

## Performance of Several Density Functional Theory Methods on Describing Hydrogen-Bond Interactions

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**Abstract:** We have investigated eleven density functionals, including LDA, PBE, mPWPW91, TPSS, B3LYP, X3LYP, PBE0, O3LYP, B97–1, MPW1K, and TPSSh, for their performances on describing hydrogen bond (HB) interactions. The emphasis has been laid not only on their abilities to calculate the intermolecular hydrogen bonding energies but also on their performances in predicting the relative energies of intermolecular H-bonded complexes and the conformer stabilities due to intramolecular hydrogen bondings. As compared to the best theoretical values, we found that although PBE and PBE0 gave the best estimation of HB strengths, they might fail to predict the correct order of relative HB energies, which might lead to a wrong prediction of the global minimum for different conformers. TPSS and TPSSh did not always improve over PBE and PBE0. B3LYP was found to underestimate the intermolecular HB strengths but was among the best performers in calculating the relative HB energies. We showed here that X3LYP and B97–1 were able to give good values for both absolute HB strengths and relative HB energies, making these functionals good candidates for HB description.

### 1. Introduction

Hydrogen-bond (HB) interactions play a very important role in biochemistry. With the rapid development of biochemistry and pharmacology, the field of the first principle computational study has grown enormously. Traditional *ab initio* methodology, such as Møller–Plesset perturbation approach (MP2, MP4),<sup>1,2</sup> and coupled-cluster theory (CCSD(T)),<sup>3</sup> etc. can yield a highly accurate description of HB interactions, provided that large basis sets are used. However, the dramatic increase in computational cost with the size of systems limits their applications to just benchmark calculations of small molecules. Density functional theory (DFT) offers a promising alternative to the wave function-based methods.<sup>4</sup> Particularly, Becke's three parameter scheme,<sup>5</sup> B3LYP, has made great success in predicting the ground-state electronic structures, reaction energetics, molecular geometries, and so

forth.<sup>4</sup> However, it is now well documented that B3LYP is unsatisfactory for the calculation of HB binding energies.<sup>6–11</sup> It has a tendency to underestimate HB strength, and errors accumulate for large systems involving multiple HB interactions.<sup>9</sup> New functionals were continually developed.<sup>12–27</sup> Some representatives are PBE,<sup>12</sup> mPWPW91,<sup>15</sup> O3LYP,<sup>22</sup> B97–1,<sup>17</sup> TPSS,<sup>25</sup> TPSSh,<sup>26</sup> X3LYP,<sup>27</sup> etc. These functionals were claimed to be a significant improvement over B3LYP in this or that aspect (see Table 1).<sup>12–27</sup> Several authors have explored the feasibility of these functionals on the description of HB interactions (see Table 2).<sup>6–11,26</sup> For example, Zhao and Truhlar<sup>11</sup> have performed an extensive test for the HB behaviors of forty-four functionals with three different basis sets against the so-called HB6/04 database. The HB6/04 set contains six HB systems, (NH<sub>3</sub>)<sub>2</sub>, (HF)<sub>2</sub>, (H<sub>2</sub>O)<sub>2</sub>, NH<sub>3</sub>/H<sub>2</sub>O, (HCONH<sub>2</sub>)<sub>2</sub>, and (HCOOH)<sub>2</sub>, with HB strengths ranging from ~13 to ~68 kJ/mol using data calculated by the W1 or W2 theory<sup>28</sup> as references. According to an integrated performance, based on the mean absolute deviations (MADs) of HB binding energies calculated by

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**Table 1.** Functionals Examined in the Present Work

name	year	HF%	type	ex corr	comments
PBE	1996	0	GGA	PBE ex PBE corr	Improves over PW91. <sup>12</sup>
PBE0	1996	25	hybrid GGA	PBE ex PBE corr	Not far from the most reliable functionals including heavy parametrization. <sup>14</sup> Multiply bonded systems are most improved. <sup>13</sup>
mPWPW91	1998	0	GGA	mPW ex PW91 corr	Significantly improves the long-range behavior. Allows to obtain remarkable results both for covalent and noncovalent interactions. <sup>15</sup> Can provide the binding states of the rare gas, although the calculated binding energies cannot reproduce the experimental trend in binding energies. <sup>16</sup>
B97-1	1998	21	hybrid GGA	B97-1 ex B97-1 corr	Improves over B3LYP and B97. <sup>17</sup> Performs well on electrical properties. <sup>18</sup> Performs well on kinetics. <sup>19</sup>
MPW1K	2000	42.8	hybrid meta-GGA	mPW ex PW91 corr	Reduces the mean unsigned error in reaction barrier heights by a factor of 2.4 over mPW1PW91 and by a factor of 3 over B3LYP. <sup>20</sup> Works very well on kinetics. <sup>21</sup>
O3LYP	2001	11.61	hybrid GGA	OPTX ex LYP corr	Substantially improves over B3LYP. <sup>22</sup> Is overall better than B3LYP, albeit not by much. <sup>23</sup> Outperforms B3LYP in most fields but failed in hydrogen bond systems. <sup>24</sup>
TPSS	2003	0	meta-GGA	TPSS ex TPSS corr	Gives generally excellent results for a wide range of systems and properties, correcting overestimated PKZB bond lengths in molecules, hydrogen-bonded complexes, and ionic solids. <sup>25</sup>
TPSSh	2003	10	hybrid meta-GGA	TPSS ex TPSS corr	In some cases surpasses in accuracy the best available semiempirical approximations such as B3LYP, B3PW91, and VSXC. <sup>26</sup>
X3LYP	2004	21.8	hybrid GGA	X ex. LYP corr	Improves over B3LYP especially for hydrogen-bonded and van der Waals complexes. Will be useful for predicting ligand binding in proteins and DNA. <sup>27</sup>

three basis sets of different sizes with and without counterpoise corrections, PBE was concluded to be the best functional for HB; while PBE0 was the best hybrid GGA, VSXC<sup>29</sup> the best meta-GGA and MPW1K,<sup>11</sup> is the best performer with the DIDZ (desert-island double- $\zeta$ ) basis set. In agreement with our previous results,<sup>24</sup> OPTX was concluded to be unsuitable for HB calculations. Staroverov et al.<sup>26</sup> has examined the performance of sixteen functionals, focusing on the new generation of nonempirical functional TPSS. It was concluded that TPSS is the most reliable nonhybrid functional for dissociation energies and geometries of H-bonded systems. The hybrid functionals are more accurate than their nonhybrid counterparts, although TPSSh surpasses TPSS only for geometries.<sup>26</sup>

It should be pointed out that all of the above works focused only on the absolute deviation of the binding energy from the corresponding reference value for an intermolecular hydrogen-bond.<sup>6–11,26</sup> The accuracy of each functional for the description of the relative HB binding energies was not examined. It is, however, the relative binding energies that determine the best binding interaction mode among different configurations. Furthermore, the functional performance for the intramolecular HB interactions has not yet been systematically investigated. Such intramolecular HB can play a decisive role in determining the conformer structure of a biomolecule.

In the present work, we have examined the performances of eleven DFT methods — LDA (SVWN5),<sup>30,31</sup> PBE, mPWPW91, TPSS, B3LYP, X3LYP, PBE0, O3LYP, B97-1, MPW1K, and TPSSh—to describe HB interactions. Fourteen model systems have been chosen to simulate the intermolecular HB interactions frequently appearing between the main function groups of amino acids (i.e., amino, hydroxyl, carboxyl, and peptide bond groups) in biochemical systems. Special attention has been paid to the relative HB strengths

for different bonding interactions originating from the same pair of monomers. The functional performance for intramolecular HB interactions has been examined by looking into the conformer stability of three amino acids (glycine, proline, and serine). Three Ramachandran conformers of glycine dipeptide have been chosen as examples to demonstrate the interplay of HB and van der Waals (vdW) interactions in the biosystems.

The remainder of this paper is organized as follows. In section 2, we show the details of our calculations. In section 3, we present our results and discussion. In the last section, we give the conclusions.

## 2. Computational Details

**2.1. Reference Value of Intermolecular HB Binding Energy— $D_e^{\text{SAPT}}$ .** It is nontrivial to establish a reliable reference set for HB from experiments, where theory shows its power. The literature data are often taken from the expensive methods such as CCSD(T) extrapolated to the complete basis set limit or the Wn theory.<sup>11,32</sup> We show here that the reference values for intermolecular HBs can be obtained satisfactorily by a relatively cheaper method, the symmetry-adapted perturbation theory (SAPT). SAPT was designed to calculate the interaction energy of a dimer, consisting of two arbitrary closed-shell monomers.<sup>33,34</sup> In SAPT, the interaction energy was expressed as a sum of a set of perturbative corrections, and each correction results from a different physical effect (i.e., electrostatic, polarization, dispersion, and exchange).

The SAPT model we employed here is approximately equivalent to the fourth order many body perturbation theory (see eq 9 in ref 33). The geometries were first optimized by MP2(full)/aug-cc-pVDZ.<sup>35,36</sup> The basis set used in SAPT interaction energy calculations was aug-cc-pVTZ basis

**Table 2.** Representative Assessments of the DFTs' Abilities on Describing Hydrogen Bonded Interactions

author and year	functionals	systems	studied properties	methods for reference values	author's conclusions
Tuma, C.; Handy, N. C. 1999 <sup>6</sup>	B3LYP, B97-1, PBE0, HCTH, BLYP, PBE, LDA, and HTCH38	(HF) <sub>2</sub> , (HCl) <sub>2</sub> , (H <sub>2</sub> O) <sub>2</sub> , (CO)(HF), (OC)(HF), (FH)(NH <sub>3</sub> ), (CIH)(NH <sub>3</sub> ), (H <sub>2</sub> O)(NH <sub>3</sub> ), (H <sub>3</sub> O <sup>+</sup> )(H <sub>2</sub> O)	binding energy	CCSD(T)/aug-cc-pVTZ or aug-cc-pVQZ BSSE corrected	Although the hybrid methods performed well in general, the new HCTH38 functional as a pure GGA predicted binding energies of better quality than the B3LYP functional.
Rabuck, A. D.; Scuseria, N. C. 2000 <sup>7</sup>	B3LYP, BHLYP, PBE, VSXC, and PBE0	(HF) <sub>2</sub> , (HCl) <sub>2</sub> , (H <sub>2</sub> O) <sub>2</sub> , (HF)(HCN), (HF)(H <sub>2</sub> O), (CN <sup>-</sup> )(H <sub>2</sub> O), (OH <sup>-</sup> )(H <sub>2</sub> O), (HCC <sup>-</sup> )(H <sub>2</sub> O), (H <sub>3</sub> O <sup>+</sup> )(H <sub>2</sub> O), (NH <sub>4</sub> <sup>+</sup> )(H <sub>2</sub> O)	binding energy and geometry	experiment and MP2 BSSE corrected	Overall, the hybrid functionals which contain a portion of Hartree-Fock exchange (B3LYP, BHLYP, and PBE0) yield the most accurate results. The kinetic-energy-density-dependent functionals, VSXC and meta-GGA, are significantly less accurate.
Sherer, E. C.; Cramer, C. J. 2003 <sup>8</sup>	BLYP, B3LYP, mB3LYP, mPWPW91, and mPW1PW91	six base pairs for all DFTs and another 22 base pairs for mPWPW91/MIDI!	interaction enthalpies	MP2/6-31G(d)//HF/6-31G(d) and experiment BSSE corrected	At the pure and hybrid density functional levels, mPWPW91/MIDI! performed most satisfactorily.
Staroverov V. N.; Scuseria G. E.; Tao, J. M.; Perdew, J. P. 2003 <sup>26</sup>	16 DFT methods, including LDSA, PW91, PBE, PBE0, PKZB, TPSS, and TPSSh	(HF) <sub>2</sub> , (HCl) <sub>2</sub> , (H <sub>2</sub> O) <sub>2</sub> , (HF)(HCN), (HF)(H <sub>2</sub> O), (CN <sup>-</sup> )(H <sub>2</sub> O), (OH <sup>-</sup> )(H <sub>2</sub> O), (HCC <sup>-</sup> )(H <sub>2</sub> O), (H <sub>3</sub> O <sup>+</sup> )(H <sub>2</sub> O), (NH <sub>4</sub> <sup>+</sup> )(H <sub>2</sub> O)	binding energy and geometry	DFT/6-311++G(3df,3pd) and MP2/6-311++G(3df,3pd)	TPSS is the most reliable nonhybrid functional. It also represents a dramatic improvement over PKZB. The hybrid functionals are more accurate than their nonhybrid counterparts, although TPSSh surpasses TPSS only for geometries.
Xu, X.; Goddard, W. A. 2004 <sup>9</sup>	SVWN, BLYP, BP86, BPW91, PW91, mPWPW, PBE, XLYP, BHLYP, B3LYP, B3P86, B3PW91, PW1PW, mPW1PW, PBE0, and X3LYP	H <sub>2</sub> O monomer and H <sub>2</sub> O dimer	geometry, vibrational frequencies, bond energy, dipole moment, kinetics, polarizability	experiment and CCSD(T)(FULL)/IO275 extrapolations to the complete basis set; BSSE corrected	The best overall performance is given by X3LYP, comparing with the exact values, suggesting that X3LYP should be generally useful for predicting accurate properties for systems dominated by hydrogen bonding, electrostatics, and van der Waals (dispersion) interactions, such as ligand/protein complexes.
Frey, J. A.; Leutwyler, S. 2005 <sup>10</sup>	BLYP, B3LYP, X3LYP, PBE, PW91, and mPWPW91	(formamide) <sub>2</sub> and (2-pyridone) <sub>2</sub>	binding energy	MP2/CBS	PW91 consistently gives the best agreement with the MP2 basis-set limit binding energies, closely followed by PBE. The mPWPW91, B3LYP, and the recently proposed X3LYP functionals are in less good agreement.
Zhao, Y.; Truhlar, D. G. 2005 <sup>11</sup>	44 DFT methods, including PBE, PBE0, B3P86, MPW1K, B97-1, BHLYP, and X3LYP.	(HF) <sub>2</sub> , (NH <sub>3</sub> ) <sub>2</sub> , (H <sub>2</sub> O) <sub>2</sub> , NH <sub>3</sub> /H <sub>2</sub> O, (HCONH <sub>2</sub> ) <sub>2</sub> , (HCOOH) <sub>2</sub>	binding energy	W1 and W2 theory <sup>25</sup>	Among the tested methods, the PBE, PBE0, B3P86, MPW1K, B97-1, and BHandHLYP functionals give good performance for hydrogen bondings.

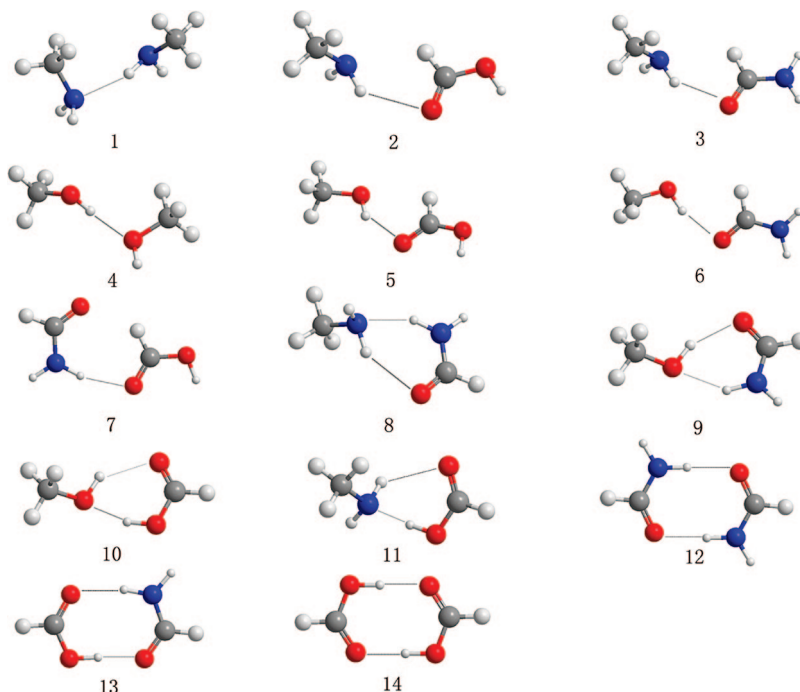
set<sup>35,36</sup> modified by removing the f and g functions. The recommended MC+BS approach was used.<sup>33,34</sup> A bond

function of 3s2p1d was added, centered in the H-bond area. The keyword scfcp was used to correct the basis set

**Table 3.** Comparison between Results of SAPT and Wn for the Benchmark Database HB6/04<sup>a</sup>

	(NH <sub>3</sub> ) <sub>2</sub>	(HF) <sub>2</sub>	(H <sub>2</sub> O) <sub>2</sub>	(NH <sub>3</sub> )(H <sub>2</sub> O)	(HCONH <sub>2</sub> ) <sub>2</sub>	(HCOOH) <sub>2</sub>	MAD <sup>c</sup>
D <sub>e</sub> <sup>SAPT</sup>	13.01	18.54	20.29	26.48	61.17	66.90	0.6
HB6/04 <sup>b</sup>	13.18	19.12	20.79	26.82	62.51	67.57	

<sup>a</sup> Units: kJ/mol. <sup>b</sup> Benchmark database HB6/04 was introduced by Zhao and Truhlar in ref 11; the values of (NH<sub>3</sub>)<sub>2</sub>, (HF)<sub>2</sub>, (H<sub>2</sub>O)<sub>2</sub>, and (NH<sub>3</sub>)(H<sub>2</sub>O) are W2 results, and the values of (HCONH<sub>2</sub>)<sub>2</sub> and (HCOOH)<sub>2</sub> are W1 results. <sup>c</sup> MAD are calculated using Wn values as references.

**Figure 1.** Fourteen intermolecular H-bonded complexes. Color codes: O (red), N (blue), C (dark gray), and H (light gray).

superposition errors (BSSE). The original SAPT results are equivalent to the vertical bond dissociation energies, that is, such SAPT calculations do not consider the structure relaxation energy, which results from the difference between the geometry of the isolated monomer and the geometry of the monomer in the dimer. On the other hand, the HB binding energies for DFT were calculated by using the supermolecular model. To facilitate the comparison with the DFT results, we calculated the relaxation energy at the MP4(SDTQ)/aug-cc-pVTZ//MP2(full)/aug-cc-pVDZ level and added it to the SAPT results to obtain the SAPT supermolecular binding energy  $D_e^{\text{SAPT}}$  (see eq 1)

$$D_e^{\text{SAPT}} = -E_{\text{int}}^{\text{SAPT}} + (E_{\text{monomer}}^{\text{A}} - E_{\text{dimer}}^{\text{A}}) + (E_{\text{monomer}}^{\text{B}} - E_{\text{dimer}}^{\text{B}}) \quad (1)$$

where  $E_{\text{monomer}}^{\text{A}}$  and  $E_{\text{dimer}}^{\text{A}}$  are the calculated energies adopting the optimized geometry of the isolated monomer and the geometry of the monomer in the dimer, respectively. This methodology has been applied to the HB06/04 database.<sup>11</sup> The results are shown in Table 3. Clearly, SAPT achieved a similar accuracy for the HB binding energies as the Wn theory, with a MAD of 0.6 kJ/mol.

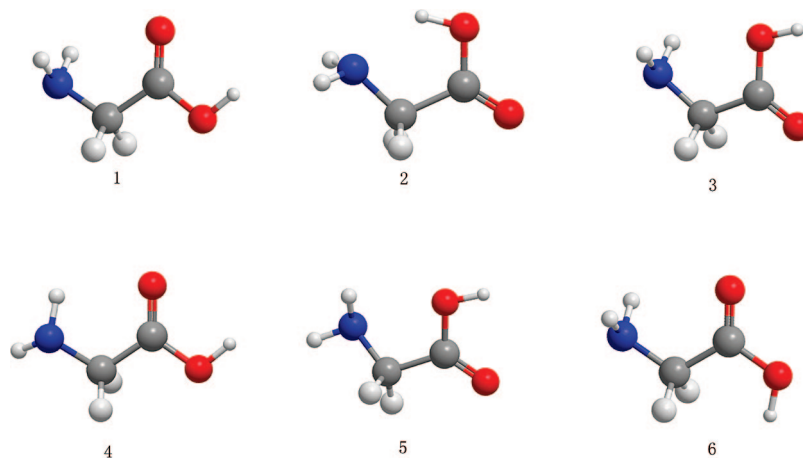
**2.2. Intermolecular HB Complexes.** The HB complexes shown in Figure 1 were chosen to simulate the intermolecular HBs between the main function groups of amino acids (i.e., amino, hydroxyl, carboxyl, and peptide bond group).<sup>37</sup> They are representatives of HB interactions most frequently

appearing in biochemical systems. Each dimer in D1-D7 contains a single XH...Y HB, where X, Y = N or O. Each dimer in D8-D11 contains a cyclic XH...Y HB, where X (N or O) acts both as a proton donor and acceptor. Such kinds of HBs are believed to play an important role in proton transfer reactions. Each dimer in D12-D14 contains two XH...Y HBs that form a cycle. HB interactions in D12-D14 are usually strong.

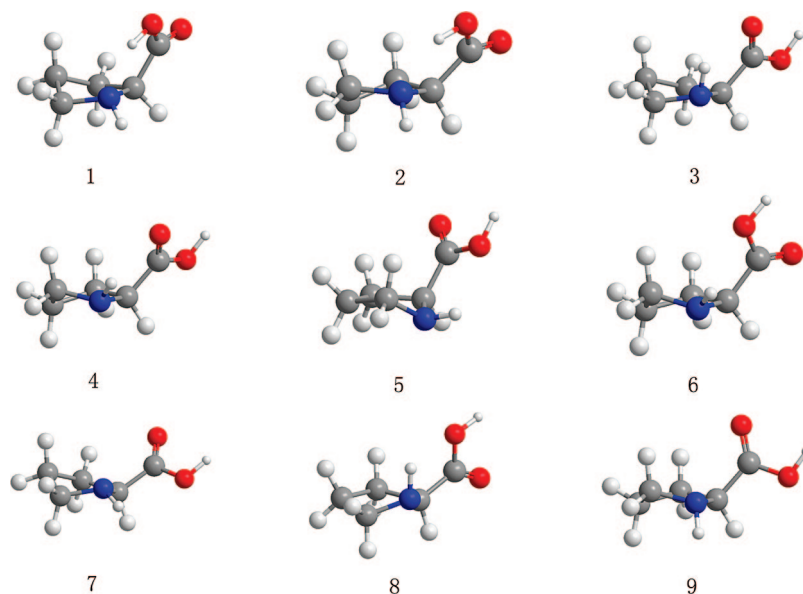
We do not include XH... $\pi$  interactions in our testing set. This type of interactions deserves special attention for its biologic significance.<sup>38</sup> While the electrostatic interaction is mainly responsible for the attraction in the conventional XH...Y HBs, the major source of attraction in the XH... $\pi$  interaction is the dispersion interaction,<sup>39</sup> and it is well-known that the commonly used LDA and GGA, designed for nonuniform electron gases, fail to capture the essence of vdW energies.<sup>40</sup> Hence the conclusion of the present work should be taken with caution for the biological systems containing aromatic side-chains.

**2.3. Conformational Analysis for Amino Acids and Glycine Dipeptide.** Amino acids and peptides are building blocks of proteins. From the simplest glycine to more complex peptides, each molecule may have many conformers. These conformers are stabilized by intramolecular HBs, which are counterbalanced by destabilizing steric strain and lone-pair electron-repulsion interaction. The performance of the DFT methods on describing the intramolecular HB





**Figure 2.** Six conformers of gaseous glycine. Color codes: O (red), N (blue), C (dark gray), and H (light gray).



**Figure 3.** Nine conformers of gaseous proline. Color codes: O (red), N (blue), C (dark gray), and H (light gray).

interactions may be judged via the conformational analysis of the amino acids. We selected six conformers of glycine,<sup>41</sup> nine conformers of proline,<sup>42</sup> and twelve conformers of serine,<sup>43</sup> where some of their accurate energetics are available in the literature.<sup>41,42</sup> The geometries are depicted in Figures 2, 3, and 4, respectively.

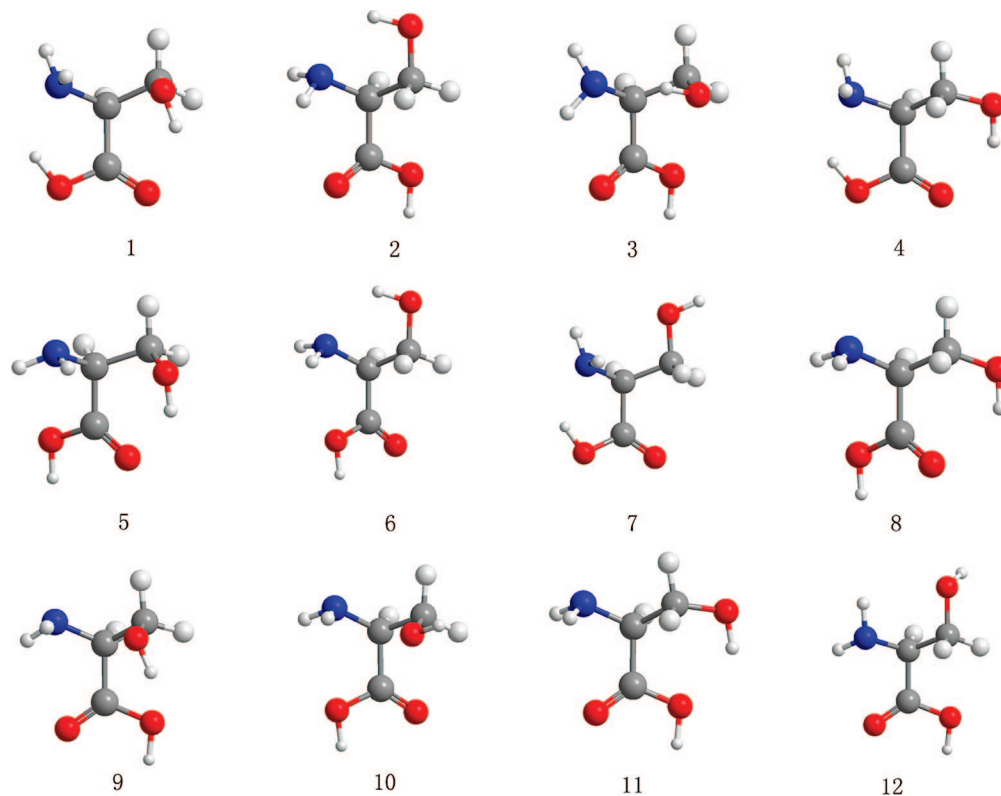
While single amino acids provide simple examples of intramolecular HBs, small peptides are better representatives of proteins. Figure 5 depicted three conformers of glycine dipeptide.<sup>44</sup> However, it should be noted that there may exist  $\pi-\pi$  interactions, resulting from each amide plane of the polypeptide backbone. The interplay between HB interactions and vdW interactions is very important in a bioapplication, which poses a great challenge to DFT.

**2.4. Computational Methods.** Eleven DFT methods, including LDA, PBE, mPWPW91, TPSS, B3LYP, X3LYP, PBE0, O3LYP, B97-1, MPW1K, and TPSSh, have been examined here. At the beginning, we have also included VSXC. It turned out VSXC has a strong tendency to overestimate CH...Y (Y = N or O) interactions, which

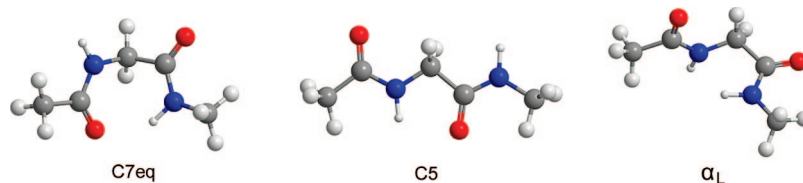
frequently led to failure of optimizations or wrong structures. Hence VSXC's results are not presented in this paper.

All geometries were optimized with the 6-311++G-(2d,2p) basis sets.<sup>45,46</sup> Analytical vibrational frequency calculations were performed to ensure that each minimum is a true local minimum, containing only positive frequencies. For HB complexes, single point calculations with the 6-311++G(3df,2pd) basis sets<sup>45-47</sup> were employed to calculate the zero-point-exclusive binding energies,  $D_e$ , which were then compared to the corresponding reference values to check validity of a functional. Relative energies of the different HB conformations made from the same pair of monomers were calculated by subtracting the binding energies (which is equivalent to the subtractions of the total energies). Functional performances were evaluated based on MADs as well as variance analysis (VAR) from the reference data.

For conformational analysis of the amino acids and glycine dipeptide, the geometries and energies were obtained with the 6-311++G(2d,2p) basis sets. The reference values were



**Figure 4.** Twelve conformers of gaseous serine. Color codes: O (red), N (blue), C (dark gray), and H (light gray).



**Figure 5.** Three Ramachandran conformers of glycine dipeptide. Color codes: O (red), N (blue), C (dark gray), and H (light gray).

calculated by using the G3 theory, which were then compared with the high level *ab initio* results in the literatures.<sup>41,42</sup>

In the present work, the SAPT interaction energy calculations were performed by using the SAPT2006 program package.<sup>33</sup> All other calculations were performed by using the Gaussian 03 program package.<sup>48</sup>

### 3. Results and Discussion

#### 3.1. Intermolecular Hydrogen Bonded Complexes.

**3.1.1. HB Binding Energies.** Table 4 shows the calculated binding energies of fourteen HB dimers as shown in Figure 1. With respect to  $D_e^{\text{SAPT}}$ , errors of LDA are dramatic, ranging from 10 to 50 kJ/mol. On average, LDA overestimates the bond strength of a single HB by 15 kJ/mol. But errors are more than tripled when forming a cyclic HB complex (i.e., D13 or D14 in Table 4 and Figure 1), which comprises two HBs. GGAs significantly amend this error. MADs of the PBE and PBE0 functionals are only 2.55 and 2.64 kJ/mol, respectively, being the best functionals as claimed by Zhao and Truhlar.<sup>11</sup> MADs associated with TPSS and TPSSH are 5.09 and 5.10 kJ/mol, which argue the advantage of meta-GGAs for the description of HBs.<sup>26</sup> Table 4 shows that B97-1 and X3LYP are the second best

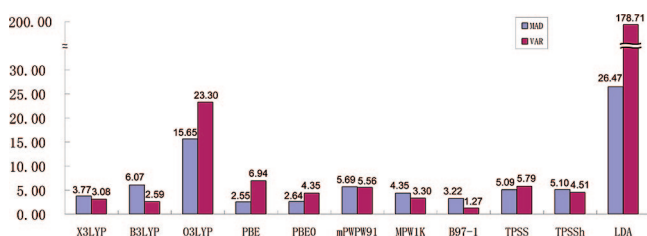
performers, giving MADs of 3.24 and 3.77 kJ/mol, respectively. Even though mPW was claimed to have improved behavior in low density (large gradient) regions,<sup>11-15</sup> which is important for HB, MADs associated with mPW are 4.34 (MPW1K) and 5.69 kJ/mol (mPWPW91). B3LYP's performance is actually not far from mPWPW91, leading to a MAD of 6.07 kJ/mol. A severe underestimation (about 10–23 kJ/mol) can be found with O3LYP (Table 4), reconfirming the conclusion that O3LYP cannot be recommended for treating HB systems.<sup>11,24</sup>

As seen from Figure 6 and Table 4, the functional performance based on the VAR data is not identical to that based on MADs. As HB strengths for D1-D14 are ranging from 16 to 67 kJ/mol, a small VAR associated with a method may suggest that this method is able to deal with HB of varying strength on an equal footing. From Table 4, it is clear that LDA leads to too high VAR (178.71 kJ<sup>2</sup>/mol<sup>2</sup>), as errors may accumulate for multiple HB complexes. Errors associated with O3LYP (VAR = 23.30 kJ<sup>2</sup>/mol<sup>2</sup>) are also very large, rendering it again an unsuitable method for HBs. MPW1K (VAR = 3.30) improves over mPWPW91 (VAR = 5.56 kJ<sup>2</sup>/mol<sup>2</sup>), even though the former was originally fitted against the kinetic data.<sup>11</sup> The larger portion of the exact

**Table 4.** Binding Energies of the Intermolecular Hydrogen-Bonded Complexes<sup>a</sup>

dimer <sup>b</sup>	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	MAD	VAR <sup>e</sup>
LDA	31.43	28.93	33.11	39.06	38.01	46.85	55.31	63.77	72.24	83.76	89.61	96.30	110.07	119.51	26.47	178.71
PBE	13.93	13.81	15.82	21.88	19.41	26.19	30.42	35.61	39.66	45.65	54.94	59.12	66.36	69.25	2.55	6.94
mPWPW91	11.09	10.67	12.47	19.08	16.28	23.01	26.11	31.42	35.27	41.30	50.88	54.10	61.38	64.22	5.69	5.56
TPSS	11.31	11.28	12.93	19.54	16.67	23.43	27.00	31.79	36.03	42.51	50.90	55.05	62.36	65.31	5.09	5.79
B3LYP	10.29	11.51	13.35	19.46	17.53	23.77	27.99	29.75	35.02	39.87	46.99	53.64	60.50	62.30	6.07	2.59
X3LYP	11.88	13.31	15.23	21.21	19.50	25.77	30.50	32.05	37.61	42.55	48.83	56.61	63.64	65.56	3.77	3.08
PBE0	13.01	14.06	16.02	21.25	19.83	26.36	31.30	34.31	38.83	44.22	52.72	58.66	66.02	68.74	2.64	4.35
O3LYP	6.78	7.32	8.62	13.51	12.05	17.24	18.62	20.71	23.10	26.69	36.78	38.87	43.76	44.02	15.65	23.30
B97-1	13.64	14.69	16.48	21.21	19.87	25.90	31.34	33.56	37.57	42.09	50.25	56.94	63.22	64.85	3.22	1.27
MPW1K	11.05	12.68	14.52	19.62	18.58	24.94	29.79	31.55	36.40	41.71	49.54	55.94	63.60	66.40	4.35	3.30
TPSSh	11.16	11.60	13.27	19.44	17.03	23.66	27.62	31.53	35.87	41.99	50.23	55.06	62.35	65.17	5.10	4.51
D <sub>e</sub> <sup>SAPTc</sup>	16.36	18.95	21.21	22.89	22.93	28.74	36.40	37.11	40.17	43.39	54.14	61.17	66.65	66.90		
W1 <sup>d</sup>												62.51		67.57		

<sup>a</sup> Units: kJ/mol. <sup>b</sup> The structures of D1-D14 are depicted in Figure 1. <sup>c</sup> D<sub>e</sub><sup>SAPT</sup> refers to the SAPT supermolecular binding energies, obtained by the combination of the SAPT interaction energies and the corresponding structural relaxation energies at MP4 (see eq 1). <sup>d</sup> W1 values are taken from ref 11. <sup>e</sup> VAR =  $[n\sum X^2 - (\sum X)^2]/n(n-1)$ , where  $X$  is the difference between DFT results and the corresponding SAPT results, and  $n = 14$ . Units: kJ<sup>2</sup>/mol<sup>2</sup>.



**Figure 6.** Statistic data of DFTs on binding energy calculations of fourteen intermolecular hydrogen-bonded complexes. MAD (mean absolute deviation) in kJ/mol and VAR (variance) in kJ<sup>2</sup>/mol<sup>2</sup>.

exchange should contribute to the improvement. Significantly, the best performers, based on the VAR data, are B97-1 (1.27), B3LYP (2.59), and X3LYP (3.08 kJ<sup>2</sup>/mol<sup>2</sup>). On the other hand, VARs of PBE (6.94) and PBE0 (4.35 kJ<sup>2</sup>/mol<sup>2</sup>) are considerably high. This may be related to the fact that PBE and PBE0 overshoot the target values of D<sub>e</sub><sup>SAPT</sup> such as those in D10 and D14 but underestimate HB strengths of other conformers. From Table 4, we see that TPSS improves over PBE, having a smaller VAR of 5.79 kJ<sup>2</sup>/mol<sup>2</sup>. A smaller VAR may suggest that errors be more systematic. This property is very important when the relative energies rather than the absolute energies are concerned. We will see this in the following discussion.

**3.1.2. Relative HB Energies.** Complexes D11 and D2 are formed with the same pair of monomers. The geometric difference between them is the reorganization of hydrogen bonds. The same relationship can be found between other four pairs of monomers (i.e. D8 and D3, D10 and D5, D9 and D6, D13 and D7). Table 5 summarizes the reorganization energies obtained by using SAPT and various flavors of DFT methods. MADs for these five pairs with respect to the SAPT values are also presented. Clearly, B97-1, B3LYP, and X3LYP are the best performers, giving MADs less than 1.5 kJ/mol.

In terms of MAD of the relative HB energies, data in Table 5 show that there is a general improvement over the calculated HB data as listed in Table 4. This is understandable, as errors associated with a functional may cancel out, to some extent, when we take the difference of two HB systems. On the other hand, we should note that errors can

**Table 5.** Relative Energies between Dimers Made of the Same Pair of Monomers<sup>a</sup>

dimer <sup>b</sup>	D11-D2	D8-D3	D10-D5	D9-D6	D13-D7	MAD
LDA	60.68	30.65	45.75	25.39	54.77	20.80
PBE	41.09	19.79	26.23	13.47	35.94	4.64
mPWPW91	40.21	18.91	25.02	12.22	35.27	3.68
TPSS	39.62	18.86	25.84	12.60	35.35	3.80
B3LYP	35.48	16.40	22.38	11.21	32.55	1.05
X3LYP	35.48	16.82	23.05	11.84	33.14	1.42
PBE0	38.66	18.28	24.39	12.47	34.73	3.05
O3LYP	29.46	12.09	14.64	5.86	25.15	5.23
B97-1	35.56	17.11	22.22	11.67	31.84	1.05
MPW1K	36.86	17.03	23.14	11.51	33.81	1.80
TPSSh	38.64	18.26	24.96	12.20	34.74	3.11
D <sub>e</sub> <sup>SAPTc</sup>	35.19	15.90	20.46	11.46	30.25	

<sup>a</sup> Units: kJ/mol. <sup>b</sup> The structures are depicted in Figure 1. Each dimer pair differs only in interaction modes. <sup>c</sup> MAD are calculated using SAPT values as references.

be irregular. Take D11-D2 as an example, errors may depend on type and strength of the HB interactions. Hence, different errors encounter at a single HB of the N-H...O type of 16 kJ/mol as in D2 and a cyclic HB of the O...H-N...H-O type of 52 kJ/mol as in D11. Clearly, the accuracy of a functional to describe the relative HB binding energies is very important, as the relative binding energies play a decisive role in determining the best binding interaction mode among different configurations.

As compared data in Tables 5 and 4, we see that the largest improvement (10.42 kJ/mol) on the description of the relative HB strength is seen for O3LYP. Nevertheless, a MAD of 5.23 kJ/mol still ranks O3LYP as the second poorest method other than LDA. Noteworthy, PBE and PBE0 provide an exception. Instead of error cancelation, errors accumulate for the relative binding energy predictions, leading to MADs of 4.64 and 3.05 kJ/mol, respectively. We conclude that such a disturbing behavior significantly downplays the role of PBE and PBE0 for the description of a biosystem, where HB interactions of different types and strengths compete with each other.

**3.1.3. Hydrogen Bond Distances.** We also looked into the hydrogen bond distances predicted by each DFT method. Table 6 shows that there is a simple correlation between the calculated H-bond distance and the calculated binding energy,

**Table 6.** Hydrogen Bond Distances (DH...A<sup>b</sup>) of the Intermolecular Hydrogen-Bonded Complexes<sup>a</sup>

	1 NH...N	2 NH...OC	3 NH...OC	4 OH...OC	5 OH...OC	6 OH...OC	7 NH...OC	8 NH...N	9 OH...OC	10 OH...O	11 OH...N	12 NH...OC	13 OH...OC	14 OH...OC
LDA	1.99	2.09	2.00	1.71	1.81	1.70	1.76	1.76	1.65	1.49	1.45	1.62	1.41	1.37
PBE	2.21	2.42	2.19	1.89	1.99	1.87	1.97	1.95	1.86	1.69	1.62	1.81	1.59	1.59
mPWPW91	2.25	2.50	2.21	1.91	1.99	1.88	1.99	1.96	1.87	1.69	1.63	1.82	1.60	1.60
TPSS	2.25	2.52	2.21	1.90	1.99	1.88	1.98	1.97	1.87	1.70	1.66	1.82	1.61	1.61
B3LYP	2.29	2.45	2.22	1.93	2.02	1.91	2.02	2.03	1.92	1.75	1.70	1.87	1.65	1.67
X3LYP	2.27	2.41	2.20	1.91	2.02	1.90	2.00	2.02	1.91	1.75	1.70	1.86	1.64	1.66
O3LYP	2.52	2.96	2.46	2.07	2.16	2.03	2.19	2.11	2.05	1.82	1.72	1.98	1.71	1.73
PBE0	2.23	2.39	2.19	1.90	1.99	1.87	1.97	1.98	1.88	1.71	1.65	1.83	1.61	1.62
B97-1	2.28	2.44	2.23	1.93	2.05	1.92	2.02	2.02	1.93	1.76	1.69	1.87	1.65	1.67
MPW1K	2.26	2.40	2.19	1.91	2.00	1.88	1.98	2.00	1.89	1.73	1.68	1.84	1.62	1.63
TPSSh	2.25	2.49	2.21	1.90	1.99	1.88	1.98	1.98	1.87	1.71	1.67	1.83	1.61	1.62

<sup>a</sup> Units: Å. <sup>b</sup> DH...A is the shortest hydrogen-acceptor distance in each complex.**Table 7.** Relative Energies of Six Conformers of Glycine Given by DFTs with 6-311++G(2d,2p)<sup>a</sup>

conformer <sup>b</sup>	1p	2n	3n	4n	5n	6p	MAD <sup>d</sup>
LDA	0.00	-11.19	6.30	1.60	11.13	20.22	3.84 (3.66)
PBE	0.00	-2.27	6.17	5.10	11.83	19.41	1.68 (1.31)
mPWPW91	0.00	-1.96	6.18	5.36	11.92	19.52	1.61 (1.28)
TPSS	0.00	-2.06	6.09	5.43	11.61	19.71	1.56 (1.23)
B3LYP	0.00	2.50	6.72	5.56	11.63	21.08	0.41 (0.66)
X3LYP	0.00	2.47	6.76	5.42	11.57	21.21	0.40 (0.65)
O3LYP	0.00	3.20	6.63	6.18	11.95	20.29	0.71 (0.84)
PBE0	0.00	0.53	6.91	5.19	12.24	20.77	0.78 (0.90)
B97-1	0.00	2.00	6.68	5.74	11.96	20.58	0.59 (0.59)
MPW1K	0.00	2.47	7.35	5.39	12.47	21.78	0.71 (1.06)
TPSSh	0.00	-0.82	6.42	5.42	11.76	20.26	1.17 (1.04)
G3	0.00	2.68	6.98	5.25	10.66	20.75	—
'best' literature value <sup>c</sup>	0.00	2.05	6.70	5.15	10.51	19.76	0.43

<sup>a</sup> Units: kJ/mol. <sup>b</sup> See Figure 2 for structures. The labeling scheme was introduced by Császár who used p to denote conformers of  $C_s$  symmetry and n to those of  $C_1$  symmetry.<sup>41</sup> <sup>c</sup> The 'best literature value' is Császár's 'final prediction',<sup>41</sup> which is the extrapolation of the MP2 energy to the infinite-order. <sup>d</sup> MADs are given with respect to the G3 values. Numbers in parentheses are MADs with respect to the 'best' literature values.

i.e., a method that predicts a stronger H-bond always gives a shorter H-bond distance. For example, the H-bond distances obtained by X3LYP are systematically shorter than those of B3LYP. This is consistent with the trend that B3LYP generally underestimates HB energies. Hence, O3LYP gives the longest H-bond distances and the lowest binding energies, while LDA give the shortest H-bond distances and the highest binding energies.

**3.2. Conformational Analysis of Amino Acids.** **3.2.1. Glycine.** Table 7 shows the relative energies of six selected conformers of gaseous glycine (see Figure 2). We follow the labeling scheme introduced by Császár who used p to denote conformers of  $C_s$  symmetry and n to those of  $C_1$  symmetry.<sup>41</sup> Our calculated values by the G3 theory compare well with Császár's 'final prediction', which is the extrapolation of the MP2 energy to the infinite-order with an estimated maximum error of ~1.2 kJ/mol. We anticipate that the G3 values are more accurate, as it is extrapolated to QCISD(FULL,T)/6-311+G(3d2f,2df,2p) plus an empirical high level correction. The MAD data with respect to G3 in Table 7 seem to suggest that all functionals, other than PBE and mPWPW91, work well, with X3LYP, B3LYP, and B97-1 being better than others (MADs = 0.40–0.59 kJ/mol). There is a significant improvement for B3LYP to estimate the relative HB energies. Even O3LYP leads to only a MAD of 0.71 kJ/mol. Noteworthily, LDA, PBE, mPWPW91, and TPSS give MADs larger than 1.50 kJ/mol, respectively. In fact, these functionals fail to correctly predict the most stable conformer, erroneously putting 2n lower in energy than 1p. Even though PBE, mPWPW91, and TPSS have been suggested to be good performers for HB,<sup>11,26</sup> clearly, such a conclusion has to be taken with caution based on our present results.

**3.2.2. Proline.** Table 8 shows the relative energies of nine conformers of gaseous proline (see Figure 3). The 'best' literature values were taken from ref 42. These are from the focal-point approach, by extrapolating the RHF and MP2 energies to the complete basis set limit, appending coupled-cluster energy increments to the extrapolated results, and finally adding the core correlation corrections and relativistic



**Table 8.** Relative Energies of Nine Conformers of Proline Given by DFTs with 6-311++G(2d,2p)<sup>a</sup>

conformer <sup>b</sup>	1	2	3	4	5	6	7	8	9	MAD <sup>d</sup>
LDA	0.00	4.21	19.59	20.51	26.74	26.74	31.05	28.96	32.59	12.00 (12.58)
PBE	0.00	2.14	11.39	11.48	18.39	19.00	20.52	20.18	21.17	4.09 (4.33)
mPWPW91	0.00	2.08	11.22	11.19	18.36	18.71	20.20	19.82	20.76	3.86 (4.10)
TPSS	0.00	2.18	11.28	11.14	17.88	18.36	19.86	19.73	20.70	3.69 (3.93)
B3LYP	0.00	1.75	6.89	6.15	13.61	13.87	14.22	15.24	15.60	0.93 (0.47)
X3LYP	0.00	1.84	6.83	6.13	13.47	13.87	14.19	15.35	15.71	0.88 (0.41)
O3LYP	0.00	1.18	6.05	5.54	13.93	13.33	14.21	14.02	15.32	1.48 (0.96)
PBE0	0.00	2.48	8.97	8.66	15.97	16.96	17.81	18.84	19.41	2.11 (2.42)
MPW1K	0.00	2.60	7.27	6.63	14.38	15.40	15.75	17.78	17.95	0.86 (1.05)
B97-1	0.00	1.93	7.37	7.03	13.94	14.68	15.55	15.99	16.63	0.53 (0.49)
TPSSh	0.00	2.33	10.30	9.91	16.81	17.49	18.66	19.14	19.92	2.83(3.10)
G3	0.00	3.56	7.11	7.43	13.43	14.72	14.90	16.67	16.57	—
'best' literature value <sup>c</sup>	0.00	2.20	6.64	6.80	13.19	14.68	14.78	15.48	15.97	0.58

<sup>a</sup> Units: kJ/mol. <sup>b</sup> See Figure 3 for structures. <sup>c</sup> The 'best' literature values are from ref 42, which are the extrapolation of the CCSD(T) energies to the infinite-order. The value for conformer 7 was miscalculated to be 18.54 kJ/mol. We updated it here as 14.78 kJ/mol. See text for more details. <sup>d</sup> MADs are given with respect to the G3 values. Numbers in parentheses are MADs with respect to the 'best' literature values.

**Table 9.** Relative Energies of Twelve Conformers of Serine Given by DFTs with 6-311++G(2d,2p)<sup>a</sup>

conformer <sup>b</sup>	1	2	3	4	5	6	7	8	9	10	11	12	MAD <sup>c</sup>
LDA	0.00	9.51	9.68	-5.11	14.45	18.08	9.04	20.54	24.41	30.47	22.47	33.04	9.81
PBE	0.00	3.35	7.13	0.03	9.18	10.46	8.81	13.38	14.96	20.01	16.66	22.52	3.46
mPWPW91	0.00	3.04	7.14	0.27	9.01	10.02	8.45	13.01	14.60	19.50	16.36	22.15	3.21
TPSS	0.00	3.16	7.13	0.62	8.47	10.03	8.76	12.70	14.71	19.49	16.52	22.71	3.16
B3LYP	0.00	0.56	3.95	1.47	5.83	7.46	7.74	8.56	10.25	14.05	12.33	17.60	1.09
X3LYP	0.00	0.73	3.82	1.42	5.81	7.70	7.93	8.62	10.32	14.13	12.41	17.68	1.02
O3LYP	0.00	-0.54	4.63	2.23	6.78	6.25	7.20	8.56	9.44	13.84	12.16	16.98	1.44
PBE0	0.00	2.65	5.36	1.02	8.59	10.11	8.91	11.80	13.10	17.57	15.48	21.23	2.29
MPW1K	0.00	1.97	4.27	1.69	7.50	9.60	8.91	10.40	11.80	15.83	14.51	20.25	1.34
B97-1	0.00	1.23	4.66	1.57	6.77	8.30	8.42	9.66	10.96	15.28	13.12	19.09	1.01
TPSSh	0.00	2.87	6.33	1.03	8.36	9.92	8.75	12.13	13.85	18.38	15.98	22.01	2.66
G3	0.00	1.79	2.93	3.02	5.49	8.81	9.39	9.43	9.59	12.96	13.46	18.74	

<sup>a</sup> Units: kJ/mol. <sup>b</sup> See Figure 4 for structures. <sup>c</sup> MADs are given with respect to the G3 values.

corrections. The uncertainty of these final values was estimated to be 2 kJ/mol. Our G3 values are also listed in Table 8. We anticipate that the G3 values are less accurate due to the finite basis set effect. There is, however, an inconsistency among data of ref 42 for conformer 7. We recalculated the MP2/cc-pVTZ data and concluded that the energy reported in ref 42 for conformer 7 is in error. Our final value following the same focal-point approach<sup>42</sup> led to 14.78, instead of 18.54 kJ/mol.

The MAD data with respect to the best numbers show that the results of X3LYP, B3LYP, and B97-1 (0.41–0.49 kJ/mol) are much better than those of PBE and mPWPW91 (4.33 and 4.10 kJ/mol, respectively). MAD of PBE is ten times larger than that of X3LYP. For conformers 3–9, PBE and mPWPW91 significantly underestimate their stabilities.

All DFT methods correctly predict that conformer 1 is the global minimum, and the trend of relative stabilities of different conformers is generally correct. However, there are some notable exceptions. While conformers 3 and 4 have comparable stabilities, the reference value suggests that conformer 3 is more stable than conformer 4. All DFT methods, except LDA and PBE, predict the reverse relative stability. From Table 8, we see that LDA, PBE, and TPSS erroneously predict that conformer 8 is more stable than conformer 7. O3LYP also reverses the relative stability of 5 and 6 as well as 7 and 8.

**3.2.3. Serine.** Table 9 shows the relative energies of twelve conformers of gaseous serine (see Figure 4). We calculate

the reference values by using the G3 theory, as there are no reliable and accurate reference data available in the literature. MADs of X3LYP, B3LYP, and B97-1 are around 1 kJ/mol, being the best performers. LDA is again the worst performer (MAD = 9.81 kJ/mol). MADs of PBE, mPWPW91, and TPSS are 3.46, 3.21, and 3.16 kJ/mol, respectively, being unsatisfactory. O3LYP leads to a MAD of 1.44 kJ/mol. Nevertheless, it erroneously predicts conformer 2, instead of conformer 1, as the global minimum. X3LYP, B3LYP, and B97-1 generally give the correct trend for the relative stability of different conformers, although they reverse the trend between conformers 3 and 4 as well as conformers 10 and 11. From Table 9, we can see that LDA, PBE, PBE0, mPWPW91, TPSS, and TPSSh fail to give a qualitative trend. They reverse the trend between conformers 10 and 11 and mess up conformers from 2 to 7. Hence these functionals may not be suitable for the description of intramolecular HB interactions.

Taking all three amino acids into consideration (Tables 7–9), we may conclude that as the complexity of the amino acid increases, the accuracy of PBE, PBE0, mPWPW91, TPSS, or TPSSh decreases. The performance of X3LYP, B3LYP, and B97-1 is stable, giving MADs of 1 kJ/mol or less in conformational analysis of all three amino acids, holding promise for the study of HBs of peptides and proteins, which are linkages of amino acids.

**3.2.4. Glycine Dipeptide.** Table 10 shows the relative energies of three Ramachandran conformers of gaseous

**Table 10.** Relative Energies of Three Ramachandran Conformers of Glycine Dipeptide Given by DFTs with 6-311++G(2d,2p)<sup>a</sup>

conformer <sup>a</sup>	C7	C5	$\alpha_L$	MAD <sup>b</sup>
LDA	0.00	7.29	14.81	1.34
PBE	0.00	2.75	8.85	3.92
mPWPW91	0.00	2.54	8.58	4.16
TPSS	0.00	3.20	8.99	3.62
B3LYP	0.00	1.14	8.79	4.75
X3LYP	0.00	1.38	9.17	4.44
O3LYP	0.00	-1.19	5.73	7.45
PBE0	0.00	0.96	8.62	4.93
MPW1K	0.00	-0.31	8.19	5.78
B97-1	0.00	1.64	8.53	5.09
TPSSh	0.00	2.24	8.78	4.21
G3	0.00	6.91	12.52	

<sup>a</sup> Units: kJ/mol. <sup>a</sup> See Figure 5 for structures. <sup>b</sup> MADs are given with respect to the G3 values.

glycine dipeptide (see Figure 5). We followed the labeling scheme in ref 44, using C7eq, C5, and  $\alpha_L$  to label the H-bonded cycle conformer, the unfolded conformer, and the "L" conformer. The structures were taken from ref 44 and reoptimized by using each method examined here. It is known that the  $\alpha_R$  conformer is not an energy minimum for dipeptide,<sup>49</sup> so this conformer is not considered in this work. We calculated the reference values by using the G3 theory.

Though all functionals, except O3LYP and MPW1K, gave the right trend for the relative energy, none of them, with the exception of LDA, gave results which were quantitatively similar to those of the G3 theory. From the results and discussion in the preceding sections, we see that B97-1, X3LYP, and B3LYP are capable of giving a good description of the relative bond strengths of HB interactions, the degraded performance for these functionals for dipeptide has to be attributed to their limitations in the description of inter-residual nonbonded interactions.<sup>49</sup> It should be noted that there are  $\pi$  electrons, delocalized in the orbitals that are perpendicular to the amide plane. According to the Ramachandran map, the C5 conformer has ( $\Phi$ ,  $\Psi \approx 180^\circ$ ,  $180^\circ$ ), the C7eq conformer has ( $\Phi$ ,  $\Psi \approx -60^\circ$ ,  $60^\circ$ ), and the  $\alpha_L$  conformer has ( $\Phi$ ,  $\Psi \approx 60^\circ$ ,  $60^\circ$ ). Hence, the  $\pi$ - $\pi$  interactions are minimized in C5 and maximized in C7eq, while the strength of the  $\pi$ - $\pi$  interaction in  $\alpha_L$  is placed in the middle of the three. To take effective error cancelations for the dispersion interactions, one may choose  $\alpha_L$  as the reference conformer, such that MADs are reduced to 2.64–2.89 kJ/mol for B97-1, X3LYP, and B3LYP from the original 4.44–4.75 kJ/mol as shown in Table 10 where C7eq is used as the reference conformer.

For the performance of other functionals, it is a result from error cancelations (or accumulations) for the description of HB and vdW interactions. Hence, the interplay between HB and vdW interactions is very important in a bioapplication, which poses a great challenge to DFT. Significantly, LDA, being so poor for the description of HBs and vdWs<sup>11</sup> either alone, gave a very good performance in the case of glycine dipeptide (see Table 10). It would be interesting to see how effectively this error cancelation can carry on for the description of longer peptides.

## 4. Conclusion

We have examined the performance of some popular DFT methods (i.e., LDA, PBE, mPWPW91, TPSS, B3LYP, X3LYP, PBE0, O3LYP, B97-1, MPW1K, and TPSSh) on describing hydrogen-bond interactions. Here the emphasis has been laid not only on functionals' abilities to calculate the intermolecular hydrogen bonding energies but also on their performances of predicting the relative energies of intermolecular H-bonded complexes and the conformer stabilities due to intramolecular hydrogen bondings. As compared to the best theoretical values, we conclude the following:

(1) In terms of the intermolecular hydrogen bonding energies, PBE and PBE0 give the smallest MADs. These two functionals, however, always lead to large errors for the prediction of the relative energies, giving wrong orders of intermolecular binding configurations and intramolecular conformations. Such conclusions can also be applied to mPWPW91 and MPW1K. TPSS and TPSSh did not always improve over PBE and PBE0.

(2) B3LYP, especially O3LYP, has a severe tendency to underestimate the intermolecular HB bindings. However, errors tend to cancel out in the predictions of relative HB energies and conformational energy differences. Errors associated with O3LYP are usually too large, lending this functional to not be recommended for bioapplications, whereas errors associated with B3LYP are usually small for relative HB energies, showing the value of this functional.

(3) X3LYP and B97-1 treat well all of the HB systems examined here. Not only do they give good results for intermolecular HB energies but also they are the best performers on calculating the relative energies of intermolecular HB complexes and amino acid conformers. We anticipate these functionals be good for systems where hydrogen bondings of varying types and strengths are all important.

(4) The interplay between HB and vdW interactions is very important in a bioapplication, which poses a great challenge to DFT. Other newer functionals (especially, the M06 series),<sup>50</sup> which are very promising but have not yet been available in the commercialized Gaussian package, will be examined in due time.

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