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Density Functionals for Noncovalent Interaction Energies of Biological Importance

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Abstract: Forty density functionals and one wavefunction method are assessed against a recently published database of accurate noncovalent interaction energies of biological importance. The comparison shows that two newly developed density functional theory (DFT) methods, PWB6K and M05-2X, give the best performance for this benchmark database of 22 noncovalent complexes, including both hydrogen-bonding and dispersion-dominated complexes. In contrast, the more popular B3LYP and PBEh functionals fail to describe the interactions in the dispersion-dominated complexes. The local spin density approximation and BHandH functionals give good performance for dispersion-dominated interactions at the expense of a large error for hydrogen bonding. PWB6K and M05-2X constitute a new generation of DFT methods based on simultaneously optimized exchange and correlation functionals that include kinetic energy density in both the exchange and correlation functional, and the present study confirms that they have greatly improved performance for noncovalent interactions as compared to previous DFT methods. We interpret this as being due to an improved treatment of medium-range correlation effects by the exchange-correlation functional. We recommend the PWB6K and M05-2X methods for investigating large biological systems and soft materials.

1. Introduction

Noncovalent interactions[1–10] play very important roles in biological science for problems such as protein folding and nucleobase packing and stacking. An accurate description of noncovalent interactions is also a key to predicting ligand binding and structures in proteins, DNA, and RNA. The accurate description of noncovalent interactions is also one of the challenges in modeling solvation, supramolecular chemistry, and soft materials. However, the available computational methods are not entirely satisfactory. On one hand, state-of-the-art correlated wave function theory [WFT; for example, CCSD(T)[11]] is prohibitively expensive to apply to the complex systems of interest. On the other hand, the more affordable density functional theory (DFT)[12–14] has only been widely validated for its capabilities to treat covalent interactions such as heat of formation and atomization energies, and validations are less complete for noncovalent interac-

tions. Furthermore, until very recently,[15–21] available density functionals were too inaccurate for many demanding problems including noncovalent interactions.[22–26]

The first step toward improving the functionals is to assess the quality of existing functionals to establish a baseline. To accomplish this, we developed[27] a database for noncovalent interactions that contains six hydrogen-bonded complexes (HB6/04), seven charge-transfer complexes (CT7/04), six dipole-interaction complexes (DI6/04), and nine weak-interaction complexes (WI9/04). More recently, we split the WI9/04 data and added more data to create a WI7/05 data set that excludes π–π stacking plus a separate data set of five π–π stacking complexes (PPS5/05).[28] Merging the HB6, CT7, DI6, WI7, and PP5 data sets gives a noncovalent database (NC31/05) that is composed of small complexes involving first-row and second-row elements. This has been employed to test DFT[27] and other model chemistry methods.[29] We have also employed this noncovalent database (along with other data including covalent interactions, barrier

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heights, and ionization potentials) to develop new DFT functionals, such as PWB6K[17] and M05-2X.[21] In a short communication,[19] we compared the performances of six DFT methods for the prediction of interaction energies of two hydrogen-bonded Watson−Crick base pairs, six stacked nucleobase pairs, and five amino acid residue pairs, and we found that PWB6K gives very good performance. In the present study, we expand the work in that communication, and we assess the capability of 40 density functionals and one level of WFT, namely Møller−Plesset second-order perturbation theory (MP2),[30] for predicting interaction energies against a benchmark noncovalent data set recently proposed by Jurecka et al.[31] Although the 40 functionals considered here represent a wide variety of functional types [local spin density,[32] generalized gradient approximation (GGA),[33−42] hybrid,[39−41,43−49] meta GGA,[50−52] and hybrid meta GGA[17,21,48,50,51,53−56]], none of them model the asymptotic dipolar nature of dispersion interactions explicitly. Thus, these functionals can be accurate at the distances of van der Waals minima but not in the long-range limit that would be important, for example, for small-angle scattering of rare gases in molecular beams.[57] Another class of functionals that considers the long-range functional forms explicitly is also being developed,[58−61] and these functionals are very promising. Nevertheless, they are beyond our scope in the present study.

Since 2003, the research groups of Hobza and Sponer have published several papers on accurate stabilization energies of hydrogen-bonded and stacked DNA and RNA base pairs[9,62−66] as well as amino acid residue pairs.[67] Recently, they merged all these data into a data set, called JCSH-2005.[31] The JSCH-2005 set consists of more than 100 DNA base pairs, amino acid residue pairs, and model complexes which are of biological importance. They also proposed a smaller screening set (S22) of 22 model complexes to quickly assess the quality of theoretical models. In the present study, the S22 database is employed to test 40 DFT functionals and one level of WFT: MP2. It is particularly appropriate to include MP2 in this study because it is widely used to study noncovalent interactions, when affordable (for moderate-size and large systems, it is considerably more expensive than DFT).

Section 2 describes the S22 database and the computational methods used in the present work. Section 3 presents results and discussion, and section 4 has concluding remarks.

2. Database and Computational Methods

2.1. S22 Database. The S22 database is a data set of 22 weakly bonded molecular complexes of biological importance. This database was developed by Jurecka et al., who divided the S22 set into three subsets, namely, seven hydrogen-bonded complexes, eight dispersion-dominated complexes (it might have been preferable to call the interactions in these complexes dispersion-like because some theorists define dispersion interactions only in the long-range limit, but we will use their label for consistency), and seven mixed complexes. The reference interaction energies for the S22 data set were calculated by the following scheme:

$$\Delta E^{CCSD(T)} \text{ CBS} = \Delta E^{MP2} \text{ CBS} + (\Delta E^{CCSD(T)} - \Delta E^{MP2})_{\text{small basis}} \quad (1)$$

where a complete basis set (CBS) limit CCSD(T) interaction energy is approximated by a CBS MP2 interaction energy plus a difference between CCSD(T) and MP2 interaction energies ($\Delta E^{CCSD(T)} - \Delta E^{MP2}$) evaluated with a relatively small basis set that was specifically designed[1,62] for this purpose. This is based on the assumption that the ($\Delta E^{CCSD(T)} - \Delta E^{MP2}$) term has faster convergence than $\Delta E^{CCSD(T)}$ with respect to the basis set, and thus this difference can be evaluated with a small or mid-sized basis set. This assumption has been validated for some model hydrogen-bonded[68] and stacked model complexes.[62] The best estimates of the interaction energies in the S22 database were taken from the paper by Jurecka et al.,[31] and they are listed in the Supporting Information (Table S1). The structures of these noncovalent complexes are shown in Figures 1−3.

2.2. Computational Methods. All DFT calculations were carried out using a locally modified *Gaussian 03*[69] program. The tested density functionals are detailed in Table 1. In each case, we specify the year that the functional was first published, the functional forms used for dependence on spin density (ρ_σ, where σ is the component of spin angular momentum along an axis) and the spin density gradient ($\nabla\rho_\sigma$), whether or not the functional includes spin kinetic energy density (τ_σ) in the exchange and correlation functionals, and whether the correlation functional is self-correlation-free (SCorF). Table 2 also contains two columns (one for the exchange functional and one for the correlation functional) that tell whether or not the functional reduces to the correct uniform electron gas (UEG) limit when $\nabla\rho_\sigma \rightarrow 0$ and $\tau_\sigma \rightarrow \tau_\sigma^{LSDA}$ (where τ_σ^{LSDA} is the value assumed by τ_σ in the UEG limit; LSDA stands for local spin density approximation) and another column that tells the percentage X of Hartree−Fock (HF) exchange in the functional.

Because many conventional DFT functionals (e.g., B3LYP and X3LYP) fail[23] to predict the minima of the stacked complexes in the S22 database, we test all 40 density functionals with the best estimated geometries specified in Table S1, and these geometries were obtained from the Supporting Information of the paper by Jurecka et al.[31] We also performed geometry optimization with the best performing functional, M05-2X, and these will be discussed separately (in section 3.6).

We used an augmented polarized valence double-ζ basis set labeled DIDZ [which is denoted 6-31+G(d,p)][70] for most of the calculations (all calculations except those discussed in section 3.5) We use the 6-31+G(d,p) basis set because the goal of the present paper is not to obtain benchmark interaction energies for these noncovalent complexes or study the prediction of the functionals in the theoretically interesting infinite-basis limit, but rather to assess the performance of DFT methods for the calculation of noncovalent interactions with a moderate basis set suitable for practical calculations on complex systems. Csonka et al.[71−73] reported that the diffuse functions are very important to obtain reasonable DFT results, but they also showed that the 6-31+G(d) basis set gives a systematic overbinding for weak
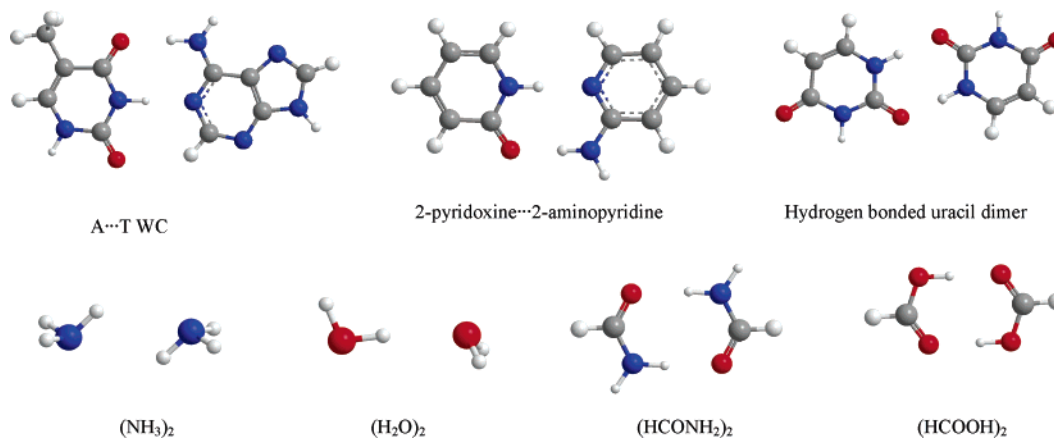
Noncovalent Interaction Energies

J. Chem. Theory Comput., Vol. 3, No. 1, 2007 **291**

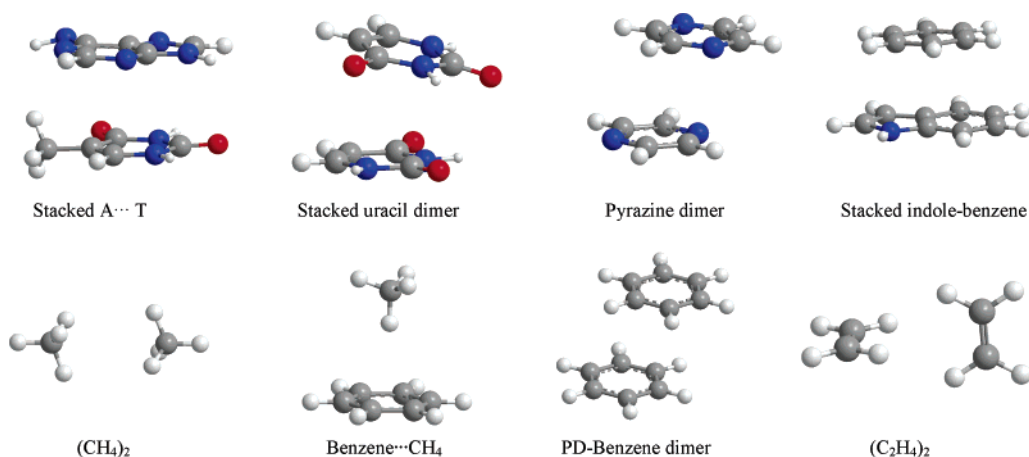**Figure 1.** Structures of hydrogen-bonded complexes.

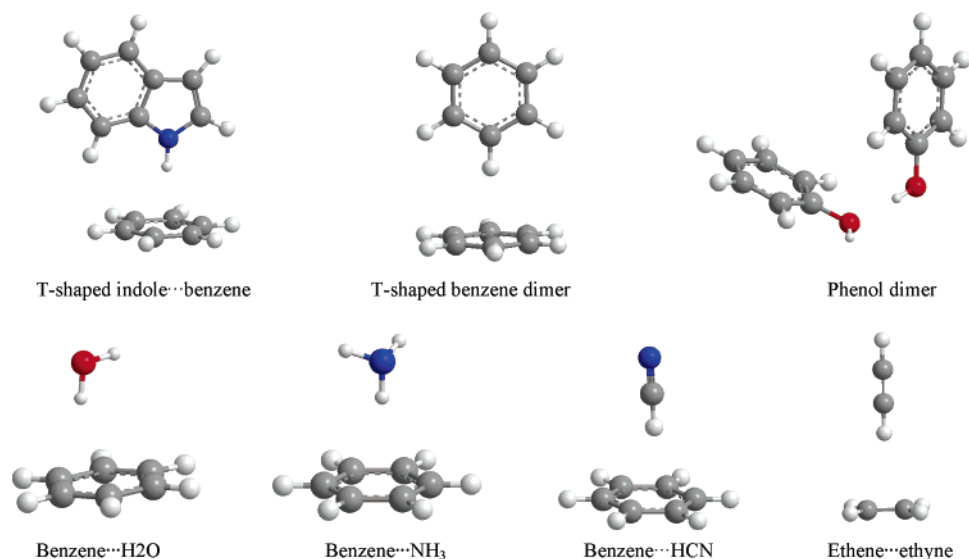**Figure 2.** Structures of dispersion-dominated complexes.

Figure 3. Structures of mixed complexes.

interactions, so we performed calculations both with and without counterpoise (CP) corrections[74,75] for basis set superposition error (BSSE). To investigate the effect of basis set size and confirm that the methods that give good results with the 6-31+G(d,p) basis set do not do so because of some accidental cancellation of functional-related errors and basis-set-related errors, we also performed calculations with a triple-ζ basis set, namely, 6-311+G(2df,2p).

For further analyses, and following the work by Shibasaki et al.,[76] we calculated the intermolecular potential of the $C_6H_6-CH_4$ complex with the 6-311+G(2df,2p) basis set.

3. Results and Discussion

The statistical errors for 15 methods (the four best-performing hybrid meta functionals, three best-performing hybrid GGAs, three best-performing meta-GGAs, three best-performing

Table 1. Tested DFT Methods

method	year	ref(s)	exchange				correlation			
			$\rho_\sigma \nabla\rho_\sigma$	X	τ?	UEG?	$\rho_\sigma, \nabla\rho_\sigma$	τ?	SCorF?	UEG?
BP86	1988	33, 34	B88	0	no	yes	P86	no	no	yes
BLYP	1988	34, 35	B88	0	no	yes	LYP	no	yes	no
PW91	1991	36	PW91	0	no	yes	PW91	no	no	yes
LSDA[a]	1992	32, 103	Slater	0	no	yes	PW91-L	no	no	yes
BHandH[b]	1993	34, 35	Slater	50	no	yes	LYP	no	yes	no
BHandHLYP[b]	1993	34, 35	B88	50	no	yes	LYP	no	yes	no
B3LYP	1994	34, 35, 43	B88	20	no	yes	LYP	no	yes	no
BB95	1996	34, 50	B88	0	no	yes	B95	yes	yes	yes
B1B95	1996	34, 50	B88	28	no	yes	B95	yes	yes	yes
G96LYP	1996	35, 37	G96	0	no	yes	LYP	no	yes	no
PBE	1996	38	PBE	0	no	yes	PBE	no	no	yes
mPWPW[c]	1998	36, 39	mPW	0	no	yes	PW91	no	no	yes
MPWLYP	1998	35, 39	mPW	0	no	yes	LYP	no	yes	no
mPWB95	1998	50, 39	mPW	0	no	yes	B95	yes	yes	yes
mPW1PW[d]	1998	36, 39	mPW	25	no	yes	PW91	no	no	yes
B98	1998	44	B98	21.98	no	no	B98	no	no	no
VSXC	1998	104	VSXC	0	yes	no	VSXC	yes	yes	no
HCTH	1998	40	HCTH	0	no	no	HCTH	no	no	no
B97−1	1998	40	B97-1	21	no	no	B97-1	no	no	no
PBEh[e]	1999	45	PBE	25	no	yes	PBE	no	no	yes
MPW1K	2000	46	mPW	42.8	no	yes	PW91	no	no	yes
B97-2	2001	40	B97-2	21	no	no	B97-2	no	no	no
OLYP	2001	41	OPTX	0	no	no	LYP	no	yes	no
O3LYP	2001	41	OPTX	11.61	no	no	LYP	no	yes	no
τ-HCTH	2002	51	τ-HCTH	0	yes	no	τ-HCTH	no	no	no
τ-HCTHh	2002	51	τ-HCTHh	15	yes	no	τ-HCTHh	no	no	no
TPSS	2003	52	TPSS	0	yes	yes	TPSS	yes	yes	yes
TPSSh	2003	53	TPSS	10	yes	yes	TPSS	yes	yes	yes
X3LYP	2004	35, 47	X	21.8	no	yes	LYP	no	yes	no
BB1K	2004	34, 50, 54	B88	42	no	yes	B95	yes	yes	yes
BMK	2004	55	BMK	42	yes	no	BMK	no	no	no
MPW3LYP	2004	50, 48	mPW	20	no	yes	B95	yes	yes	yes
MPW1B95	2004	50, 39, 48	mPW	31	no	yes	B95	yes	yes	yes
MPWB1K	2004	50, 39, 48	mPW	44	no	yes	B95	yes	yes	yes
PW6B95	2005	17	PW6B95	28	no	yes	PW6B95	yes	yes	yes
PWB6K	2005	17	PWB6K	46	no	yes	PWB6K	yes	yes	yes
PBE1W	2005	42	PBE	0	no	yes	Scaled PBE	no	no	yes
B97-3	2005	49	B97-3	26.93	no	no	B97-3	no	no	no
M05	2005	56	M05	28	yes	yes	M05	yes	yes	yes
M05-2X	2006	21	M05-2X	56	yes	yes	M05-2X	yes	yes	yes

[a] Instead of using VWN, we use PW91-local for the LSDA correlation. [b] Although inspired by Becke's paper,[105] the BHandH and BHandHLYP functionals defined in Gaussian03 are different from the original ones in Becke's paper. (See http://www.gaussian.com/g_ur/k_dft.htm.) [c] Also called mPWPW91. [d] Also called mPW1PW91, mPW0 or MPW25. [e] Also called PBE0 or PBE1PBE.

GGAs, one LSDA, and MP2) are tabulated in Tables 2−4, and the calculated interaction energies for 40 functionals and MP2 are given in Tables S2−S4 of the Supporting Information. Statistical errors comparable to those in Tables 2−4 for all 41 methods are given in Tables S5−S7 of the Supporting Information. In Tables 2−4, we tabulate mean unsigned error (MUE, same as mean absolute deviation), mean signed error (MSE), and MMUE, which is defined as

$$MMUE = 0.5MUE + 0.5MUE\text{-}CP \qquad (2)$$

where we use the convention that CP denotes a mean error computed from calculations that include CP corrections for BSSE, and an error specified without "CP", as in the first term on the right side of eq 2, is computed without such corrections.

In general, the use of CP corrections is problematic for several reasons. First, although they usually improve the accuracy for very small basis sets [smaller than 6-31+G-(d,p)], they sometimes make the results less accurate for moderate and large basis sets [such as 6-31+G(d,p) and larger]. Second, for complex systems like biopolymers and soft materials, even for trimers, the CP correction is often ambiguous[77] or impractical[78] or both. Because there are strong proponents of including CP corrections and other workers strongly persuaded by practical reasons for not including it, we base most of our discussion on MMUE, which is a middle ground between the two positions, but the results are in the tables both ways for readers who strongly prefer to include or exclude CP corrections. The

Noncovalent Interaction Energies

J. Chem. Theory Comput., Vol. 3, No. 1, 2007 **293**

Table 2. Mean Errors (kcal/mol) for the Interaction Energies of Hydrogen-Bonded Complexes[a]

method	MSE-CP	MUE-CP	MSE	MUE	MMUE[b]
PWB6K	0.40	0.83	−0.30	0.68	0.76
PBEh	0.65	0.92	−0.06	0.67	0.79
M05-2X	0.49	0.90	−0.15	0.69	0.80
PW91	0.50	0.94	−0.23	0.68	0.81
MPWB1K	1.08	1.26	0.39	0.87	1.06
PBE	1.05	1.31	0.35	0.94	1.13
B97-1	1.10	1.36	0.43	0.98	1.17
M05	1.08	1.45	0.41	1.06	1.26
TPSS	1.80	1.83	1.08	1.35	1.59
MP2	2.46	2.46	−0.08	0.81	1.64
PBE1W	1.81	1.92	1.13	1.56	1.74
τ-HCTH	2.02	2.02	1.24	1.49	1.76
B3LYP	1.94	1.97	1.31	1.56	1.77
BHandH	−4.89	4.89	−5.54	5.54	5.21
LSDA	−5.21	5.21	−5.88	5.88	5.55

[a] The 6-31+G(d,p) basis is used for all calculations on which this table is based. The signed error is defined as the calculated energy minus the best estimate. [b] MSE denotes mean signed error, and MUE denotes mean unsigned error. MMUE is the average of MUE and MUE-CP (also defined in eq 2).

Table 3. Mean Errors (kcal/mol) for the Interaction Energies of the Dispersion-Dominated Complexes[a]

method	MSE-CP	MUE-CP	MSE	MUE	MMUE[b]
LSDA	−0.08	0.36	−0.75	0.75	0.56
BHandH	0.02	0.60	−0.61	0.84	0.72
M05-2X	1.33	1.33	0.69	0.70	1.01
PWB6K	2.02	2.02	1.37	1.37	1.69
MP2	1.30	1.30	−2.60	2.76	2.03
MPWB1K	2.79	2.79	2.14	2.14	2.46
M05	3.47	3.47	2.85	2.85	3.16
PW91	4.42	4.42	3.73	3.73	4.07
B97-1	4.47	4.47	3.83	3.83	4.15
PBEH	4.59	4.59	3.93	3.93	4.26
PBE	4.86	4.86	4.20	4.20	4.53
PBE1W	5.54	5.54	4.89	4.89	5.21
TPSS	5.95	5.95	5.29	5.29	5.62
B3LYP	6.53	6.53	5.91	5.91	6.22
τ-HCTH	7.09	7.09	6.41	6.41	6.75

[a] The 6-31+G(d,p) basis is used for all calculations on which this table is based. The signed error is defined as the calculated energy minus the best estimate. [b] MSE denotes mean signed error, and MUE denotes mean unsigned error. MMUE is the average of MUE and MUE-CP (also defined in eq 2).

Table 4. Mean Errors (kcal/mol) for the Interaction Energies of the Mixed Complexes[a]

method	MSE-CP	MUE-CP	MSE	MUE	MMUE[b]
M05-2X	0.34	0.47	−0.11	0.40	0.43
PWB6K	0.66	0.66	0.24	0.44	0.55
MPWB1K	1.22	1.22	0.80	0.80	1.01
M05	1.30	1.30	0.85	0.88	1.09
MP2	1.00	1.00	−1.45	1.45	1.23
LSDA	−1.06	1.06	−1.60	1.60	1.33
BHandH	−1.10	1.10	−1.57	1.57	1.34
PW91	1.60	1.60	1.07	1.11	1.35
B97-1	1.65	1.65	1.17	1.18	1.42
PBEh	1.70	1.70	1.22	1.22	1.46
PBE	1.91	1.91	1.40	1.40	1.66
PBE1W	2.30	2.30	1.79	1.79	2.04
TPSS	2.61	2.61	2.11	2.11	2.36
B3LYP	2.89	2.89	2.40	2.40	2.64
τ-HCTH	2.92	2.92	2.42	2.42	2.67

[a] The 6-31+G(d,p) basis is used for all calculations on which this table is based. The signed error is defined as the calculated energy minus the best estimate. [b] MSE denotes mean signed error, and MUE denotes mean unsigned error. MMUE is the average of MUE and MUE-CP (also defined in eq 2).

functions except LSDA and BHandH underestimate the interaction energies in these seven hydrogen-bonded complexes, whereas LSDA and BHandH severely overestimate the interaction energies. Table 2 also shows the failure of the OLYP and O3LYP functionals for describing hydrogen bonding.

From the statistical errors in Table S5 of the Supporting Information, we can also see the importance of HF exchange in DFT for describing hydrogen bonding. The percentages of HF exchange (see Table 1) in mPWPW91, mPW1PW91, and MPW1K are 0, 25, and 42.8, respectively, and the order of the MMUEs is mPWPW91 > mPW1PW91 > MPW1K. The same trends can be seen for the (mPWB95, MPW1B95, MPWB1K) sequence, the (PBE, PBEh) sequence, the (BLYP, B3LYP, BHandHLYP) sequence, and the (BB95, B1B95, BB1K) sequence. We discuss this point further in section 3.4.

The four best performers, on the basis of their small MMUEs, are PWB6K, PBEh, M05-2X, and PW91.

3.2. Dispersion-Dominated Complexes. Table 3 shows that LSDA, BHand H, M05-2X, PWB6K, and MP2 are the best performers for the prediction of interaction energies of the dispersion-dominated (or dispersion-like-dominated) complexes. Our previous papers[17,21] show that LSDA gives good predictions for the energetics of the stacked benzene dimers, but LSDA gives large errors for hydrogen bonding, charge-transfer complexes, dipole interactions, and other types of dispersion-like interactions. Kurita et al.[79] showed previously that a post-LSDA method can give reasonable results for stacking. Waller et al.[80] also found that the BHandH functional, which is a hybrid of LSDA exchange and HF exchange (50:50) plus LYP correlation, gives a binding energy for the parallel-displaced benzene dimer in fortuitously good agreement with the best available high-level methods. Nevertheless, BHandH suffers the same problems as LSDA (as shown in Tables 2 and 4).

Among the best five performers in Table 3, M05-2X and PWB6K are also among the best five performers in Table

reader will see that our major conclusions are independent of whether or not we include CP corrections.

In Table 5, AMUE is the average of the MUEs in Tables 2 (or S5), 3 (or S6), and 4 (or S7), each weighted one-third, and AMUE-CP is the average of the MUE-CPs in Tables 2−4, again each weighted one-third. MAMUE is the overall mean error defined by

$$\text{MAMUE} = 0.5\text{AMUE} + 0.5\text{AMUE-CP} \qquad (3)$$

In Tables 2−5, the density functionals and MP2 are always arranged in increasing order of the mean error in the last column.

3.1. Hydrogen-bonded Complexes. Table 2 gives the results for the hydrogen-bonded complexes. All tested DFT

Table 5. Overall Performance (kcal/mol)[a]

	AMUE-CP	AMUE	MAMUE
M05-2X	**0.90**	**0.60**	**0.75**
PWB6K	**1.17**	**0.83**	**1.00**
MPWB1K	**1.75**	**1.27**	**1.51**
MP2	**1.59**	1.67	**1.63**
PW6B95	**1.96**	1.46	**1.71**
M05	2.07	1.60	1.83
MPW1B95	2.08	**1.59**	1.84
PW91	2.32	1.84	2.08
PBEh	2.40	1.94	2.17
B97-1	2.49	2.00	2.24
BB1K	2.63	2.09	2.36
BHandH	2.20	2.65	2.42
PBE	2.69	2.18	2.44
MPW1K	2.71	2.22	2.46
LSDA	2.21	2.75	2.48
mPWB95	2.83	2.30	2.57
MPW3LYP	2.85	2.36	2.60
τ-HCTHh	2.86	2.36	2.61
B98	2.87	2.37	2.62
BMK	2.85	2.39	2.62
BHandHLYP	2.88	2.45	2.66
mPW1PW	3.15	2.61	2.88
B1B95	3.20	2.65	2.93
X3LYP	3.19	2.70	2.95
PBE1W	3.25	2.74	3.00
TPSSh	3.29	2.74	3.01
TPSS	3.46	2.91	3.19
MPWLYP	3.54	3.01	3.28
mPWPW	3.73	3.17	3.45
B97-3	3.77	3.26	3.52
B3LYP	3.80	3.29	3.54
B97-2	3.98	3.41	3.69
τ-HCTH	4.01	3.44	3.73
BP86	4.06	3.51	3.79
BB95	4.27	3.69	3.98
HCTH	4.41	3.82	4.11
BLYP	4.90	4.31	4.60
O3LYP	6.35	5.66	6.00
G96LYP	7.35	6.75	7.05
OLYP	7.48	6.75	7.12
VSXC	7.05	7.33	7.19

[a] AMUE-CP is the average of the MUE-CPs in Tables 2−4 for the 14 featured functionals and MP2 and of those in Tables S5−S7 of the Supporting Information for the other 26 functionals. AMUE is the average of the MUEs (without CP) in the same tables. MAMUE = 0.5 AMUE-CP + 0.5 AMUE. The 6-31+G(d,p) basis set is used for all calculations on which this table is based.

2. It is encouraging that these two fairly new functionals, M05-2X and PWB6K, give equally good performance for calculating interaction energies in both hydrogen-bonded and dispersion-dominated complexes. The second and fourth best performers in Table 2, PBEh and PW91, give much greater MMUEs in Table 3 than M05-2X and PWB6K do. Tables S2 and S6 of the Supporting Information also show that VSXC severely overestimates the dispersion-dominated noncovalent interactions in these complexes.

3.3. Mixed Complexes. Because M05-2X and PWB6K give balanced high accuracy for hydrogen-bonding (Table 2) and dispersion-dominated interactions (Table 3), it is not surprising that they are the best two methods for the

predictions of interaction energies in the mixed complexes (Table 4), followed by MPWB1K. All of these leading functionals were published in 2004 or later (see Table 1).

3.4. Overall Performance. Table 5 shows the overall performance for all tested DFT methods and for MP2. With CP correction for BSSE, M05-2X, PWB6K, MP2, and MPWB1K give the best performance. Without CP, M05-2X, PWB6K, MPWB1K, and PW6B95 are the best four performers. Averaging the performance for CP and without CP, the best four methods for describing noncovalent interactions in the S22 database are M05-2X, PWB6K, MPWB1K, and MP2.

Tables S5−S7 of the Supporting Information and Table 5 show that, all other factors being the same, a higher percentage of HF exchange in DFT improves the performance for describing noncovalent interactions in biological systems. However, for some functionals, like BHandHLYP, the predictions for other quantities like covalent bond energies deteriorate badly when X is raised.[46,81] For others, like MPW1K, the predictions for covalent bond energies deteriorate only slightly.[46,81] For M05-2X, the predictions of main-group covalent bond energies improve in quality along with the quality of the predictions for noncovalent interactions.[21] Thus, a key development in recent functional design is that we now have functionals that are more broadly accurate over a range of properties: thermochemistry,[21] barrier heights,[21] torsional potential and proton affinities of conjugated systems,[82] and noncovalent interactions.[20,21,29]

3.5. Dependence on Basis Set. All results in Tables 2−5 are based on the 6-31+G(d,p) basis set. It is also interesting to examine the performance of the DFT functionals for larger basis sets. Table 6 gives the interaction energies and mean errors by the two best hybrid meta-GGAs (M05-2X and PWB6K) and the two best hybrid GGAs (B97-1 and PBEh) with the 6-311+G(2df,2p) basis set. Table 6 also gives the MP2/CBS results from Jurecka et al.[31]

Table 6 shows that MP2/CBS is more accurate than DFT for the hydrogen-bonded complexes; it gives a MUE of 0.15 kcal/mol, and four DFT functionals with the 6-311+G-(2df,2p) basis set give errors in the range of 0.7~1.1 kcal. Comparing Tables 2 and 6, we can see that increasing the basis set size from 6-31+G(d,p) to 6-311+G(2df,2p) reduces the MMUEs for M05-2X, PWB6K, and B97-1 and increases the MMUE for PBEh; in all four cases, the MMUEs change by only 14% or less. Comparing the interaction energies of the hydrogen-bonded complexes in Table S2 of the Supporting Information and Table 6, we can see that the BSSEs are reduced significantly for the larger basis set.

Table 6 also shows that MP2/CBS overestimates the interaction energies by a large margin for the dispersion-dominated complexes, especially for those involving delocalized π systems. In fact, the mean signed error of MP2/CBS is 1.5 kcal/mol. In contrast, all four density functionals underbind these complexes. Encouragingly, M05-2X gives smaller MUEs than MP2/CBS for this type of interaction energy. Comparing Tables 3 and 6, we can see that, when the basis set is increased from 6-31+G(d,p) to 6-311+G-(2df,2p), the MMUEs of the M05-2X, PBEh, and B97-1 methods get smaller, whereas the MMUE of PWB6K gets

Table 6. Interaction Energies (kcal/mol) with the 6-311+G(2df,2p) Basis Set[a]

complex	best estimate	MP2/CBS[b]	M05-2X		PWB6K		PBEh		B97-1	
			CP	noCP	CP	noCP	CP	noCP	CP	noCP
Hydrogen-Bonded Complexes										
$(NH_3)_2$	−3.17	−3.20	−3.23	−3.34	−3.20	−3.32	−2.87	−3.00	−2.95	−3.06
$(H_2O)_2$	−5.02	−5.03	−5.09	−5.50	−5.14	−5.58	−4.93	−5.40	−4.89	−5.32
formic acid dimer	−18.61	−18.60	−18.87	−19.49	−18.68	−19.32	−18.49	−19.17	−17.59	−18.23
formamide dimer	−15.96	−15.86	−15.58	−15.96	−15.44	−15.84	−15.14	−15.55	−14.64	−15.02
uracil dimer	−20.65	−20.61	−19.36	−19.89	−19.44	−19.97	−19.02	−19.58	−18.45	−18.95
2-pyridoxine·2-aminopyridine	−16.71	−17.37	−15.22	−15.71	−15.15	−15.63	−15.31	−15.80	−14.77	−15.21
adenine·thymine WC	−16.37	−16.54	−14.69	−15.22	−14.52	−15.05	−14.45	−15.00	−14.01	−14.51
MSE[c]		−0.10	0.64	0.20	0.70	0.26	0.90	0.43	1.31	0.88
MUE[c]		0.15	0.75	0.63	0.77	0.66	0.90	0.70	1.31	0.97
MMUE[c]			0.69	0.69	0.71	0.71	0.80	0.80	1.14	1.14
Dispersion-Dominated Complexes										
$(CH_4)_2$	−0.53	−0.51	−0.50	−0.53	−0.52	−0.54	−0.04	−0.05	−0.23	−0.24
$(C_2H_4)_2$	−1.51	−1.62	−1.40	−1.49	−1.40	−1.47	−0.35	−0.41	−0.62	−0.68
benzene·CH_4	−1.5	−1.86	−1.15	−1.35	−1.00	−1.18	−0.12	−0.31	−0.30	−0.46
benzene dimer	−2.73	−4.95	−1.41	−2.00	−0.42	−1.13	1.70	1.13	1.46	0.99
pyrazine dimer	−4.42	−6.90	−2.99	−3.67	−1.96	−2.54	0.45	−0.17	0.30	−0.25
uracil dimer	−10.12	−11.39	−8.47	−9.52	−6.87	−7.84	−3.38	−4.41	−3.56	−4.46
indole·benzene	−5.22	−8.12	−2.65	−3.55	−1.47	−2.25	1.89	1.05	1.76	1.04
adenine·thymine stack	−12.23	−14.93	−9.58	−10.88	−8.21	−9.35	−2.27	−3.50	−2.19	−3.27
MSE[c]		−1.50	1.26	0.66	2.05	1.49	4.52	3.95	4.36	3.87
MUE[c]		1.51	1.26	0.66	2.05	1.50	4.52	3.95	4.36	3.87
MMUE[c]			0.96	0.96	1.77	1.77	4.23	4.23	4.11	4.11
Mixed Complexes										
ethene·ethyne	−1.53	−1.69	−1.42	−1.49	−1.37	−1.44	−1.16	−1.24	−1.30	−1.37
benzene·H_2O	−3.28	−3.61	−3.50	−3.89	−3.07	−3.48	−2.20	−2.66	−2.29	−2.70
benzene·NH_3	−2.35	−2.72	−2.23	−2.50	−1.95	−2.22	−1.06	−1.35	−1.21	−1.46
benzene· HCN	−4.46	−5.16	−4.80	−5.15	−4.51	−4.83	−3.26	−3.61	−3.18	−3.49
benzene dimer	−2.74	−3.62	−1.95	−2.35	−1.55	−1.91	−0.30	−0.68	−0.40	−0.73
indole·benzene T-shape	−5.73	−7.03	−4.68	−5.20	−3.89	−4.37	−2.32	−2.84	−2.29	−2.75
phenol dimer	−7.05	−7.76	−6.00	−6.62	−5.62	−6.22	−4.17	−4.80	−4.18	−4.76
MSE[c]		−0.64	0.37	−0.01	0.74	0.38	1.81	1.42	1.75	1.41
MUE[c]		0.64	0.53	0.40	0.76	0.54	1.81	1.42	1.75	1.41
MMUE[c]			0.47	0.47	0.65	0.65	1.62	1.62	1.58	1.58
AMUE[d]		0.76	0.84	0.57	1.19	0.90	2.41	2.02	2.48	2.07
MAMUE[d]			0.71	0.71	1.05	1.05	2.22	2.22	2.27	2.27

[a] CP denotes "counterpoise correction", and no-CP denotes "without counterpoise correction". [b] The MP2/CBS results are from Jurecka et al.[31] [c] MSE denotes mean signed error, and MUE denotes mean unsigned error. MMUE is the average of MUE and MUE-CP (also defined in eq 2). [d] AMUE is the average of the three MUEs in each class of complexes. MAMUE = 0.5 AMUE-CP + 0.5 AMUE.

larger, but the MMUEs for all four functionals change by only 5% or less when the basis set size is increased.

For the interaction energies in the seven mixed complexes, MP2/CBS gives an error of 0.64 kcal/mol, whereas M05-2X outperforms MP2 by a small margin. Comparing Tables 4 and 6, we can see that, upon increasing the basis set size from 6-31+G(d,p) to 6-311+G(2df,2p), the performance of all four density functionals for the prediction of this type of interaction energies deteriorates, but again, the change is small, in this case, 18% or less and only 8−11% in three of the cases. Again, the MMUEs change only marginally with the increase of basis set size.

Finally, let us compare AMUEs and MAMUEs in Table 5 to those in Table 6 for these four functionals. The comparison shows that AMUE and MAMUE for M05-2X decrease when the basis set size is increased, whereas the AMUEs and MAMUEs for PWB6K, PBEh, and B97-1 increase. However, the changes in these mean errors are very

small. This observation gives us confidence of the validity of the conclusions drawn on the basis of the results in Table 2−6 and Tables S2−S7 of the Supporting Information. One of the reviewers pointed out that MP2 requires large basis sets, and it is a strength of DFT that it does not. It is encouraging that the bottom line accuracy of M05-2X in Table 6 (0.71 kcal/mol) and the comparable number from Table 5 (0.75 kcal/mol) are both better than that of MP2, even when MP2 is taken to the CBS limit.

3.6. Geometry Optimization. In previous sections, we based our discussions on single-point energies calculated with the best estimated geometries for these noncovalent complexes. However, for many applications, it is important that a method can predict good geometries for these noncovalent complexes. To test the quality of the geometry predictions, we performed geometry optimizations for all 22 complexes with the M05-2X method. Encouragingly, M05-2X can locate the optimal structures for all noncovalent complexes in the

Table 7. M05-2X Interaction Energies (kcal/mol) with the M05-2X/6-31+G(d,p) Geometries

complex	best estimate	6-31+G(d,p)		6-311+G(2df,2p)	
		CP	noCP	CP	noCP
Hydrogen-Bonded Complexes					
$(NH_3)_2$	−3.17	−3.90	−4.14	−3.23	−3.34
$(H_2O)_2$	−5.02	−5.82	−6.61	−5.16	−5.56
formic acid dimer	−18.61	−19.39	−20.22	−19.86	−20.50
formamide dimer	−15.96	−15.64	−16.14	−15.66	−16.03
uracil dimer	−20.65	−19.54	−20.27	−19.43	−19.95
2-pyridoxine·2-aminopyridine	−16.71	−15.92	−16.57	−15.72	−16.21
adenine·thymine WC	−16.37	−15.15	−15.90	−14.94	−15.47
MSE		0.16	−0.48	0.36	−0.08
MUE		0.82	0.76	0.77	0.68
MMUE-HB[a]		0.79	0.79	0.73	0.73
Dispersion-Dominated Complexes					
$(CH_4)_2$	−0.53	−0.55	−0.56	−0.50	−0.53
$(C_2H_4)_2$	−1.51	−1.33	−1.46	−1.41	−1.49
benzene·CH_4	−1.5	−1.10	−1.24	−1.17	−1.34
benzene dimer	−2.73	−1.52	−2.02	−1.70	−2.20
pyrazine dimer	−4.42	−3.04	−3.66	−3.10	−3.73
uracil dimer	−10.12	−9.07	−10.42	−9.03	−10.19
indole·benzene	−5.22	−3.05	−3.76	−3.15	−3.89
adenine·thymine stack	−12.23	−9.67	−11.20	−9.57	−10.86
MSE		1.12	0.49	1.08	0.50
MUE		1.12	0.57	1.08	0.52
MMUE-D		0.85	0.85	0.80	0.80
Mixed Complexes					
ethene·ethyne	−1.53	−1.48	−1.67	−1.40	−1.48
benzene·H_2O	−3.28	−3.59	−4.02	−3.52	−3.94
benzene·NH_3	−2.35	−2.18	−2.50	−2.19	−2.45
benzene· HCN	−4.46	−4.61	−4.96	−4.78	−5.14
benzene dimer	−2.74	−2.01	−2.38	−2.02	−2.39
indole·benzene T-shape	−5.73	−4.64	−5.16	−4.72	−5.22
phenol dimer	−7.05	−6.70	−7.57	−6.30	−6.88
MSE		0.28	−0.16	0.32	−0.05
MUE		0.40	0.42	0.48	0.36
MMUE-Mix		0.41	0.41	0.42	0.42
AMUE[b]		0.78	0.59	0.78	0.52
MAMUE[b]		0.69	0.69	0.65	0.65

[a] CP denotes "counterpoise correction", and no-CP denotes "without counterpoise correction". [b] MSE denotes mean signed error, and MUE denotes mean unsigned error. MMUE is the average of MUE and MUE-CP (also defined in eq 2). [c] AMUE is the average of the three MUEs in each class of complexes. MAMUE = 0.5 AMUE(CP) + 0.5 AMUE(noCP).

S22 databases. We note that this is not a trivial triumph for the M05-2X method, because Cerny and Hobza have shown that the X3LYP functional, which was designed to describe noncovalent interactions, fails badly for locating the minima of the dispersion-dominated stacked structures of nucleic acid pairs such as the stacked AT pairs in the present study. The geometries optimized by M05-2X are given in the Supporting Information, and they agree well with the best estimated geometries.

Table 7 shows the M05-2X interaction energies with the geometries optimized at the M05-2X/6-31+G(d,p) level. Comparing the results in Tables 2−7, we can see that the overall performance of M05-2X is improved when we use the M05-2X/6-31+G(d,p) geometries, which is another encouraging result.

3.7. Rationale for the Success of M05-2X for Noncovalent Interactions. There are some common misunderstandings about the performance of DFT for noncovalent interactions. In the literature, one sometimes sees the success of DFT for noncovalent interactions labeled as "fortuitous" or "spurious". It is true that most DFT functionals cannot describe the $-C_6/R^6$ interaction of nonoverlapped densities, where R is the interaction distance of the monomers. Nevertheless, at the equilibrium distance of noncovalent complexes, the lack of explicit R^{-6} terms need not be a serious issue because the higher terms (R^{-8} etc.) in the asymptotic expansion are not negligible,[60,83−88] the dispersion interaction is damped,[86,89,90] the expansion in the inverse power of R is divergent,[84,91] overlap and exchange forces are not negligible,[47,85,86,90,92−94] and the change in intra-atomic correlation energy cannot be neglected.[95,96] In fact, the decomposition of the correlation contribution to the interaction energy into intra-atomic and interatomic (dispersion-like) parts is not unique.[94,95] Thus, DFT is not excluded as a potentially useful theory for the medium-range part of noncovalent interactions, as is shown by our previous papers.[16,19,97]
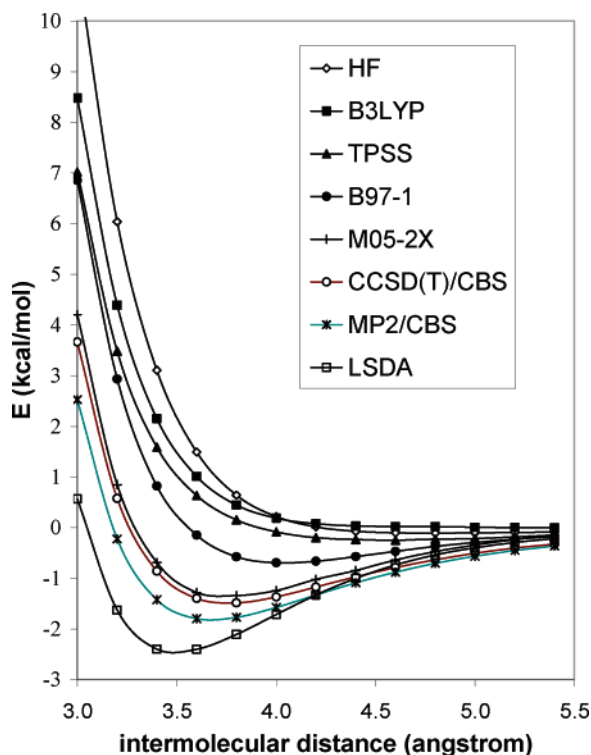
Figure 4. Binding energy curves for the $C_6H_6-CH_4$ complex with the 6-311+G(2df,2p) basis set. The intermolecular distance is defined as the distance between the carbon atom in CH_4 and the C_6H_6 plane. The CCSD/CBS and MP2/CBS results are taken from Shibasaki et al.[76]

Figure 5. Exchange-only binding energy curves for the $C_6H_6-CH_4$ complex with the 6-311+G(2df,2p) basis set. The intermolecular distance is defined as the distance from the carbon atom in CH_4 to the C_6H_6 plane.

Recently, Tao and Perdew[98] and Ruzsinszky et al.[73] have analyzed the performance of several DFT functionals for describing the medium-range part of the weak interactions.

In order to better understand the physical origin of the wells predicted by M05-2X and the range of distances over which M05-2X is suitable for treating noncovalent interactions, we compare the intermolecular potentials of the C_6H_6-CH$_4$ complexes calculated by five density functionals (B3LYP, TPSS, B97–1, M05-2X, and LSDA) and HF in Figure 4, along with the CCSD(T)/CBS and MP2/CBS results by Shibasaki et al.[76] Figure 4 shows that MP2 and LSDA overestimate the strength of the $C_6H_6-CH_4$ complex as compared to the CCSD(T)/CBS results. HF, B3LYP, and TPSS give an almost repulsive potential for this van der Waals complex; B97-1 gives a well with the minimum around 4.0 Å, and M05-2X gives the best agreement with the CCSD(T)/CBS results.

Exchange-only calculations (that is, calculating interaction energies without correlation contributions) employing HF and five density functionals are shown in Figure 5. As can be seen from Figure 5, the exchange-only potentials obtained using M05-2X, B3LYP, TPSS, and B97-1 exchange functionals are repulsive for the $C_6H_6-CH_4$ system, which agrees with the HF results. However, the exchange-only calculation based on the LSDA exchange gives a "spurious" well. (Although this comparison is interesting, one should be careful not overinterpret it because the distinction between exchange and correlation is different in DFT and WFT.)

The correlation contribution to the intermolecular potentials of the $C_6H_6-CH_4$ complexes are plotted in Figure 6.
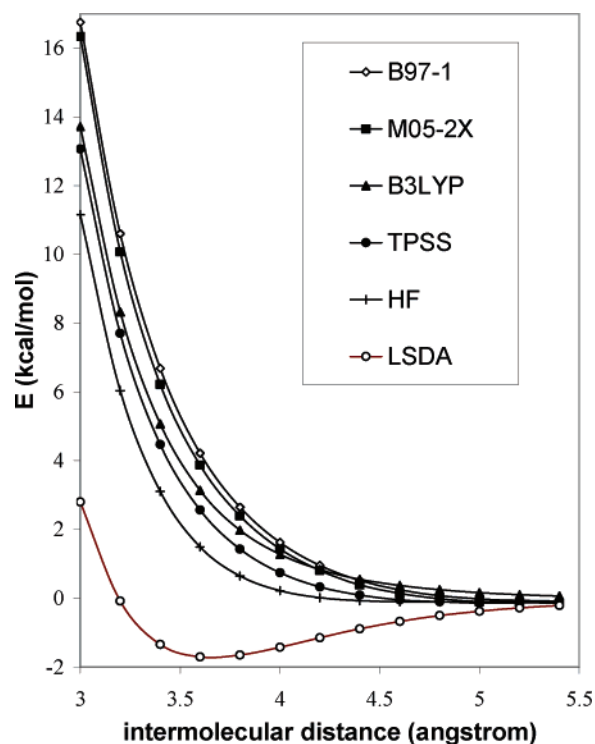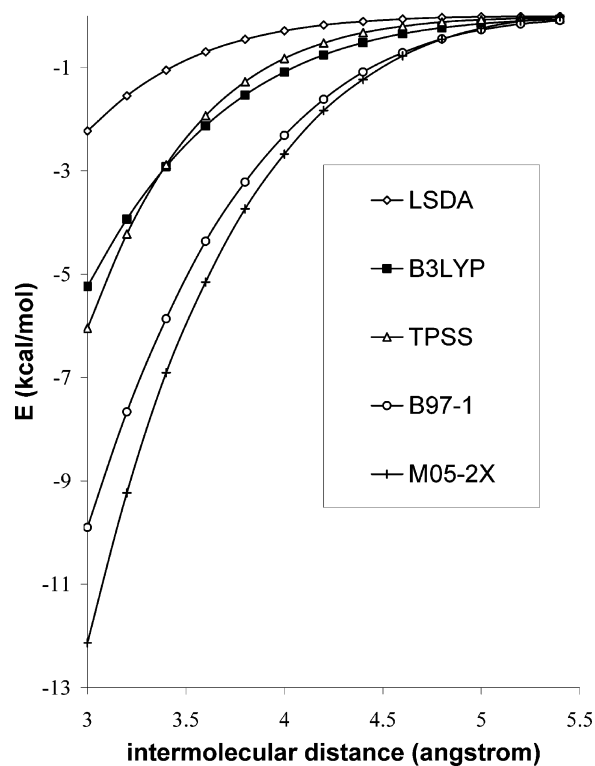

Figure 6. Correlation contribution to binding energy curves for the $C_6H_6-CH_4$ complex with the 6-311+G(2df,2p) basis set.

Figure 6 shows that the good performance of M05-2X comes from its correlation part; it gives the most attractive contribution in the range of 3–5 Å. The LSDA correlation contribu-

tion is the least attractive; this confirms that the good performance of LSDA and BHandH for $\pi-\pi$ stacking is a case of "getting the right answer with the wrong reason". It is interesting to see that TPSS correlation and the B3LYP correlation show very similar behaviors in the range of 3–5 Å for the $C_6H_6-CH_4$ system.

Comparing the results in Figures 4–6, we conclude that the good performance of M05-2X for describing the medium-range part of noncovalent interaction is because M05-2X has a better correlation functional, which gives the most attractive contribution to the potential energy. In fact, the success of M05-2X for medium-range correlation energy is also reflected in its performance for isomerization energies of hydrocarbons.[99]

3.8. Limitation of M05-2X for Noncovalent Interactions. Although M05-2X shows good performance for all noncovalent interactions in the S22 database, M05-2X does not give the asymptotic $-C_6/R^6$ tail for the interaction energy of two systems with no permanent multipole moments; it gives an exponential decay of the interaction energy for such systems at long range.

From the results in section 3.6, M05-2X can safely be applied to describe the interactions of noncovalent complexes with intermolecular distances less than ~5 Å. For the study of dispersion-dominated noncovalent interactions at long-range (>6 Å), one should probably use wave function theory or functionals[58,60,61,100,101] that build in the correct asymptotic $-C_6/R^6$ dispersion tail.

4. Concluding Remarks

For many years, MP2 [and, for small enough systems, higher-order methods like CCSD(T)] was considered to be the standard method for estimating noncovalent interactions, when affordable. In a previous paper,[16] when the M05-2X and PWB6K functionals had not yet been developed, we concluded that MPWB1K was the best DFT method for noncovalent interactions and that it outperforms MP2 for noncovalent interactions. This general result was confirmed recently by a study by Slanina et al.;[102] they showed that MPWB1K gives very good stabilization energies for the encapsulation of H_2, Ne, and N_2 into C_{60}. Now, on the basis of the assessment in the present study, we see that the M05-2X and PWB6K functionals give even better performance than MPWB1K for noncovalent interactions, and fortunately these functionals, especially M05-2X, also have excellent performance for a broad range of other main-group chemistry.

The PWB6K and M05-2X functionals employ exchange and correlation functionals that include kinetic energy density and that were optimized together. The present study shows that these functionals constitute a new generation of DFT methods that have greatly improved performance for noncovalent interactions as compared to previous DFT methods. In particular, it shows that they give good performance for a benchmark database of noncovalent interactions of biological importance; it also confirms that the widely used B3LYP and PBEh functionals fail to describe the interactions in complexes dominated by dispersion-like interactions. The LSDA and BHandH functionals give good performance for dispersion-dominated interactions at the expense of large errors for covalent interaction, hydrogen bonding, and other types of noncovalent interactions;[16] we show here that the success of these methods is fortuitous. By studying the intermolecular potential of the $C_6H_6-CH_4$ complex, we found that the good performance of the M05-2X functional comes from its improved correlation functional, which gives a better description of the medium-range part of the nonco-valent interactions.

We recommend the PWB6K and M05-2X functionals for investigating large biological systems and soft materials.

Supporting Information Available: S22 database, calculated interaction energies and mean errors for 41 methods, $C_6H_6-CH_4$ potential energy data, and the M05-2X/6-31+G(d,p) optimized geometries. This information is available free of charge via the Internet at http://pubs.acs.org.

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Noncovalent Interaction Energies

J. Chem. Theory Comput., Vol. 3, No. 1, 2007 **299**

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