detecting a hydrogen bond solely on one single quantum chemically determined descriptor. We present an improvement of the method introduced by Reiher et al. (*Theor. Chim. Acta* **2001**, *106*, 379),[1] who mapped the strength of the hydrogen bond onto an easily accessible quantity, namely, the two-center shared-electron number σ_{HA}. First, we show that the linear dependence between the interaction energy from the supermolecular approach and σ_{HA} is valid for a test set of about 120 hydrogen-bonded complexes. Furthermore, we demonstrate that a classification according to acceptor atoms of the hydrogen-bonded complexes can give more accurate results. We thus recommend to detect hydrogen bonds with a specific acceptor atom according to our subset linear regression analysis. Case studies on alcohols and isolated base pairs and trimers from RNA and DNA show the utility of the detection criterion. The shared-electron number method yields that the strength of the N1···N3 hydrogen bond is in the range of 30 kJ/mol. Furthermore the A−U pair is indeed stronger bound than the A−T complex if environmental effects are incorporated in the calculations.

1. Introduction

The importance of the hydrogen bond concept[2−7] in chemistry and biology is highlighted in numerous articles published each year on this subject. It plays, for instance, a prominent role in supermolecular and template chemistry (see, e.g., refs 8−16). The cooperative character of hydrogen bonding is under intensive investigation[16−20] and the question of a hydrogen bond radius was discussed.[21] Despite the fact that hydrogen bonding is a rather old and well-known concept, still IUPAC conferences are held on the question of how to properly detect and define hydrogen bonds.[22]

The first definition of the hydrogen bond was given by Pauling:[23] “Under certain conditions a hydrogen atom is attracted by rather strong forces to two atoms, instead of only one, so that it may be considered to be acting as a bond between them.” This implies that there are three atoms forming the hydrogen bond. The (hydrogen) donor X, the acceptor A and the hydrogen atom between these two atoms. Pauling further added that “it is now recognized that the hydrogen atom, with only one stable orbital (the 1s orbital), can form only one covalent bond, that the hydrogen bond is largely ionic in character, and that it is formed only between the most electronegative atoms.” In principle, the second statement by Pauling limits the hydrogen bond to a few atoms with high electronegativity, excluding bonding situations such as C−H···A. A second definition was given by Pimentell and McClellan:[24] “A hydrogen bond exists when (1) there is evidence of a bond, and (2) there is evidence that this bond sterically involves a hydrogen atom already bonded to another atom.” This definition does not require a specific charge on one of the three involved atoms and therefore includes a wider range of donors and acceptors. Later on, Steiner and Saenger[25] defined the hydrogen bond as “any cohesive interaction X−H···A where H carries a positive and A a negative (partial or full) charge and the charge on X is more negative than the one on H.” Although this definition neglects the covalent and thus the directional character of the hydrogen bond, it highlights that the hydrogen bond is a structural motif and involves at least three atoms.

The main disadvantages of all these definitions is that they are mainly phenomenological in nature and require terminology like the partial charge and electronegativity concepts. Concepts like these are less well defined from a puristic quantum mechanical point of view. Also, they do not provide a quantitative means for assessing the strength of the hydrogen bond. However, a simple measure to detect hydrogen bonds and to quantify their strength in terms of interaction energies is desirable for the investigation of hydrogen-bonded systems,[26] because deeper understanding can be gained by detecting individual hydrogen bonds. For example, the mechanism of reactions, binding and structural behavior of biochemical systems and nature of hydrogen-bonded liquids can be better understood when the concept of single hydrogen bonds is adopted and their detection and quantification is possible.

From the quantum mechanical point of view, total interaction energies of hydrogen-bonded complexes can be obtained in a supermolecular ansatz (see also refs 27 and 28). In this ansatz the *total intrinsic* interaction energy is defined as

$$E_I(\mathbf{R}_A,\mathbf{R}_B) = E_{AB}(\mathbf{R}_A,\mathbf{R}_B) - E_A(\mathbf{R}_A) - E_B(\mathbf{R}_B) \qquad (1)$$

where $\mathbf{R}_A$ and $\mathbf{R}_B$ are the coordinates of the atoms of the constituents A and B in the complex. E_{AB} is the total energy of the hydrogen-bonded complex (HBC), and E_A and E_B are the total energies of the constituents in the basis of the HBC. However, the supermolecular approach cannot be applied to determine individual hydrogen bond energies if there is more than one hydrogen bond present and if they are all broken upon dissociation.

This is the reason semiquantitative criteria for the estimation of hydrogen bond strengths on the basis of quantum chemical

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calculations should be considered seriously. Two examples are the 1s-orbital-energy method[29,30] and the shared-electron number (SEN) method.[1,31] The 1s-orbital method interprets the orbital energy of the molecular orbital that possesses almost solely 1s-atomic-orbital character of the acceptor atom as a descriptor for the strength of the hydrogen bond. The SEN method can be seen as the simple, sufficiently reliable descriptor in a sense as required by Chandler.[26]

In the SEN approach[1,31] a linear relationship between the two-center SEN σ_{HA} (obtained from population analysis[32,33]) and the energy of the hydrogen bond E^{σ}_{HA} is assumed,

$$E^{\sigma}_{HA} = m\sigma_{HA} \tag{2}$$

where H denotes the proton and A denotes the hydrogen bond acceptor. The slope m is determined by comparing E^{σ}_{HA} to E_I of a reference set of hydrogen-bonded complexes that are chosen to contain only one single hydrogen bond. Because the interaction energy as calculated by the supermolecular approach is negative for bound complexes, the slope m takes negative values. The basic idea of the SEN method is to estimate the strength of a hydrogen bond by means of only one variable. This variable is the two-center shared-electron number σ_{HA}. It has the property to describe the directional nature of the hydrogen bond. This allows the detection of hidden or unrecognized hydrogen bonds. It is particularly useful for the assignment of an interaction energy for a particular hydrogen bond when there is more than one present in a given hydrogen-bonded complex.

The SEN method was successfully applied to various chemical questions ranging from the description of associated liquids to intramolecular hydrogen bonding within transition metal complexes.[16,31,34−37] However, the original study[1] checked for general applicability whereas the reference test set of hydrogen-bonded complexes was comparatively small. In this article we reparametrize the method and provide a detailed analysis on the basis of a wealth of new reference data. We also cover a broader range of interaction energies. This opens the possibility to distinguish between strong and weak hydrogen bond complexes in terms of interaction energy. Furthermore, owing to the size of the new reference test set, we can subdivide the complete set into subsets each consisting of a sufficiently large number of complexes featuring the same acceptor atoms or into subsets with the same donor atoms. Because some definitions of hydrogen bonding explicitly involve the intuitive view of the hydrogen bond as a three-center bond, a closer inspection of the merits of three-center shared-electron numbers appears to be useful.

All calculations are carried out in the framework of density functional theory because this is the working horse of quantum chemistry and *first-principles* molecular dynamics and because it is applicable to large systems. To arrive at method-independent results, a comparison of results for two different density functionals, namely BP86 and B3LYP, and two basis sets of different size, SV(P) and TZVP, is included in this work.

2. Interaction Energies of the Reference Test Set

We carefully select more than 120 hydrogen-bonded complexes for this study (see the Quantum Chemical Methodology in the Appendix for details). This is much larger than the reference set used for the first parametrization of the SEN method given in ref 1. The detailed data of all interaction energies E_I are given in the tables in the Supporting Information. In all tables, the first molecule in each row is the donor and the second molecule is the acceptor of the hydrogen bond. Some interaction energies are positive, showing that the constituents of the complex are not bound for the chosen density functional and basis set. This is most likely a result of the missing dispersion interactions in density functional theory. It is supported by the fact that the supposedly better functional B3LYP as well as the larger basis set TZVP yield more complexes which are bound; i.e., their interaction energies are negative. However, for the larger basis set fewer complexes are suitable for the analysis, because the SEN between the donor atom and the acceptor atom of the neglected complexes exceeds 0.005, indicating additional interactions so that the total interaction energy E_I cannot be solely attributed to the hydrogen bond. This is the reason their values are not given in the tables in the Supporting Information.

The hydrogen-bonded complexes with the smallest interaction energies, often involve donor units such as alkyl, phenyl, PHR_2 and SHR and acceptor units such as FNF_2. This suggests that weak Brönsted acids and weak Lewis bases tend to form very weak hydrogen bonds. Desiraju summarizes complexes with bond energies smaller than −16.7 kJ/mol in the class of weak hydrogen bonds.[38] In our test set most examples feature weak hydrogen bonds after this definition. Following Desiraju strong hydrogen bond complexes exhibit interaction energies from −16.7 to −62.8 kJ/mol. Our set contains examples that include mostly water, methanol, hydrogen fluorine and hydrogen chlorine as donors, and water, ammonia and secondary amines as acceptors.

3. Reparametrization of the SEN Method and Analysis of the New SEN Parameters

In this section, we discuss the regression analyses but present in the following only plots of the BP86/SV(P) data because the qualitative behavior is similar for all methods unless otherwise stated. Additional plots can be found in the Supporting Information. These tables summarize the regression results for the selected HBCs for the functionals BP86 and B3LYP respectively with the basis sets SV(P) and TZVP. For tables and figures in this section we use the following conventions: Set(tot) comprises all data points (E_I, σ_{HA}) of the complete set of HBCs included in the analysis for a given functional and basis set. Set(x,y) is a subset of set(tot). In set(D,y) the donor atom D is the same for all HBCs, and in set(x,A) the acceptor atom A is the same for all HBCs.

The least-squares fit

$$f_{tot}(\sigma_{HA}) = m\,\sigma_{HA} + b \tag{3}$$

of set(tot) is given as a reference in all figures. Additionally, the least-squares fit

$$f_{x,y}(\sigma_{HA}) = m\sigma_{HA} + b \tag{4}$$

of set(x,y) is given if set(tot) is split up into sets containing the same donor atom or sets with the same acceptor atom. For all regression analyses the standard deviation σ^{st}, the error Δm of m, and the percentage point of the Student t-distribution of a probability of 99% are given.

3.1. Analysis of the Complete Data Set. For the complete reference set, the result of the linear regression for all functionals and basis sets are listed in Table 1. Figure 1 shows the correlation between the total interaction energy and the shared-electron number σ_{HA} for all complexes calculated with the functional BP86 and the SV(P) basis set.

The linear regression which yields $f_{tot}(\sigma_{HA})$ according to eq 3 is shown as a straight line in Figure 1. HBCs with interaction

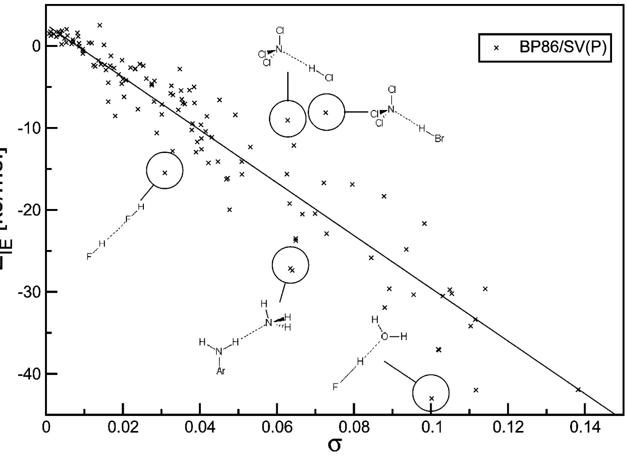

Figure 1. Total interaction energies E_I counterpoise corrected at unrelaxed hydrogen bond donors and acceptors plotted against the two-center shared-electron numbers σ_{HA}.

TABLE 1: Results from Linear Regression Analysis According to Eq 3

method	basis	*m*, kJ/(mol e)	*b*, kJ/mol	σ^{st}, kJ/mol	*N*	$t(N-2)$	Δm, kJ/(mol e)
BP86	SV(P)	−322	2.61	3.74	127	2.6	24
BP86	TZVP	−354	1.61	3.64	113	2.6	34
B3LYP	SV(P)	−399	0.24	3.02	115	2.6	29
B3LYP	TZVP	−406	0.14	3.73	119	2.6	39

energies that differ considerably from this resulting line $f_{tot}(\sigma_{HA})$ are explicitly depicted by their Lewis structures in this figure. Such exceptional HBCs with an interaction energy much smaller than what would be expected from $f_{tot}(\sigma_{HA})$ often possess NCl_3 as the acceptor. HBCs with acceptors such as HF and H_2O as well as donors such as HF and NH_2R are often found far below $f_{tot}(\sigma_{HA})$, showing an exceptional high interaction energy. This suggests that a decomposition of the complete set into acceptor and donor sets will enhance the linear regression analysis. Comparing those kinds of acceptors that exhibit an extreme positive (NCl_3) or negative (HF, H_2O) deviation from $f_{tot}(\sigma_{HA})$ suggests that the atomic charge of the acceptor atom should be investigated. We recognize that the statistical spread around $f_{tot}(\sigma_{HA})$ is small (<2 kJ/mol) for small SENs $\sigma_{HA} < 0.01$ and rises up to 12 kJ/mol for larger SENs $\sigma_{HA} \approx 0.1$. However, values of $\sigma_{HA} < 0.01$ correspond to energies $f_{tot}(0.01) = -0.6$ kJ/mol and values of $\sigma_{HA} \approx 0.1$ correspond to energies $f_{tot}(0.1) = -29.6$ kJ/mol. If we now consider the statistical spread relative to the value of $f_{tot}(\sigma_{HA})$, we calculate over 300% for the small σ_{HA} values and only 50% for the higher σ_{HA} values.

The results of the linear regression analysis obtained with the functionals BP86 and B3LYP with both basis sets SV(P) and TZVP are given in Table 1.

The slope *m* for B3LYP is generally larger than for BP86 in accordance with the analysis from ref 1 where the intercept *b* was set equal to zero. Neglecting *b* results in an increase of *m* with a larger basis set as opposed to the results of ref 1. In our analysis the slope for B3LYP as well as the BP86 data does not depend very much on the basis set, i.e., m(B3LYP, SV(P)) − m(B3LYP, TZVP) = 7 kJ/(mol e) and m(BP86, SV(P)) − m(BP86, TZVP) = 32 kJ/(mol e), in contrast to a rather large difference (>100 kJ/(mol e)) in ref 1. The axis intercept *b* is close to zero for all methods and basis sets. It further approaches zero with a larger basis set and upon changing from BP86 to B3LYP. This justifies a regression analysis without accounting for an intercept as was done previously.[1]

Figure 2. BP86/SVP configuration of both FH···OH_2 HBCs: left, $\sigma_{HA} = 0.1002$; right, $\sigma_{HA} = 0.1117$.

TABLE 2: Complex, Shared-Electron Number σ_{HA}, Hydrogen Bond Energy E_I Provided by the Supermolecular Approach, $f_{tot}(\sigma_{HA})$ Calculated with the Given Value of σ_{HA} and the Parameters Given in Table 1 for BP86/SV(P), Difference Δ between E_I and $f_{tot}(\sigma_{HA})$ and $\Delta/f_{tot}(\sigma_{HA})$ Denoted as %[a]

complex	σ_{HA}, e	E_I, kJ/mol	$f_{tot}(\sigma_{HA})$, kJ/mol	Δ, kJ/mol	%	ref 1, kJ/mol
		BP86/SV(P)				
BrH···NCl_3	0.0727	−8.2	−20.8	−12.6	154	−36.0
FH···OH_2	0.1002	−43.0	−29.7	13.3	31	−49.6
FH···OH_2	0.1117	−42.0	−33.4	8.6	20	−55.3
HOH···NH_2Ph	0.0633	−19.2	−17.8	1.4	7	−31.3
PhOH···BrH	0.0197	−4.6	−3.7	0.9	20	−9.8
FH···NH_2Ph	0.1382	−42.0	−41.9	0.1	<1	−68.4
		B3LYP/TZVP				
BrH···NCl_3	0.0387	−6.8	−15.6	−8.8	130	−19.9
FH···OH_2	0.0696	−40.2	−28.1	12.1	30	−35.8
FH···OH_2	0.0770	−40.5	−31.1	9.4	23	−39.6
HOH···NH_2Ph	0.0482	−21.5	−19.4	2.1	10	−24.8
PhOH···BrH	0.0152	−4.0	−6.0	2.0	50	−7.8
FH···NH_2Ph	0.1181	−45.7	−47.8	2.1	5	−60.7

[a] The last column gives the value as calculated by the fit of ref 1.

The standard deviation as well as the number of HBCs is similar for all fit functions. The error of the slope is in the range of 24−39 kJ/(mol e). Keeping in mind that the investigated σ_{HA} values range from 0 to 0.14, we estimate that the error of the presented fits is smaller than 5.5 kJ/(mol e).

To demonstrate the reliability of the fits, we provide some examples for hydrogen bond energies as calculated with the BP86/SV(P) and B3LYP/TZVP SEN parameters from Table 1. The first three examples are exceptional HBCs that show an E_I that deviates much from $f_{tot}(\sigma_{HA})$ and the last three lines provide complexes that lie very close to $f_{tot}(\sigma_{HA})$. There are two complexes consisting of the same donor and acceptor molecules, namely, the FH···OH_2 HBCs, but in different configurations, as illustrated in Figure 2.

As expected by the choice of the different hydrogen-bonded complexes, the first three $f_{tot}(\sigma_{HA})$ energies show comparatively large absolute deviations of about 10 kJ/mol from E_I with B3LYP/TZVP being a bit closer than BP86/SV(P). The deviations of E_I from $f_{tot}(\sigma_{HA})$ for the well-behaved examples are in the range of 2 kJ/mol. Here the BP86/SV(P) SEN energies are closer to E_I than the B3LYP/TZVP ones. Table 2 also lists the energies as calculated with the ansatz from ref 1 for comparison. The new fit agrees significantly better with E_I and the deviations between E^{σ}_{HA} of the reference data and E_I of the investigated complex can become as large as 20 kJ/mol.

3.2. Acceptor Atom and Donor Atom Subsets. In this section we investigate whether the accuracy of the new fit can be improved further by restricting the linear regression to the subsets classified according to given donor or acceptor atoms, respectively. Because the number of data points is smaller, we concentrate in the following on the characterization by acceptor or donor atoms instead of acceptor or donor molecules. The detailed composition of reference data distinguished by certain acceptor or donor atoms is given in the Supporting Information.

The correlations between E_I and σ_{HA} are presented in Figure 3 (acceptor atom classification) and Figure 4 (donor atom

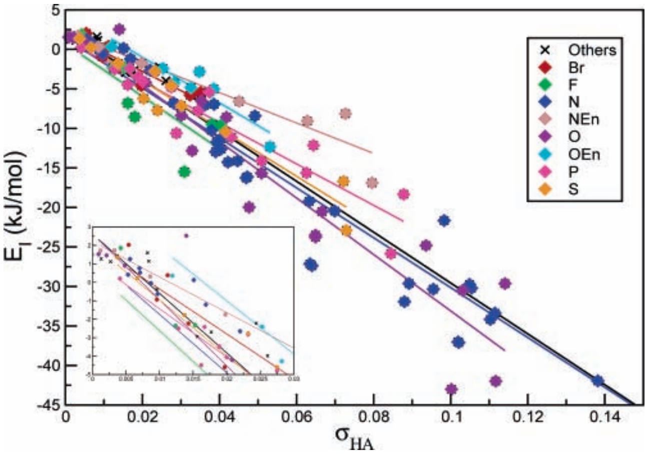

Figure 3. E_I against σ_{HA} calculated with BP86/SV(P). Set consists of the same acceptor atom. Note, En indicates neighboring atoms with a larger Pauling electronegativity than the acceptor atom.

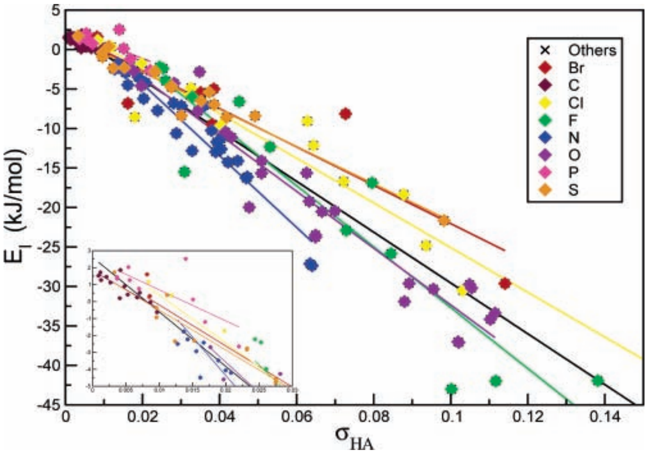

Figure 4. E_I against σ_{HA} calculated with BP86/SV(P). Set built up by the same donor atom.

classification). All complexes with the same acceptor atom (Figure 3) respectively donor atom (Figure 4) are shown in the same color. Note that NEn and OEn indicate acceptor atoms O and N that are bonded to electronegative atoms (En), namely O and Cl. For the sake of clarity sets(x,y) containing less than 6 HBCs are taken into account under "Others". For every set(x,y) a linear regression analysis is performed. The least-squares fits of $f_{x,y}(\sigma_{HA})$ of different subsets are indicated in Figures 3 and 4 by lines of different colors. The color is chosen to correspond to the according atom defining the subset.

One can observe in Figure 3 that complexes with acceptor atoms such as NEn and OEn show interaction energies weaker (more positive values) than what one would obtain by $f_{tot}(\sigma_{HA})$; see gray and light blue line. Not surprisingly, this is in good agreement with the observations from the previous section that such complexes show large deviations from the total fit function $f_{tot}(\sigma_{HA})$. Consequently, these subsets $f_{x,NEn}(\sigma_{HA})$ and $f_{x,OEn}(\sigma_{HA})$ cover the largest positive deviations from $f_{tot}(\sigma_{HA})$ in the range of $\sigma_{HA} = 0$ to $\sigma_{HA} = 0.08$, which underlines the necessity of this decomposition of the complete reference set. The fact that the least-squares fits $f_{x,P}(\sigma_{HA})$ and $f_{x,Br}(\sigma_{HA})$ lie above $f_{tot}(\sigma_{HA})$ as well indicates that the same energetic contributions as for OEn and NEn govern their hydrogen bond nature. Below the total fit function we find in green $f_{x,F}(\sigma_{HA})$ and purple $f_{x,O}(\sigma_{HA})$ of the F and O acceptor sets (not having electronegative atoms attached); i.e., they show a larger slope than $f_{tot}(\sigma_{HA})$. This also agrees well with the previous observation. Because the subset(x,N) is the largest of all subsets, it is not surprising that $f_{x,N}(\sigma_{HA})$ comes very close to $f_{tot}(\sigma_{HA})$. The total curve is likely to be dominated by this subset. Figure 4 allows to consider the calculated complexes distinguished by the donor atom.

TABLE 3: Results from Linear Regression Analysis for Sets Determined by the Acceptor Atom (First Block) and the Donor Atom (Second Block) for BP86/SV(P)

	m, kJ/(mol e)	b, kJ/mol	σ^{st}, kJ/mol	N	$t(N-2)$	Δm, kJ/(mol e)
			Acceptor Atom			
O	−356	2.50	4.58	19	2.898	81
F	−333	0.70	3.60	8	3.707	381
tot	**−322**	**2.61**	**3.74**	**127**	**2.6**	**24**
N	−315	1.48	3.62	44	2.7	34
S	−302	2.07	2.02	11	3.250	90
OEn	−288	4.77	1.60	7	4.032	190
P	−265	1.12	2.61	17	2.947	83
Br	−243	2.06	1.30	7	4.032	176
NEn	−192	2.21	2.17	8	3.707	92
			Donor Atom			
N	−454	1.84	4.72	27	2.787	70
F	−386	5.91	5.60	13	3.106	136
O	−360	3.62	3.14	25	2.807	61
tot	**−322**	**2.61**	**3.74**	**127**	**2.6**	**24**
Cl	−283	3.23	3.06	15	3.012	47
Br	−243	2.24	4.27	8	3.707	162
S	−236	1.86	1.15	17	2.947	39
C	−228	1.90	0.36	12	3.169	115
P	−161	2.15	1.19	10	3.355	201

Hydrogen-bonded complexes with donor atoms F (green), N (blue) and O (purple) possess relatively large interaction energies (i.e., their fit functions lie below f_{tot}), whereas HBCs with donor atoms Cl (yellow), Br (red), P (magenta) and S (orange) have relatively low interaction energies.

Table 3 summarizes the parameters for the linear regression analysis $f_{x,y}(\sigma_{HA})$ for different sets(x,y). As pointed out before in Figures 3 and 4, the slope m holds large values ($m < -300$ kJ/mol) for the acceptor atoms F and O and the donor atoms F, N, and O. A low slope ($m > -250$ kJ/mol) is observed for the donor atoms Br, C, P, S and the acceptor atoms Cl, Br and NEn. Naturally, the error of the slope for all $f_{x,y}(\sigma_{HA})$ is larger than the error of the slope of $f_{tot}(\sigma_{HA})$, with the exception that the error of the slope of $f_{x,N}(\sigma_{HA})$ is very close to ΔM of $f_{tot}(\sigma_{HA})$. This observation can be mostly attributed to the number of data points in each set $f_{x,y}(\sigma_{HA})$, which is small except for set(x,N). An important point to note is the fits are somewhat limited in their accuracy, because the distinction between donor atoms on one side does not take the influence of the acceptor atoms into account. The same applies for all subsets(x,A), which do not take the influence of the donor atoms into account.

Set(x,N) and set(O,y) are relatively close to $f_{tot}(\sigma_{HA})$. In the case of the donor atom the set for O is relatively close to f_{tot}. From this we can deduce that hydrogen-bonded complexes that exhibit N as acceptor atom and O as donor atom should be described rather well by our SEN method $f_{tot}(\sigma_{HA})$. As opposed to this combination, selections involving NEn as acceptor and P or N as donor should give less accurate results. We examine again test calculations, their values are given in Table 4.

In Table 4 we show the performance of the individual regression analysis to both acceptor and donor atom. We also list a third quantity f_c, where we obtain the data by the combination rules as they are used in classical force fields to derive parameters for mixed atom pairs:

$$f_c(\sigma_{HA}) = \sqrt{f_{x,A}(\sigma_{HA})\cdot f_{D,y}(\sigma_{HA})}$$

TABLE 4: Complexes, Shared-Electron Number (σ_{HA}), Hydrogen Bond Energy E_I Provided by the Supermolecular Approach[a]

complex	σ_{HA}, e	E_I, kJ/mol	$f_{tot}(\sigma_{HA})$, kJ/mol	$f_{D,y}(\sigma_{HA})$, kJ/mol	$f_{x,A}(\sigma_{HA})$, kJ/mol	$f_c(\sigma_{HA})$, kJ/mol
			BP86/SV(P)			
$BrH\cdots NCl_3$	0.0727	−8.2	−20.8	−15.4	−11.7	−13.5
$FH\cdots OH_2$	0.1002	−43.0	−29.7	−32.8	−33.2	−33.0
$FH\cdots OH_2$	0.1117	−42.0	−33.4	−37.2	−37.3	−37.2
$HOH\cdots NH_2Ph$	0.0633	−19.2	−17.8	−19.2	−18.5	−18.8
$PhOH\cdots BrH$	0.0197	−4.6	−3.7	−3.5	−2.7	−3.1
$FH\cdots NH_2Ph$	0.1382	−42.0	−41.9	−47.4	−42.1	−44.7
			B3LYP/TZVP			
$BrH\cdots NCl_3$	0.0387	−6.8	−15.6	−12.9	−8.7	−10.6
$FH\cdots OH_2$	0.0696	−40.2	−28.1	−27.7	−34.9	−31.1
$FH\cdots OH_2$	0.0770	−40.5	−31.1	−30.8	−34.4	−34.4
$HOH\cdots NH_2Ph$	0.0482	−21.5	−19.4	−20.4	−20.2	−20.3
$PhOH\cdots BrH$	0.0152	−4.0	−6.0	−6.1	−4.0	−4.9
$FH\cdots NH_2Ph$	0.1181	−45.7	−47.8	−48.3	−48.9	−48.6

[a] $f_{tot}(\sigma_{HA})$, $f_{D,y}(\sigma_{HA})$, $f_{x,A}(\sigma_{HA})$ and $f_c(\sigma_{HA})$ are calculated using the given value of σ_{HA} and the parameters given in Tables 3 and 1 (for BP86/SV(P)) for the appropriate donor and acceptor atom. $f_c(\sigma_{HA})$ is calculated according to eq 5.

We introduce this mixing scheme to account for both the acceptor and donor.

It is immediately apparent that the most accurate values are provided by the fit of the acceptor curves $f_{x,A}(\sigma_{HA})$. This is not surprising, because we measure the shared-electron number between hydrogen atom and acceptor atom. Although less accurate, even the donor curves $f_{D,y}(\sigma_{HA})$ provide better agreement with the supermolecular approach E_I than the total fit $f_{tot}(\sigma_{HA})$ and so do the combined fits $f_c(\sigma_{HA})$. However, in no case does $f_c(\sigma_{HA})$ yield the most accurate data, which is why it is not reasonable to include both the acceptor and the donor contributions in this way. We will come back to this point in a following section. For the three problematic cases (see first three entries in Table 4) we observe significant improvement if we calculate the energy according to the acceptor fit function $f_{x,A}(\sigma_{HA})$. The BP86/SV(P) differences to E_I are reduced to −3.5 kJ/mol (from −12.6 kJ/mol of $f_{tot}(\sigma_{HA})$) for $BrH\cdots NCl_3$ and to 9.8 kJ/mol (from 13.3 kJ/mol of $f_{tot}(\sigma_{HA})$) for $FH\cdots OH_2$. The B3LYP/TZVP data are reduced to −1.9 kJ/mol (from −8.8 of $f_{tot}(\sigma_{HA})$) for $BrH\cdots NCl_3$ and to 5.3 kJ/mol (from 13.3 kJ/mol of $f_{tot}(\sigma_{HA})$) for $FH\cdots OH_2$ respectively. Thus, we recommend to apply the acceptor fit given in Table 3 for practical use.

3.3. Comparison of Different Methods. Although we include in the previous test cases B3LYP/TZVP results, we want to compare the different methods in this section in more detail. Because the acceptor curves provide the more accurate interaction energies, we focus in the following on the behavior of the acceptor curves. Again the behavior of the donor can be inspected in the Supporting Information.

Figure 5 shows the fits for the B3LYP functional and the TZVP basis set. It is obvious for reasons of B3LYP/TZVP being the more accurate electronic structure method that the fluctuations around the fitted lines are now smaller than for the BP86/SV(P), as inspected in the previous section. The range of the shared-electron number σ_{HA} is smaller for B3LYP/TZVP than for BP86/SV(P) and the interaction energies are in general stronger. The smaller range for B3LYP/TZVP is due to the exclusion of complexes with a SEN contact greater than 0.005 between donor and acceptor atom. Again, the atoms P, S, OEn, and NEn result in fit curves that lie above the total function $f_{tot}(\sigma_{HA})$. And the curves of F, O and N lie below the total fit function. The same is reflected in Table 5. These atoms exhibit larger absolute values for the slopes, whereas the former have smaller values.

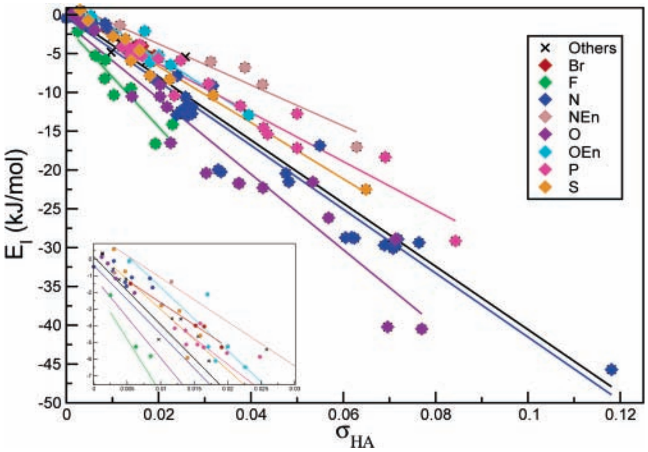

Figure 5. E_I against σ_{HA} at B3LYP/TZVP. Data sets distinguished by the acceptor atom.

TABLE 5: Results from Linear Regression Analysis for Sets Determined by the Acceptor Atom with B3LYP/TZVP

atom	*m*, kJ/(mol e)	*b*, kJ/mol	σ^{st}, kJ/mol	*N*	*t*(*N*−2)	Δ*m*, kJ/(mol e)
F	−643	−1.59	1.92	8	3.707	383
O	−486	−1.07	3.46	18	2.921	100
N	−411	−0.38	2.45	43	2.7	37
OEn	−378	2.09	1.23	7	4.032	188
S	−362	0.60	1.08	10	3.355	67
P	−314	−0.02	1.82	13	2.947	64
Br	−266	0.05	0.28	4	9.925	153
NEn	−264	1.52	1.64	6	4.604	139

For the intercepts we now find even negative values and we notice that their absolute values are smaller than the BP86/SV(P) values. Small or vanishing values for the intercepts seem to be more reasonable from a physical point of view. Additionally, the standard deviations are smaller and the order of largest absolute slope is not the same as before with the BP86/SV(P) data.

In Table 6 we show the parameters for the regression analysis depending on the different methods. We provide also test calculations to compare different methods.

As noticed before for the total fit functions, the hybrid functional B3LYP exhibits larger absolute slopes than the BP86 functional. Usually, the slope with the larger basis set is also larger in absolute values, but there are a few exceptions; see for instance the NEn block in Table 6 for B3LYP/SV(P) and B3LYP/TZVP data. The intercepts are smaller for larger basis sets and mostly for the B3LYP/TZVP functional. Often the standard deviation is smaller for B3LYP than for the BP86 functional, but also here we find exceptions and the values are so close that we could not prefer a special combination of functional and basis set. This is also reflected in the differences Δ between E_I and $f_{x,A}(\sigma_{HA})$. It is not surprising and also very useful, because the particular population analysis used here should not be functional and basis set depend.

3.4. Taking Donor and Acceptor Contributions Explicitely into Account. In most definitions of the hydrogen bond, it is described as consisting of three atoms, the hydrogen atom, the donor atom, and the acceptor atom. This suggests use of three-center shared-electron number σ_{XHA} instead of σ_{HA}. As opposed to the choice in the previous section, we choose in this section a test case with the same donor atom. One reason is that the donor curves $f_{D,y}(\sigma_{HA})$ exhibit larger deviations from the super

TABLE 6: Results from Linear Regression Analysis for Sets Determined by O, N, and NEn as Acceptor Atoms for Different Methods[a]

			O				FH···OH_2		
method	basis set	m, kJ/(mol e)	b, kJ/mol	σ^{st}, kJ/mol	Δm, kJ/(mol e)	σ_{HA}, e	E_I	$f_{x,A}(\sigma_{HA})$, kJ/mol	Δ
BP86	SV(P)	−356	2.50	4.58	81	0.1117	−42.0	−37.3	4.7
BP86	TZVP	−457	1.33	2.16	63	0.0942	−40.1	−41.7	−1.6
B3LYP	SV(P)	−498	2.52	2.78	78	0.0970	−43.4	−45.8	−2.4
B3LYP	TZVP	−486	−1.07	3.46	100	0.0770	−40.5	−38.5	2.0

			N				HOH···NH_2Ph		
method	basis set	m, kJ/(mol e)	b, kJ/mol	σ^{st}, kJ/mol	Δm, kJ/(mol e)	σ_{HA}, e	E_I	$f_{x,A}(\sigma_{HA})$, kJ/mol	Δ
BP86	SV(P)	−315	1.48	3.62	34	0.0633	−19.2	−18.5	0.7
BP86	TZVP	−368	1.38	2.44	34	0.0594	−21.2	−20.5	−0.7
B3LYP	SV(P)	−378	0.74	2.72	36	0.0530	−20.2	−19.3	0.9
B3LYP	TZVP	−411	−0.38	2.45	37	0.0482	−21.5	−20.2	1.3

			NEn				BrH···NCl_3		
method	basis set	m, kJ/(mol e)	b, kJ/mol	σ^{st}, kJ/mol	Δm, kJ/(mol e)	σ_{HA}, e	E_I	$f_{x,A}(\sigma_{HA})$, kJ/mol	Δ
BP86	SV(P)	−192	2.21	2.17	92	0.0727	−8.2	−11.7	−3.5
BP86	TZVP	−191	2.09	1.53	153				
B3LYP	SV(P)	−300	1.87	2.01	165	0.0462	−9.2	−12.0	−2.8
B3LYP	TZVP	−264	1.52	1.64	139	0.0387	−6.8	−8.7	−1.9

[a] The last four columns give the shared-electron number σ_{HA}, the interaction energies E_I as well as the difference Δ between E_I and $f_{x,A}(\sigma_{HA})$ for one particular example. $f_{x,A}(\sigma_{HA})$ is calculated with the parameters from Table 1 (BP86/SV(P)) and the given σ_{HA}.

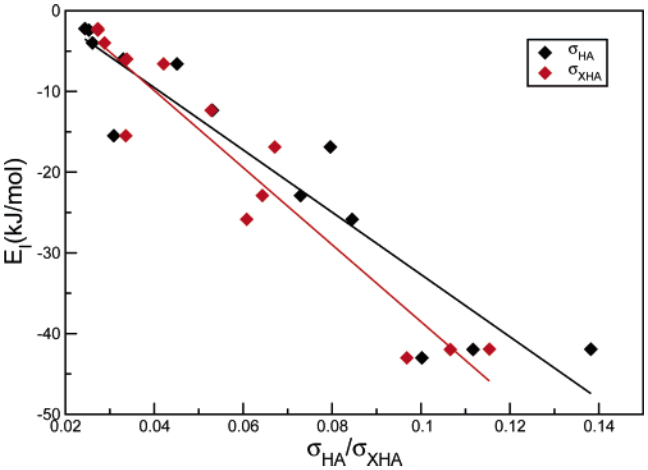

Figure 6. Three-center σ_{HA} and two-center shared-electron number σ_{HA} and E_I for the HBCs with the donor atom F.

TABLE 7: Results from Linear Regression Analysis for $Set_3(F,y)$ and Set(F,y) Determined by the Donor for BP86/SV(P)

	m, kJ/(mol e)	b, kJ/mol	σ^{st}, kJ/mol	N	$t(N-2)$	Δm, kJ/(mol e)
σ_{XHA}	−477	9.21	4.65	13	3.106	136
σ_{HA}	−386	5.91	5.60	13	3.106	136

TABLE 8: Three-Center Shared-Electron Number σ_{XHA}, Two-Center Shared-Electron Number σ_{HA}, and E_I for the HBCs with the Donor Atom F

complex	$-\sigma_{XHA}$, e	σ_{HA}, e	E_I, kJ/mol	$f_{F,y}(\sigma^3_{HA})$, kJ/mol	$f_{F,y}(\sigma_{HA})$, kJ/mol
FH···OH_2	0.0968	0.1002	−43.0	−37.0	−31.5
FH···OH_2	0.1070	0.1117	−42.0	−41.8	−37.2
FH···NH_2Ph	0.1150	0.1382	−41.9	−45.6	−47.4
FH···PH_2Me	0.0608	0.0845	−25.8	−19.8	−26.7
FH···SH_2	0.0643	0.0729	−22.9	−21.5	−22.2
FH···NCl_3	0.0671	0.0796	−16.9	−22.8	−24.8
FH···FH	0.0336	0.0309	−15.5	−6.8	−6.0
FH···OCl_2	0.0528	0.0531	−12.3	−16.0	−14.6
FH···NF_3	0.0421	0.0451	−6.6	−10.9	−11.5
FH···ClOCl	0.0338	0.0330	−6.0	−6.9	−6.8
HF···FOF	0.0288	0.0261	−4.0	−4.5	−4.2
FH···OF_2	0.0273	0.0253	−2.4	−3.8	−3.9
FH···FNF_2	0.0273	0.0244	−2.2	−3.8	−3.5

molecular interaction energy E_I than the acceptor curve $f_{x,A}(\sigma_{HA})$. Consequently, we expect changes to be more significant in such cases. We take the set(F,*y*) due to its high fluctuation around $f_{F,y}(\sigma_{HA})$. The results are summarized in Figure 6 and Table 7.

As one can see from Figure 6, the three-center shared-electron numbers can also be used as the primary variable on which one wants to map the strength of the hydrogen bond. Table 7 summarizes the least-squares fit for $set_3(F,y)$ and set(F,*y*) for comparison.

Using the σ_{XHA} values we obtain a much steeper slope *m*. Also the intercept is reduced by almost a factor of 2. The standard deviation σ^{st} is significantly smaller for the three-center shared-electron number, but the error of the slope remains the same for both shared-electron numbers, mostly attributed to the steeper slope of $f_{(F,y)}(\sigma_{XHA})$.

In Table 8 we show the shared-electron numbers, the total interaction energies E_I and the resulting interaction energies $f_{F,y}(\sigma_{HA})$ and $f_{F,y}(\sigma_{XHA})$ from the regression analysis.

For the very weak hydrogen-bonded complexes (E_I < 10 kJ/mol) in Table 8 we find no improvement using σ_{XHA} and even worse almost more deviating values from E_I than if we apply the two-center shared-electron number. The situation changes for complexes with interaction energies (E_I > 10 kJ/mol). Applying σ_{XHA} leads to closer values to E_I. Large improvements are found for the hydrogen bonds with interaction energies of about 40 kJ/mol. Here the data points with similar interaction energy depending on σ_{XHA} come closer together than the data points depending on σ_{HA}. This can be attributed to the shared-electron number contact between the donor and the acceptor atom. The value of this contact rises with increasing interaction energy indicating a shift of different energetic contributions to the total hydrogen bond strength. These contributions might not be covered by the two-center shared-electron number between

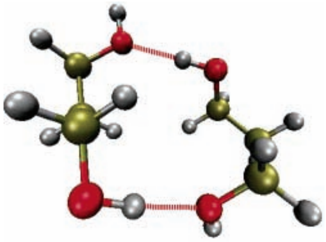

Figure 7. Configuration of 1,3-propanediol dimer with two hydrogen bonds.

hydrogen atom and acceptor atom. Furthermore, if this contact exceeds the value of 0.005, HBCs were excluded from analysis. The improvement could be larger when complexes with stronger donor−acceptor contact are included. We will investigate this in a forthcoming publication. That means that a reparametrization with regard to σ_{XHA} can include more data points. Thus, the method is valuable for a much broader range of hydrogen bond examples.

4. Case Studies

In the following we choose some cases to show the limitations and the benefits of the SEN method. We will also provide a test case to show the utility of the shared-electron number method. All examples are obtained with the B3LYP functional and the TZVP basis set.

4.1. Simple Hydrogen-Bonded Systems. For the acetic acid dimer we find an interaction energy E_I of −39.1 kJ/mol per monomer, whereas the SEN method yields $f_{x,O}(\sigma_{HO}) = -46.8$ kJ/mol and $f_{tot}(\sigma_{HO}) = -38.2$ kJ/mol. This is not surprising because the oxygen SEN parametrization did not contain any carboxy functional group; we expect systems with a carboxyl group acceptor to be better reproduced with the total fit function $f_{tot}(\sigma_{HO})$. In comparison to the original SEN parametrization of Reiher et al.[1] (−41 kJ/mol), we find improvement. For the formic acid the interaction energy E_I per monomer yields −36.8 kJ/mol. The SEN values are $f_{x,O}(\sigma_{HO}) = -43.4$ kJ/mol and $f_{tot}(\sigma_{HO}) = -35.7$ kJ/mol, whereas the original SEN fit values of Reiher et al.[1] are −47 kJ/mol. To show that the acceptor parametrization works in general better, we calculated the interaction energy for two alcohols. A configuration of the ethanol dimer that holds an E_I of −22.5 kJ/mol gives a SEN energy $f_{x,O}(\sigma_{HO})$ of −21.4 kJ/mol and $f_{tot}(\sigma_{HO})$ yields −16.9 kJ/mol.

For a propanediol shown in Figure 7, we obtain an E_I of −42.6 kJ/mol, whereas $f_{x,O}(\sigma_{HO})$ is −38.1 kJ/mol and $f_{tot}(\sigma_{HO})$ yields −30.8 kJ/mol. It is important to note that the SEN energy does not necessarily need to reproduce the interaction energy, because it is only parametrized to yield hydrogen bond energies. Interactions that are not incorporated in the parametrization should not occur in the SEN energy.

4.2. Hydrogen Bonding in DNA and RNA. In a very recent communication it was inferred by experiment that N1···N3 hydrogen bonds are stronger in dsRNA A−U than in dsDNA A−T base pairs.[39] The observations are based on one-bond ^{15}N−^{1}H J-coupling constants $^{1}J_{NH}$.

In Table 9 we list results from calculations on the isolated base pairs and trimers as shown in Figure 8. For the base pairs we find no difference in structure or binding energy. Although there is a slight trend for the A−U dimer in the binding energy as well as in the SEN hydrogen bond energy for N1···N3, this trend is too less pronounced to reveal the difference between the hydrogen bonds; see Table 9, first two lines.

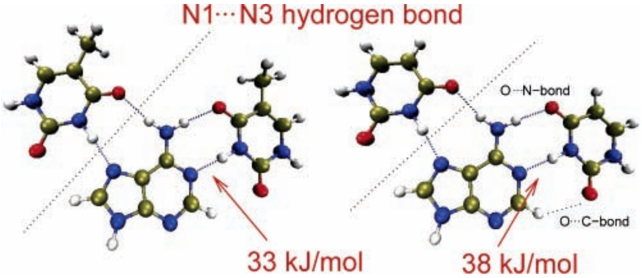

Figure 8. Base pairs (see dotted lines) and trimers that were investigated. The marked hydrogen bond is the N1···N3 hydrogen bond, which is according to the SEN method stronger in the U·A−U trimer (right) than in the T·A−T (left) trimer.

TABLE 9: Total Interaction Energies E_I and SEN Hydrogen Bond Energy $f_{x,N}(\sigma_{HA})$ for Dimers and Trimers, Intermolecular Distance between the Two Nitrogen Atoms and Intramolecular N−H Distance, and M···HN Angle

system	E_I, kJ/mol	$f_{x,N}(\sigma_{HN})$, kJ/mol	r_{NN}, pm	r_{NH}, pm	$\angle_{N\cdots HN}$, deg
A−U dimer	−57.1	−33.4	288.9	104.5	178.6
A−T dimer	−56.1	−32.9	288.9	104.5	178.6
U·A−U trimer	−110.6	−38.4	288.3	104.5	179.5
T·A−T trimer	−109.7	−33.4	287.9	104.5	179.4

Comparing the T·A−T trimer and the A−T dimer, we find no difference in distance and in hydrogen bond energy. The SEN method yields a N1···N3 hydrogen bond of approximately 33 kJ/mol for both dimers and the T·A−T trimer. Although the hydrogen bond distance is still in the same region (changes are of the order of promille) the SEN energy indicates a trend (13%) to stronger hydrogen bonds in the U·A−U trimer as compared to the A−U dimer and T·A−T trimer. This indicates the importance of environmental effects, but it also reflects the utility of the shared-electron number method. In ref 39 the authors also raise the question whether other hydrogen bonds are also stronger in the uracil complex than in the thymine complex. For the trimer we observe an increase in hydrogen bond strength obtained from the shared-electron number of 13% for the O···N hydrogen bond which is as large as the increase for the N1···N3 bond. The O···C hydrogen bond, which is very weak, increases by 23%.

5. General Discussion

Because population analyses neither are basis set independent nor converge to certain values with increasing size of the basis set, we cannot guarantee that larger basis sets than TZVP will provide better results. Our data show that a TZVP basis set yields more accurate results than the SV(P) basis set if the acceptor atom is taken into account. However, as pointed out before, our data indicate that the shared-electron method does not depend critically on the basis set and the chosen electronic structure method.

There is a good reason to use the hybrid density functional if available and practical though. Some complexes will be described in a more accurate fashion, because the hybrid functional (B3LYP) is a significant improvement over the gradient corrected functionals when it comes to the description of the electronic structure of the hydrogen bond. Some complexes that will not be stable with the gradient corrected functional BP86 are stable with the hybrid density functional ansatz. It is of no use when a method is able to correctly estimate a wrong energy. So far we refrain from parametrization using MP2 data, because the population analysis would be carried out with the undisturbed wave function. This would mean that two different electronic structure methods are used to obtain a particular method. Nevertheless, it is tempting to test such an empirical ansatz because the description of weak hydrogen bonds will be considerably improved using MP2.

Another important point is the varying size of the absolute slopes. This is not connected with the strength of the hydrogen bond. Large as well as small absolute slopes can be found for complexes with both weak and strong hydrogen bond strength. A closer insight of this phenomenon can only be gained by an energy decomposition. Morokuma et al.[40] investigated the hydrogen bond with the decomposition analysis and found out that the proton acceptor ability decreases in the order F > O > N due to an increasing exchange repulsion (EX). Again the exchange repulsion component of the total energy is said to prefer a contact between electron rich groups. This corresponds to the fact that in the case of the acceptor atom F, the same amount of SEN yields a larger interaction energy than in the case of O or N. However, the strength of the hydrogen bond depends not only on the exchange repulsion part but also on the electrostatic part (ES), charge transfer (CT), etc. The electrostatic part and also the other negative components are compensating the exchange repulsion part. In the case where the hydrogen bond is dominated by ES and EX, the ratio between ES and EX increases with the electronegativity, which corresponds to the observed ordering of the absolute values of the slope for the different acceptor atoms. A detailed insight can be expected by the symmetry-adapted perturbation theory analysis.[41]

6. Conclusions and Outlook

The idea to map the complete strength of the hydrogen bond onto two parameters of a linear function depending solely on the SEN value is proven to be successful in this article. This is the case if error margins of about 10% of the calculated energy value are acceptable. The linear relationship between the shared-electron number and the interaction energy from the supermolecular approach is shown to be valid inside these error bars.

Furthermore, it could be shown that these error margins cover deviations that are systematic with regard to the donor and acceptor atom. This gave rise to different ideas how to improve the accuracy of the method. The most successful ansatz is the decomposition into sets with the same acceptor atom. With the introduction of this decomposition of the total set, the standard deviation could be considerably lowered. We thus recommend to detect hydrogen bonds with a specific acceptor atom according to our subset regression analysis. However, in the case of doubly bonded oxygen atoms we recommend to apply the total fit function, because no doubly bound oxygen atom was included in the fitting procedure. Usage of a larger basis set enhances the accuracy a little. The second approach to improve the SEN method is the exchange of the two-center shared-electron number by the three-center SEN. As a result, the standard deviation could be considerably lowered for the investigated test set. However, the improvement is limited to strong hydrogen bonds.

The importance of the knowledge of individual hydrogen bond strengths has been stressed in the introduction of this article. Traditionally, the standard approach for the estimation of such local interaction energies in complex aggregates is based on geometric criteria. These solely define the interaction of two fragments of an aggregate on the basis of distances (and, occasionally, of angles).[42] It is most desirable to have a single descriptor for the interaction energy, which, however, cannot easily be identified. Chandler noted that attempts on the quantification of predictions of protein structures with hydrophobic and hydrophilic amino acids “by identifying a single parameter or function that characterizes the strength of hydrophobic interactions have been unsuccessful”.[26] Several examples in this work showed that the shared-electron number method as refined here provides such an useful measure to detect hydrogen bonds. Case studies on alcohols isolated base pairs and trimers from RNA and DNA showed the utility of the detection criterion. We observed that the strength of the N1···N3 hydrogen bond in these DNA/RNA complexes is in the range of 30 kJ/mol. Furthermore, the A−U complex is indeed stronger bound than the A−T complex if environmental effects are incorporated in the calculations.

In the future, we plan to investigate the three-center electron number for cases that explicitely exhibit large two-center shared-electron numbers between acceptor and donor. We also intend to expand our training set toward systems that include the oxygen doubly bound as acceptor and charged systems to include more examples of stronger hydrogen bonds.

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Appendix: Quantum Chemical Methodology

DFT calculations with two different density functionals BP86[43,44] and B3LYP[45,46] are performed for isolated complexes using TURBOMOLE.[47] All calculations with the gradient-corrected density functional BP86 are carried out in combination with the RI density fitting technique. Two different basis sets, namely the SV(P) and the TZVP sets from the TURBOMOLE library, are employed.[48] For the generation of the reference energy test set of hydrogen-bonded complexes, all interaction energies are calculated in the supermolecular ansatz. This requires that all energies of the isolated donor and acceptors be counterpoise corrected, which is carried out with the procedure of Boys and Bernardi.[49] However, during structure optimization counterpoise corrections have not been included. It is important to note that the very first investigation of the SEN method[1] did not take the counterpoise correction into account.

Also, the reference test set of hydrogen bond energies was limited to the most prominent examples in ref 1. Here, the reference test set consists of 113−127 hydrogen-bonded complexes (HBCs), where the interaction energy of each HBC is dominated by one hydrogen bond and contributions from interactions between other atoms are negligible. These are selected after optimization of about 740 HBCs. Only those HBCs are selected for the reference set that fulfill a predefined geometry criterion, which states that the distance between any atom of the first constituent and any atom of the second constituent of the HBC has to be at least 300 pm. Of course, the distance of the hydrogen bond is excluded from this test. Additionally, all HBCs fulfilling this criterion were checked for a non-negligible SEN larger than 0.005 between acceptor atom and donor atom. All HBCs featuring more than one SEN contact were excluded from the analysis. HBCs with a SEN for the hydrogen bond smaller than 0.005 were only accepted if they show no further SEN contacts larger than 0.001.

Supporting Information Available: Textual description of quantum chemical results (including tables of hydrogen bond energies) and linear regression analysis results (including plots of interaction energies vs σ_{HA} plots and tables of results). This material is available free of charge via the Internet at http://pubs.acs.org.

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