Estimation on the Individual Hydrogen-Bond Strength in Molecules with Multiple Hydrogen Bonds

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A simple atom-replacement approach is proposed for estimating the individual contributions of each intermolecular hydrogen bond (HB) in multiple hydrogen-bonded systems. The approach is validated by calculations on the homodimer of formylformamide and then applied to nucleic acid base pairs (adenine−thymine and guanine−cytosine) and some quadruply hydrogen-bonded dimers. With the help of this method, it is easy to distinguish the relative strength of each HB, and identify the main factors contributing to the total binding energies of multiple HBs.

1. Introduction

Hydrogen bonds (HBs) play an important role in determining the structures and properties of biological macromolecules[1] (e.g., proteins and nucleic acids) as well as many supramolecules.[2,4,5] For example, the two polynucleotide strands of the DNA double helix are held together by HBs between specific pairs of bases. The secondary structure of a protein is mostly determined by HBs between amide N−H groups of one residue and C═O groups of another.[3] A HB is usually denoted as X−H···Y, where X and Y are the electronegative donor (D) and acceptor (A), respectively, and its strength ranges from 1.0 to about 40 kcal/mol.[2] Although the strength of one HB is relatively weaker compared to that of a normal covalent bond, a combination of multiple HBs as well as other noncovalent forces may also lead to the formation of highly complex supramolecular aggregates. For example, quadruple hydrogen-bonding motifs have been used to synthesize supramolecular polymers through the efficient self-association of self-complementary monomers.[6] Obviously, the investigation of hydrogen bonding in complex hydrogen-bonded macromolecules or supramolecular assemblies is very important for understanding and predicting the stability of these systems. A great number of experimental[7] and computational[8] investigations have been reported on the energetics and geometries of intermolecular HBs in various hydrogen-bonded systems. For complexes with multiple HBs, previous studies were most aimed to estimate the total interaction energies of all HBs. Nevertheless, the evaluation of the individual strengths of each HB is also important, which allows for the main factors contributing to the total binding energies between fragments to be determined. The resulting information is expected to be helpful for the rational design of new strategies for molecular recognition or supramolecular assemblies.[6]

However, only a few studies have been devoted to evaluate the individual HB strength.[9−12] For DNA base pairs, Dannenberg et al.[9] suggested that the energy of a given HB could be estimated by computing the binding energy of a hypothetical twisted structure, in which two bases are bonded by this HB only. The hypothetical structure can be formed by rotating one of the bases with respect to the other about the axis of this HB, so that other HBs are broken. This strategy is expected to be useful in many cases but not generally applicable for complexes with complicated structures because it may be difficult to form a hypothetical structure with only one HB but without causing other steric interactions. Since the HB strength obtained in this way corresponds to the energy of a given HB in the absence of the others, the difference between the sum of the individual HB energies and the total interaction energy of all HBs could be used to measure the cooperativity of the hydrogen-bonding interactions. Grunenberg[10] suggested that compliance constants could be employed as unique bond strength descriptors. However, a recent theoretical work by Baker and Pulay[11] showed that compliance constants might not be suitable for describing individual bonding interactions. Very recently, Scheiner[12] proposed that the energy of each individual HB could be approximately taken as the energy difference between the original system and the modified system with some groups being replaced by hydrogen atoms.

In the present work, we propose a simple atom-replacement approach for evaluating the strength of each HB in molecules with multiple HBs. This approach shares some similarity with the Scheiner's approach but is expected to be applicable for more general hydrogen-bonded systems. The HB strength derived from the present approach can be considered as the energy of a given HB in the presence of the other HBs, different from the value obtained with the approach advocated by Dannenberg et al.[9]

2. Methodology and Computational Details

We will take the adenine−thymine (**AT**) base pair as an example to show how to evaluate the energy contribution of each HB with our scheme (Figure 1).

First, the geometry of this complex is fully optimized at a given theoretical level. Then the binding energy of the bases **A** and **T** is calculated as below, using the counterpoise (CP) method[13] for the basis set superposition error (BSSE)

$$\Delta E_{\mathrm{int}}{}^{\mathrm{CP}} = E^{\mathbf{AT}}(\{\chi_{\mathbf{A}}\} + \{\chi_{\mathbf{T}}\}) - E_{\mathrm{dim}}{}^{\mathbf{A}}(\{\chi_{\mathbf{A}}\} + \{\chi_{\mathbf{T}}\}) - E_{\mathrm{dim}}{}^{\mathbf{T}}(\{\chi_{\mathbf{A}}\} + \{\chi_{\mathbf{T}}\}) \quad (1)$$

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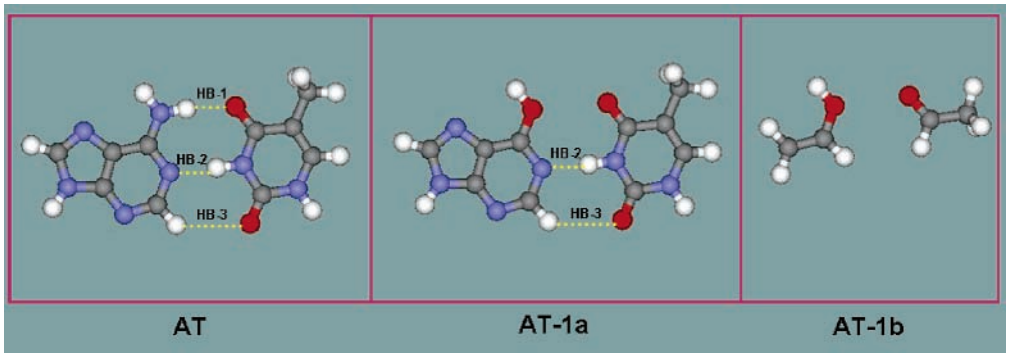

Figure 1. The base pair **AT** and the model systems constructed for estimating the strength of HB-1 in **AT**.

Here $E_{\mathrm{dim}}^{\mathbf{A}}(\{\chi_{\mathbf{A}}\} + \{\chi_{\mathbf{T}}\})$ stands for the energy of the monomer **A** at the dimer structure (the optimized structure of **AT**) with basis functions on all atoms of **AT**. Compared to the conventional definition of the binding energy, the value calculated from eq 1 can be called as the vertical binding energy (VBE). Clearly, for the **AT** base pair, the VBE value can be considered as the sum of the individual contributions of three HBs.

Next, for a given HB N−H···O (HB-1), we remove the corresponding H atom and replace the nitrogen atom with an oxygen atom to form a model system **AT**−**1a** (the other parts of **AT**−**1a** is the same as in **AT**). The replaced oxygen atom is located at the position of the original nitrogen atom, and another hydrogen atom (attached to the original nitrogen atom) is now linked to this oxygen atom. The structure of the model system **AT**−**1a** is shown in Figure 1. Apparently, this substitution will break HB-1 but leave other two HBs to be approximately the same as in the original **AT** system, since it only introduces minimal perturbation into the charge distribution of other parts of the molecule. However, it should be noticed that, the transformation of the N−H···O═C group into an O···O═C group would also introduce an additional repulsive interaction, $E_{\mathrm{Rep-1}}$, for the O···O distance is close to the sum of its van der Waals radius. Therefore, from the BSSE-corrected binding energies of the original complex **AT** and the model system **AT**−**1a**, one can obtain an approximate estimate of the energy contribution of HB-1 if $E_{\mathrm{Rep-1}}$ can be estimated in some way

$$\Delta E_{\mathrm{int}}^{\mathrm{CP}}(\mathbf{AT}) = E_{\mathrm{HB-1}} + E_{\mathrm{HB-2}} + E_{\mathrm{HB-3}} \quad (2)$$

$$\Delta E_{\mathrm{int}}^{\mathrm{CP}}(\mathbf{AT-1a}) = E_{\mathrm{Rep-1}} + E_{\mathrm{HB-2}} + E_{\mathrm{HB-3}} \quad (3)$$

$$E_{\mathrm{HB-1}} = [\Delta E_{\mathrm{int}}^{\mathrm{CP}}(\mathbf{AT}) - \Delta E_{\mathrm{int}}^{\mathrm{CP}}(\mathbf{AT-1a})] + E_{\mathrm{Rep-1}} \quad (4)$$

To estimate $E_{\mathrm{Rep-1}}$, we have to construct another model **AT**−**1b**. The general rules for designing this model system are as follows. First, we keep the fragment R═O···OH−R′ (here R and R′ are non-hydrogen atoms) to be in the original position as in **AT**−**1a**. Then, the atoms bonded to R and R′ are also retained as in **AT**−**1a**, but they are saturated with necessary hydrogen atoms. If keeping a bonded atom (to R or R′) will generate additional interactions, this bonded atom will be simply replaced with a hydrogen atom. In **AT**−**1b**, the positions of those hydrogen atoms added for saturating R and R′ or their bonded atoms are freely optimized, with the positions of all other atoms fixed in **AT**−**1a**. In this way, the local coordination environments of R and R′ in **AT**−**1a** are reasonably mimicked in **AT**−**1b**, whose structure is also shown in Figure 1. Thus, the BSSE-corrected binding energy for **AT**−**1b** should provide a good approximation to $E_{\mathrm{Rep-1}}$.

The procedure described above for HB-1 (N−H···O) can be easily generalized to an arbitrary HB X−H···Y by simply replacing the X−H group with its isoelectronic atom G. To evaluate the repulsive interaction from the close G···Y contact, one should follow the general rules (suggested above for HB-1) to build the corresponding model system. In addition, if the atom G (or Y) is involved in a ring, it is better to retain the whole ring in the corresponding model system (but the substituents connected to the atoms of this ring may be modeled by hydrogen atoms). Such situation may occur, for example, when we construct the model system for the central HB N−H···N (HB-2) in the **AT** base pair. The structures of all model systems constructed for **AT** (and other systems under study) are provided in Supporting Information.

In principle, if the replacement of the X−H group with its isoelectronic atom G brings additional secondary electrostatic interactions[14] besides the G···Y repulsion, these additional interactions should also be taken into account by constructing corresponding model systems. As a result, the eqs 3 and 4 should be modified correspondingly. However, we find that in most cases these additional interactions are quite weak and thus could be neglected, since the distance between the atom G and its neighboring atoms (except Y) is significantly longer than the sum of their van der Waals radius. In fact, the difference between the total binding energy of all HBs and the sum of the individual contributions calculated from eq 4 may reflect to some extent the magnitude of various secondary electrostatic interactions.

It should be emphasized that the strength of each individual HB obtained by our scheme represents the energy contribution of a specific HB in the presence of other HBs. Because of the cooperative effect of several HBs, the energy contribution of each HB calculated in this way may be considered as the sum of its intrinsic binding energy and an energy component resulting from the cooperative effect of several HBs. Thus, the strength of each individual HB obtained with our scheme is quite different from that obtained with the approach advocated by Dannenberg et al.[9]

In the following section, we will apply this atom-replacement approach to evaluate the individual HB strength in several typical systems with multiple HBs. For these systems, we first carry out full geometry optimizations at the B3LYP level with a 6-311++G(d,p) basis set. Then, for all model systems constructed for all HBs in these systems, we perform constrained geometry optimizations to determine the positions of added hydrogen atoms. Finally, single-point MP2 calculations with the same basis set at the geometries determined above are employed to compute the BSSE-corrected binding energy using the counterpoise method. All the calculations have been done with the Gaussian 03 package.[15]

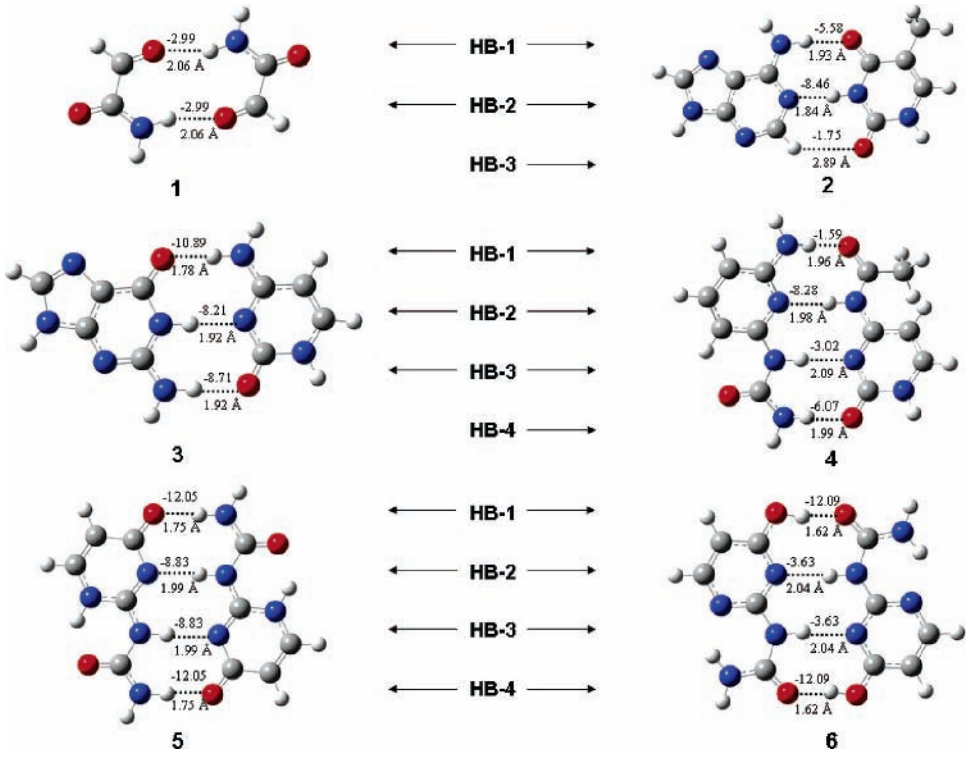

Figure 2. The lengths of individual HBs and their strengths (in kcal/mol) in selected hydrogen-bonded systems.

TABLE 1: Calculated Total Interaction Energies and Individual Contributions of Each HB (kcal/mol)

	1	2	3	4	5	6
ΔE	−6.52	−13.50	−27.19	−21.21	−45.53	−30.87
E_{HB-1}	−2.99	−5.58	−10.89	−1.59	−12.05	−12.09
E_{HB-2}	−2.99	−8.46	−8.21	−8.28	−8.83	−3.63
E_{HB-3}		−1.75	−8.71	−3.02	−8.83	−3.63
E_{HB-4}				−6.07	−12.05	−12.09
ΣE_{HB-i}	−5.98	−15.79	−27.81	−18.96	−41.76	−31.44
$\Delta E - \Sigma E_{HB-i}$	−0.54	2.29	0.62	−2.25	−3.77	0.57

3. Results and Discussions

First, the dimer of formylformamide (**1** in Figure 2) is selected to calibrate our method, because this system has two identical HBs (as seen from its bond lengths) and thus the energy contribution of each HB can be directly estimated as half of the total binding energy between two monomers. The corresponding value is −3.26 kcal/mol for each HB. With our scheme, the strength of each HB in **1** is evaluated to be −2.99 kcal/mol (as shown in Table 1), which is in good agreement with the direct estimate. Another quantity for validating the applicability of our scheme is the difference between the sum of individual strengths of each HB and the total binding energy of all HBs, ($\Delta E - \Sigma E_{HB-i}$). This quantity is calculated to be −0.54 kcal/mol for the compound **1**. Thus, both validation methods confirm that the present approach could give a reasonable estimate on the strength of each HB. In the following, we will investigate the hydrogen-bonding interactions in several representative systems with multiple HBs (**2**−**6** in Figure 2) to illustrate the applicability of the present approach. The calculated total interaction energies and individual contributions of all HBs in these complexes are collected in Table 1.

For triple hydrogen-bonded systems, we have chosen **AT** and guanine−cytosine **(GC)** base pairs as examples. For compound **2** (**AT**), the total binding energy is calculated to be −13.50 kcal/mol, while the sum of individual contributions of three HBs (ΣE_{HB-i}) is −15.79 kcal/mol. The deviation ($\Delta E - \Sigma E_{HB-i}$) of 2.29 kcal/mol means that the calculated individual energy contribution of each HB should be within an error of 1.0 kcal/mol, on the average. Among the three HBs, the relative strength of each HB decreases in the order HB-2 > HB-1 > HB-3, as listed in Table 1. The central N−H···N HB is the strongest in **AT**, while the C−H···O═C HB is the weakest. Especially, the energy contribution of HB-3 is estimated to be only −1.75 kcal/mol, which is quite close to that of the C^{α}−H···O═C HB in the dimer of *N*,*N*-dimethylformamide reported previously.[16] The results we obtained here is in accord with the traditional description that **AT** has two normal HBs (HB-1 and HB-2) and one weak C−H···O interaction (HB-3). The relative order of HB-1 and HB-2 obtained in the present work is different from the result reported by a previous study,[9] which suggested HB-1 to be the strongest.

For **3** (**GC**), the relative strength of each HB is calculated to be in the order HB-1 > HB-3 > HB-2, and all three HBs in **GC** are shown to be quite strong. The deviation ($\Delta E - \Sigma E_{HB-i}$) is only 0.62 kcal/mol for the complex. In contrast to our results, the use of compliance constants as HB descriptors leads to the order HB-2 > HB-1 > HB-3.[10] It is interesting to compare the strength of the N−H···N or N−H···O HB in similar systems **AT** and **GC**. For the central interresidue N−H···N HB (HB-2), our results indicate that its strength is comparable in **AT** and **GC** base pairs, although the H···N distance in **AT** (1.84 Å) is significantly shorter than that in **GC** (1.92 Å). Clearly, cooperative effects should be introduced to account for this effect. **AT** has only two relatively strong HBs, while **GC** has three. Since the synergic effect will enhance the strength of each HB in **GC** more than that in **AT**, it is understandable that HB-2 in **AT** and **GC** has comparable strength. Because of the same reason, the strength of HB-3 (−8.71 kcal/mol) in **GC** is predicted to be noticeably stronger than that of HB-1 in **AT** (−5.58 kcal/mol), although both HBs are of the same type (the N−H···O═C HB) and have similar H···O distances (1.92 Å in **GC** and 1.93 Å in **AT**).

For the quadruple hydrogen-bonded molecules, we have studied three systems **4**−**6** whose monomers are important quadruple hydrogen-bonding modules in supramolecular chemistry.[6] In compound **4**, our results indicate that the relative strength of four HBs is in the order HB-2 > HB-4 > HB-3 > HB-1. Among the four HBs, HB-2 and HB-3 are of the same type, while HB-1 and HB-4 fall into the same class. As seen from their individual contributions, HB-2 (−8.28 kcal/mol) is much stronger than HB-3 (−3.02 kcal/mol). As the local coordination environments of the donor and the acceptor in these two HBs are nearly the same, the relative order of HB-2 and HB-3 is in accord with the fact that the H···N distance of HB-2 is 0.11 Å shorter than that of HB-3. However, even for HBs of the same type, if the donor (or acceptor) atom is bonded to quite different substituents, their strength will not be inversely proportional to their HB distance. For example, the H···O distance of HB-1 is slightly shorter than that of HB-4, but HB-1 is predicted to be noticeably weaker than HB-4. According to previous studies on substituent effects on hydrogen-bonded complexes,[17] a HB tends to become stronger if its electron-donor is bonded to an electron-donating substituent and its electron-acceptor is linked to an electron-withdrawing substituent. Clearly, the substituents have a positive effect on the hydrogen bonding in HB-4 but a negative effect on the hydrogen bonding in HB-1. Thus, the substituent effect could account for the relative strength of HB-1 and HB-4.

For species **5**, the total binding energy (−45.53 kcal/mol) is calculated to be about twice as large as that in **4** (−21.21 kcal/mol). The main geometrical difference in **4** and **5** is that HB-1 is in favorable local environment in **5** (but is not in **4**, as discussed above). Because of the strong cooperative effect of four HBs in **5**, HB-1 and HB-4 become quite stronger than their counterparts in **4**. In addition, HB-3 in **5** now has a shorter H···N distance (1.99 Å) than HB-3 in **4**, resulting in a stronger interaction. Thus, our results show that the substantially higher binding energy in **5** could be ascribed to the enhanced strength of HB-1, HB-3, and HB-4 (HB-2 is comparable in **4** and **5**). Results on species **6** are also worth some comments. This species and **5** are both self-assembled dimers.[8d,8g] The monomer of **6** is the 4-pyrimidinol, whose tautomeric form (4[1H]-pyrimidone) is the monomer in **5**. According to the different arrangements of donor and acceptor sites in self-assembled dimers, species **5** is generally described to possess the favorable AADD-DDAA binding motif, whereas species **6** possesses a less favorable DADA-ADAD array.[14] As seen from Table 1, the total binding energy in **6** (−30.87 kcal/mol) is indeed significantly less than that in **5**. A comparison of individual contributions of all HBs shows that HB-1 (or HB-4) has almost identical strength in both molecules but HB-2 (or HB-3) is much weaker in **6** than that in **5**. The weak N−H···N HB-2 (or HB-3) in **6** is also reflected in its longer H···N distance (2.04 Å) that that in **5** (1.99 Å). Thus, a less favorable hydrogen bonding interaction in **6** (than that in **5**) is mainly caused by the fact that all HBs could not simultaneously adopt their optimal geometrical arrangements.

4. Conclusions

In the present work, we have proposed a simple and general strategy to measure the individual contributions of each HB in multiple hydrogen-bonded systems. Our study on the hydrogen bonding interaction in the formylformamide dimer validates the effectiveness of this simple approach. Illustrative applications of this approach to several typical systems with multiple HBs have been given. It should be emphasized that the energy contribution of each HB calculated from our approach represents the sum of its intrinsic binding energy and an energy component resulting from the cooperative effect of several HBs. As revealed from our analyses on several molecules, the strength of a HB with a fixed donor and acceptor is determined by the distance, connected substituents, as well as the cooperative effects of other HBs. With the help of our approach, it is easy to determine the relative strength of all HBs and identify the main factors contributing to the total binding energies of multiple HBs. Such information could help experimentalists to design suitable hydrogen-bonding motifs in supramolecular self-assemblies or protein-drug binding processes.

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Supporting Information Available: Cartesian coordinates and electronic energies of six systems and their mode systems. This material is available free of charge via the Internet at http://pubs.acs.org.

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