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How Well Can New-Generation Density Functional Methods Describe Stacking Interactions in Biological Systems?

Yan Zhao and Donald G. Truhlar
Department of Chemistry and Supercomputing Institute, University of Minnesota, Minneapolis, MN 55455-0431

Abstract

We compare the performance of four recently developed DFT methods (MPW1B95, MPWB1K, PW6B95, and PWB6K) and two previous, generally successful DFT methods (B3LYP and B97-1) for the calculation of stacking interactions in six nucleic acid bases complexes and five amino acid pairs and for the calculation of hydrogen bonding interactions in two Watson-Crick type base pairs. We found that the four newly developed DFT methods give reasonable results for the stacking interactions in the DNA base pairs and amino acid pairs, whereas the previous DFT methods fail to describe interactions in these stacked complexes. We conclude that the new generation of DFT methods have greatly improved performance for stacking interaction as compared to previously available methods. We recommend the PWB6K method for investigating large DNA or protein systems where stacking plays an important role.

1. Introduction

Stacking interactions of nucleobases and aromatic amino acids play important roles in protein and nucleic acid folding, nucleobase stacking hybridization reactions, intercalation of drugs into DNA, catalysis, and biological recognition.[1-50] It is difficult to extract the binding energy of stacking complexes from experiment. Moreover, stacking complexes of nucleobases are large enough that it is not practical to employ a well converged ab initio electronic structure calculations (for example, W1[51]) to estimate their energies. Furthermore calculations by the more affordable second-order Møller-Plesset perturbation theory[52] (MP2) method or the approximate resolution of the identity MP2 method (RI-MP2)[53] have errors of about 1–2 kcal/mol for complexation energies of stacked nucleobases.[27,31,46,54] Therefore it is essential to include higher-order treatments of correction energies for such stacking calculations. The standard approach is to combine MP2 theory in the complete basis set (CBS) limit with a ΔCCSD(T) correction computed in a smaller basis (for example, a polarized double zeta basis set) to estimate the CBS CCSD(T) results.[31,46,55,56] MP2/CBS and ΔCCSD(T) calculations are too expensive for detailed exploration of typical systems of interest.

Density functional theory (DFT) is very efficient, and it is an important tool for studying biological systems. However, the most popular DFT method, B3LYP,[57,58] cannot describe stacking interactions because B3LYP fails badly for dispersion interactions.[59-61] About one decade ago, Hobza and coworkers stated that "DFT methods with currently available functionals failed completely for London-type clusters for which no minimum was found".[5] More recently Černý and Hobza[62] showed that the X3LYP DFT method, which was *designed* for treating noncovalent interactions, also completely fails for stacking. In the present letter, we show that how well the newest generation of density functional methods can describe stacking interactions in stacked DNA base pairs and amino acid pairs. Two key differences between the new functionals and the old ones are (*i*) that the new functionals include kinetic energy density[63] (and hence they are called

meta functionals) and (*ii*) that the new functionals have a more physical dependence[60,64] on the reduced density gradient in the region important for weak interactions.

The DFT methods and computational details are described in section 2, and results and discussion are given in section 3. Section 4 contains the concluding remarks.

2. Computational Methods

All DFT calculations were carried out using a locally modified *Gaussian03*[65] program. We tested four recently proposed hybrid meta DFT methods, namely MPW1B95, MPWB1K, PW6B95, and PWB6K. The first and third of these are DFT methods designed for thermochemistry, and the second and fourth are DFT methods designed for thermochemical kinetics.[60,66] The density functionals used in these new methods are further developments of the functionals presented previously by Becke,[57,63,67] Perdew and Wang,[68] and Adamo and Barone.[64] The performance of the four methods for other type of properties can be found in our previous papers.[60,61,66] We also compared the results with two successful hybrid (but not meta) DFT methods, namely B97-1[69] and B3LYP.

We used a double zeta basis set labeled DIDZ (which denotes 6-31+G(d,p))[70].

The reference complexation energies for stacked DNA base pairs and amino acid pairs are taken from Sponer, Hobza, and coworkers' benchmark studies.[27,31,42,43,46] We studied four stacked complexes: adenine···thymine (A···T), guanine···cytosine (G···C), cytosine dimer (C···C), and uracil dimer (U···U). For the cytosine dimer, we took three different stacked configurations from a paper by Jurecka et al,[42] namely an antiparallel dimer, a displaced dimer, and a parallel dimer. In a previous paper,[61] we have shown that our new DFT methods give good predictions for small hydrogen bonded dimers, and to confirm this in the nucleobase context, we also included two planar Watson-Crick hydrogen bonded dimers, namely A···T WC and G···C WC. The reference data for these hydrogen bonded base pairs are taken from Sponer et al.[43] We also studied five stacked pairs of neutral amino acids taken from an X-ray structure[71] (1RB9), namely, Phe30-

Phe49, Phe30-Lys46, Phe30-Leu33, Phe30-Tyr13, and Phe30-Tyr4.[46] The mean complexation energy is 9.3 kcal/mol for the six stacked nucleobase pairs, and it is 4.5 kcal/mol for the five stacked amino acid pairs. We performed geometry optimization for seven attractive DNA base pairs, but for the cases where a particular DFT method does not predict a stacked minimum, we performed a single-point calculation at the PWB6K geometry for that complex. For the repulsive stacked parallel cytosine dimer, we performed single point calculations at the MP2/6-31G** geometries taken from the paper of Jurečka et al.[42] For the five stacked amino acid complexes, we performed single-point energy calculations at the biologically relevant geometries from a previous paper;[46] where the heavy-atom coordinates were taken from a crystal structure, and the hydrogen locations were calculated by DFT. The PWB6K geometries for the stacked DNA base pairs and the geometries for the amino acid pairs used in the present study are given in the supporting information.

We also studied the vertical separation profile for a stacked "face to face" cytosine dimer, which is the same as the structure 14 in the paper of Jurečka et al.[42] We used the planar rigid cytosine monomer (optimized at the MP2/6-31G** level) and the DIDZ basis set to calculate the vertical separation profile.

We performed calculations without counterpoise corrections[72,73] for basis set superposition error (BSSE) because the goal of the present paper is not to obtain benchmark interaction energies for isolated stacked complexes, but rather to assess the performance of new DFT methods for the calculation of stacking interactions with moderate basis sets and without counterpoise correction. This is important because one of the attractive features of DFT is its applicability to large systems, for which larger basis sets and counterpoise corrections can be problematic.

3. Results and Discussion

Figures 1 and 2 show the structures of the complexes studied in the present work.

3.1. DNA base pairs

Table 1 gives the results for the DNA base pairs, and positive complexation (binding) energies are associated with negative interaction energies (favorable binding). The most popular DFT method, B3LYP, fails to locate any stacked complexes. Černý and Hobza[62] found that X3LYP also fails to locate the stacked complexes. The B97-1 method, which was shown to generally give good performance for nobonded interactions in one of our recent assessment papers,[61] can only locate the two attractive stacked C···C dimers. The MPW1B95 and PW6B95 methods give five of the six attractive stacked complexes, but both methods cannot locate the stacked G···C complex. The MPWB1K and PWB6K methods locate all five attactive stacked base pairs. From the mean unsigned error (MUE, same as mean absolute deviation), we can see that PWB6K gives the best performance, followed by MPWB1K. PWB6K gives an error of only about 20% of the mean complexation energy of stacked dimers, while B3LYP gives an error of 92%.

Although the performances of the tested DFT methods for stacking interaction are quite different, Table 1 shows that all tested DFT methods give reasonable results for the two Watson-Crick hydrogen bonded base pairs, with PWB6K giving the best results followed by B97-1 and MPWB1K. One encouraging point is that PWB6K performs well both for stacking and for hydrogen bonding. One of our previous papers[66] shows that LSDA gives good predictions for energetics of the stacked benzene dimers, but LSDA gives large errors for hydrogen bonding, charge transferring, dipole interaction, and other types of dispersion interactions. Kurita et al.[16] showed previously that a post-LSDA method can give reasonable results for stacking, but it was also at the expense of a large error for hydrogen bonding and other types of nonbonded interactions.

It was shown by Sponer et al.[43] that some DFT methods like PW91, underestimate the stabilization energies but overestimate the monomer deformation energies for H-bonded base pairs. The PWB6K method gives a monomer deformation energy of 2.9 kcal/mol for the G···C WC complex, and this may be compared to the reference value:[43]

3.6 kcal/mol (extrapolated MP2 results). Note that Sponer et al.[43] pointed out that PW91 gives much worse result, i. e., 5.4 kcal/mol, and they also pointed out that PW91 fails for stacking.

As mentioned in section 2, we did not calculate the BSSE for all tested methods, but we compared the BSSE calculated by PWB6K and B3LYP for the stacked G···C dimer and the H-bonded G···C WC complex with the DIDZ basis set. PWB6K gives a BSSE of 1.6 kcal for the stacked G···C dimer, whereas B3LYP gives 1.5 kcal/mol. PWB6K gives a BSSE of 1.1 kcal/mol for the H-bonded G···C WC complex, whereas B3LYP gives 1.0 kcal/mol. These comparison shows that PWB6K and B3LYP give very similar BSSE. Our experience is that,[61,66] for a given complex with a given basis set, most DFT methods give similar BSSE.

Figure 3 is the vertical separation profile calculated by HF, MP2, and all tested DFT methods. Figure 3 shows that HF and B3LYP give very shallow wells with optimal vertical distances R_e near 4.0 Å. MP2 gives a very deep well (about 12.7 kcal/mol with R_e near 3.25 Å), which overestimates the stabilization energy (the reference D_e is 9.1 kcal/mol[42]). PWB6K underestimates the stabilization energy, and it gives a D_e of 7.0 kcal/mol and a R_e near 3.35 Å. PW6B95 and MPWB1K give similar results, and they give a D_e of 5.8 kcal/mol, and R_e is 3.4 Å for MPWB1K and 3.45 Å for PW6B95. MPW1B95 gives a D_e of 5.2 kcal/mol, and a R_e of 3.45 Å, and B97-1 gives a D_e of 4.7 kcal/mol, and a R_e of 3.6 Å. Figure 3 confirms that PWB6K describes the potential energy surfaces and geometries for the stacked base pairs quite reasonably.

For the hydrogen bonded G···C WC base pair, PWB6K with the 6-31+G(d,p) basis gives three H-bond lenths of 2.91, 2.94, and 2.80 Å, which may be compared to the H-bond lengths of 2.89, 2.90, and 2.75 Å[43] given by the RI-MP2 method with larger basis. B3LYP and B97-1 give slightly worse results: 2.93, 2.95, and 2.80 Å. These comparisons provide evidence that PWB6K can also give quite accurate geometries for the H-bonded base pairs.

3.2. Stacked amino acid pairs

Table 2 gives the results for the amino acid pairs. These represent a combination of stacking interactions (although they are not as planar as the complexes in Table 1) and interactions of aromatic rings with aliphatic chains. Note that the error given by B3LYP is more than 100% of the mean complexation energies. The best performer for the amino acid complexes is PWB6K. The worst case for the DFT method is the Phe30-Tyr4 complex, and every DFT method seriously underestimates the binding energy of this complex. From Figure 2, we can see that the Phe30-Tyr4 complex is actually an aromatic π···π interaction between rings without heteroatoms. One of our previous papers[66] also demonstrated that most DFT methods have difficulty describing this type of dispersion-dominated interaction.

Table 2 also gives two quantities labeled MUE–stacking and MUE–all. MUE–stacking is the MUE for the six stacked base pairs and five stacked amino acid pairs. MUE-all is the MUE for the all thirteen noncovalent complexes in the present paper. From the MUE–stacking results, we can see that PWB6K gives the best overall performance for biological stacking interactions, followed by MPWB1K, and PWB6K also gives the best overall MUE-all.

It is interesting to note that although all the density functionals considered here, like most modern density functionals, have empirical elements, none of them were parametrized using any data on stacking interactions or other noncovalent interactions of aromatic molecules. The fact that one can obtain realistic results for π stacking interactions without parametrizing for them is very encouraging and indicates that one could do even better if such interactions were a target element in designing new functionals. The whole question of the applicability of DFT for studying noncovalent interactions is now ripe for further study.

4. Concluding remarks

In the present study, we showed that four newly developed DFT methods give reasonable results for the stacking interactions in homonuclear DNA base pairs and heteronuclear amino acid dimers without deteriorating the results for hydrogen bonding. In contrast, the more traditional B3LYP and B97-1 functionals fail to describe the interactions in these stacked complexes. PWB6K, MPWB1K, PW6B95, and MPW1B95 represent a new generation of DFT methods that include kinetic energy density and that have greatly improved performance for non-covalent interactions as compared to previous DFT methods, as exemplified by B3LYP or B97-1. We recommend the PWB6K method for investigating large biological systems.

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1 C. E. Bugg, J. M. Thomas, M. Sundralingam and S. T. Rao, *Biopolymers*, 1971, **10**, 175.
2 C. A. Hunter, J. Singh and J. M. Thornton, *J. Mol. Biol.*, 1991, **218**, 837.
3 J. L. Kim, D. B. Nikolov and S. K. Burley, *Nature*, 1993, **365**, 532.
4 M. F. Perutz, *Philos. Trans. Roy. Soc. Chem. (London) Sec. A*, 1993, **345**, 105.
5 P. Hobza, J. Sponer and T. Reschel, *J. Comp. Chem.*, 1995, **16**, 1315.
6 O. Yamauchi, *Pure Appl. Chem.*, 1995, **67**, 969.
7 C. H. Lin and D. J. Patel, *Nature Stucture Biol.*, 1996, **3**, 1046.
8 N. S. Scrutton and A. R. C. Raine, *Biochem. J.*, 1996, **319**, 1.
9 M. J. Lane, T. Paner, I. Kashin, B. D. Faldasz, B. Li, F. J. Gallo and A. S. Benight, *Nucleic Acids Res.*, 1997, **25**, 611.
10 D. Ranganathan, V. Haridas, R. Gilardi and I. L. Karle, *J. Am. Chem. Soc.*, 1998, **120**, 10793.
11 H. Sigel, *Pure Appl. Chem.*, 1998, **70**, 969.
12 M. Mizutani, I. Kubo, K. Jitsukawa, H. Masuda and H. Einage, *Inorg. Chem.*, 1999, **38**, 420.
13 S. J. Nolan, J. C. Shiels, J. B. Tite, K. L. Cecere and A. M. Baranger, *J. Am. Chem. Soc.*, 1999, **121**, 8951.
14 A. Eschenmoser, *Science*, 1999, **284**, 2118.
15 K. Müller-Dethlefs and P. Hobza, *Chem. Rev.*, 2000, **100**, 143.
16 N. Kurita, M. Araki, K. Nakao and K. Kobayashi, *Int. J. Quantum Chem.*, 2000, **76**, 677.
17 K. S. Kim, P. Tarakeshwar and J. Y. Lee, *Chem. Rev.*, 2000, **100**, 4145.
18 S. R. Griffiths-Jones and M. S. Searle, *J. Am. Chem. Soc.*, 2000, **122**, 8350.
19 S. Jones, D. T. A. Daley, N. M. Luscombe, H. M. Berman and J. M. Thornton, *Nucleic Acids Res.*, 2001, **29**, 943.
20 H. Zhou and Y. Zhang, *J. Chem. Phys.*, 2001, **114**, 8694.
21 J. Sponer, J. Leszczynski and P. Hobza, *Biopolymers*, 2001, **61**, 3.
22 J. Norberg and M. Vihinen, *Theochem*, 2001, **546**, 51.
23 J. Jenkins and R. Pichersgill, *Prog. Biophys. Mol. Biol.*, 2001, **77**, 111.
24 F. L. Gervasio, R. Chelli, M. Marchi, P. Procacci and V. Schettino, *J. Phys. Chem. B*, 2001, **105**, 7835.
25 M. Kabelác and P. Hobza, *J. Phys. Chem. A*, 2001, **105**, 5804.
26 C. Biot, E. Buisine, J.-M. Kwasigsoch, R. Wintgens and M. Rooman, *J. Biol. Chem.*, 2002, **277**, 40816.
27 P. Hobza and J. Sponer, *J. Am. Chem. Soc.*, 2002, **124**, 11802.
28 M. L. Waters, *Curr. Opinion Struct. Biol.*, 2002, **6**, 736.
29 O. Yamauchi, A. Odani and M. Takani, *J. Chem. Soc. Dalton Trans.*, 2002, **18**, 3411.
30 F. L. Gervasio, R. Chelli, P. Procacci and V. Schettino, *Proteins*, 2002, **48**, 117.
31 P. Jurecka and P. Hobza, *J. Am. Chem. Soc.*, 2003, **125**, 15608.
32 D. P. Aalberts, J. M. Parman and N. L. Goddard, *Biophysical Journal*, 2003, **84**, 3212.
33 K. Jitsukawa, A. Katoh, K. Funato, N. Ohata, Y. Funahashi, T. Ozawa and H. Masuda, *Inorg. Chem.*, 2003, **42**, 6163.

34 G. Hill, G. Forde, N. Hill, W. A. Lester, W. A. Sokalski and J. Leszczynski, *Chem. Phys. Lett.*, 2003, **381**, 729.

35 T. Yajima, G. Maccarrone, M. Takani, A. Contino, G. Arena, R. Takamido, M. Hanaki, Y. Funahashi, A. Odani and O. Yamauchi, *Chem. Eur. J.*, 2003, **9**, 3341.

36 J. S. Lamoureux, J. T. Maynes and J. N. M. Glover, *J. Mol. Biol.*, 2004, **335**, 399.

37 P. Mathur, S. Ramakumar and V. S. Chauhan, *Biopolymers*, 2004, **76**, 150.

38 K. Murata, Y. Sugita and Y. Okamoto, *Chem. Phys. Lett.*, 2004, **385**, 1.

39 H. Hwang and J.-S. Taylor, *Biochemistry*, 2004, **43**, 14612.

40 E. Protozanova, P. Yakovchuk and M. D. Frank-Kamenetskii, *J. Mol. Biol.*, 2004, **342**, 775.

41 J. Tuma, R. Paulini, J. A. R. Stütz and C. Richert, *Biochemistry*, 2004, **43**, 1560.

42 P. Jurecka, J. Sponer and P. Hobza, *J. Phys. Chem. A*, 2004, **108**, 5466.

43 J. Sponer, P. Jurecka and P. Hobza, *J. Am. Chem. Soc.*, 2004, **126**, 10142.

44 K. Iguchi, *Int. J. Modern Phys.*, 2004, 1845.

45 J. Pittner and P. Hobza, *Chem. Phys. Lett.*, 2004, **390**, 496.

46 J. Vondrásek, L. Bendová, V. Klusák and P. Hobza, *J. Am. Chem. Soc.*, 2005, **127**, 2615.

47 V. Guallar and K. W. Borrelli, *Proc. Natl. Acad. Sci. USA*, 2005, **102**, 3954.

48 T. W. Kim and E. T. Kool, *J. Org. Chem.*, 2005, **70**, 2048.

49 M. Meyer, A. Hocquet and J. Sühnel, *J. Comp. Chem.*, 2005, **26**, 352.

50 N. Haspel, D. Zanuy, B. Ma, H. Wolfson and R. Nussinov, *J. Mol. Biol.*, 2005, **345**, 1213.

51 J. M. L. Martin and G. d. Oliveira, *J. Chem. Phys.*, 1999, **111**, 1843.

52 C. Møller and M. S. Plesset, *Phys. Rev.*, 1934, **46**, 618.

53 F. Weigend and M. Häser, *Theo. Chem. Acc.*, 1997, **97**, 331.

54 P. Hobza and J. Sponer, *Chem. Rev.*, 1999, **99**, 3247.

55 M. O. Sinnokrot, E. F. Valeev and C. D. Sherrill, *J. Am. Chem. Soc.*, 2002, **124**, 10887.

56 M. O. Sinnokrot and C. D. Sherrill, *J. Phys. Chem. A*, 2004, **108**, 10200.

57 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.

58 P. J. Stephens, F. J. Devlin, C. F. Chabalowski and M. J. Frisch, *J. Phys. Chem.*, 1994, **98**, 11623.

59 S. Tsuzuki and H. P. Luthi, *J. Chem. Phys.*, 2001, **114**, 3949.

60 Y. Zhao and D. G. Truhlar, *J. Phys. Chem. A*, 2004, **108**, 6908.

61 Y. Zhao and D. G. Truhlar, *J. Comp. Theory Comput.*, 2005, **1**, 415.

62 J. Cerny and P. Hobza, *Phys. Chem. Chem. Phys.*, 2005, **7**, 1624.

63 A. D. Becke, *J. Chem. Phys.*, 1996, **104**, 1040.

64 C. Adamo and V. Barone, *J. Chem. Phys.*, 1998, **108**, 664.

65 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, T. V. Jr., K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, G.

Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *Gaussian 03*, Revision C.01, Gaussian, Inc., Pittsburgh PA, 2003.

66 Y. Zhao and D. G. Truhlar, *J. Phys. Chem. A*, 2005, in press.

67 A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098.

68 J. P. Perdew. In *Electronic Structure of Solids '91*, ed. P. Ziesche and H. Eschig, Akademie Verlag, Berlin, 1991, p.11.

69 F. A. Hamprecht, A. J. Cohen, D. J. Tozer and N. C. Handy, *J. Chem. Phys.*, 1998, **109**, 6264.

70 W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986.

71 Z. Dauter, K. S. Wilson, L. C. Sieker, J. M. Moulis and J. Meyerk, *Proc. Natl. Acad. Sci. USA*, 1996, **93**, 8836.

72 S. F. Boys and F. Bernardi, *Mol. Phys.*, 1970, **19**, 553.

73 D. W. Schwenke and D. G. Truhlar, *J. Chem. Phys.*, 1985, **82**, 2418.

Table 1. Complexation energies (in kcal/mol) for base pairs

Complexes	B3LYP	B97-1	MPW1B95	MPWB1K	PW6B95	PWB6K	best estimate	
							D_e	Ref.
				Stacked				
A···T S	*–0.10* [a]	*3.54* [a]	7.47	8.19	7.68	9.50	11.60	31
G···C S	*7.39* [a]	*10.26* [a]	*12.83* [a]	13.68	*13.10* [a]	14.86	16.90	31
C···C antiparallel	*2.87* [a]	5.64	8.98	9.63	9.48	10.88	9.90	27
C···C displaced	*3.64* [a]	6.31	8.08	8.63	8.46	9.66	9.43	42
C···C parallel [b]	–10.70	–8.01	–7.10	–7.02	–6.56	–5.93	–2.45	42
U···U S	*1.47* [a]	*4.05* [a]	6.01	6.51	6.45	7.94	10.30	27
MSE [c]	–8.52	–5.65	–3.24	–2.68	–2.84	–1.46		
MUE [d]	8.52	5.65	3.24	2.68	2.84	1.86		
				Hydrogen Bonded				
A···T WC	12.73	14.08	13.18	13.42	13.26	14.22	15.40	43
G···C WC	26.17	27.44	26.80	27.45	26.68	28.39	28.80	43
MSE [c]	–2.65	–1.34	–2.11	–1.67	–2.13	–0.79		
MUE [d]	2.65	1.34	2.11	1.67	2.13	0.79		

[a] A number in italics means that, for that complex, the DFT method can not predict a stacked minimum, and the number in the table is obtained by using the PWB6K geometries for that stacked dimer and corresponding monomers.
[b] The complexation energies for this repulsive stacked dimer were calculated by using the MP2/6-31G** geometries taken from the paper of Jurečka et al.[42] (Structure 1 in the original paper).
[c] mean signed error.
[d] mean unsigned error.

Table 2. Complexation energies (in kcal/mol) for the stacked amino acid pairs

Complexes	B3LYP	B97–1	MPW1B95	MPWB1K	PW6B95	PWB6K	best estimate	
							D_e	Ref.
Phe30–Phe49	–0.24	1.08	0.72	0.85	1.04	1.49	3.30	46
Phe30–Lys46	0.42	1.69	1.47	1.55	1.82	2.20	3.10	46
Phe30–Leu33	–0.66	1.65	2.41	2.76	2.91	3.87	5.00	46
Phe30–Tyr33	0.49	2.17	1.93	2.05	2.36	2.87	3.90	46
Phe30–Tyr4	–1.81	0.72	1.53	1.81	2.03	2.80	7.00	46
MSE [a]	–4.82	–3.00	–2.85	–2.66	–2.43	–1.81		
MUE [b]	4.82	3.00	2.85	2.66	2.43	1.81		
MUE–stacking [c]	6.84	4.44	3.06	2.67	2.65	1.84		
MUE–all [c]	6.19	3.97	2.91	2.51	2.57	1.68		

[a] mean signed error of five pairs in this table.
[b] mean unsigned error of five pairs in this table.
[c] MUE–stacking is the MUE for the six stacked base pairs and five stacked amino acid pairs. MUE-all is the MUE for the all thirteen noncovalent complexes in the present paper.

Figure caption

Figure 1. Structures of the nucleobase pairs. (A) A···T WC, (B) G···C WC, (C) A···T stacking, (D) G···C stacking, (E) C···C antiparallel, (F) C···C displaced, (G) C···C parallel, (H) U···U stacking.

Figure 2. Structures of the stacked amino acid pairs. (A) Phe30–Phe49, (B) Phe30–Lys46 , (C) Phe30–Leu33, (D) Phe30–Tyr13, (E) Phe30–Tyr4.

Figure 3. Vertical separation profiles for the "face to face"stacked cytosine dimer (the structure 14 of the paper of Jurecka et al.[42]). The rigid monomer is optimizated at the MP2/6–31G** level, and it is keep frozen along the profile. The DIDZ basis set is used for all methods.

Figure 1

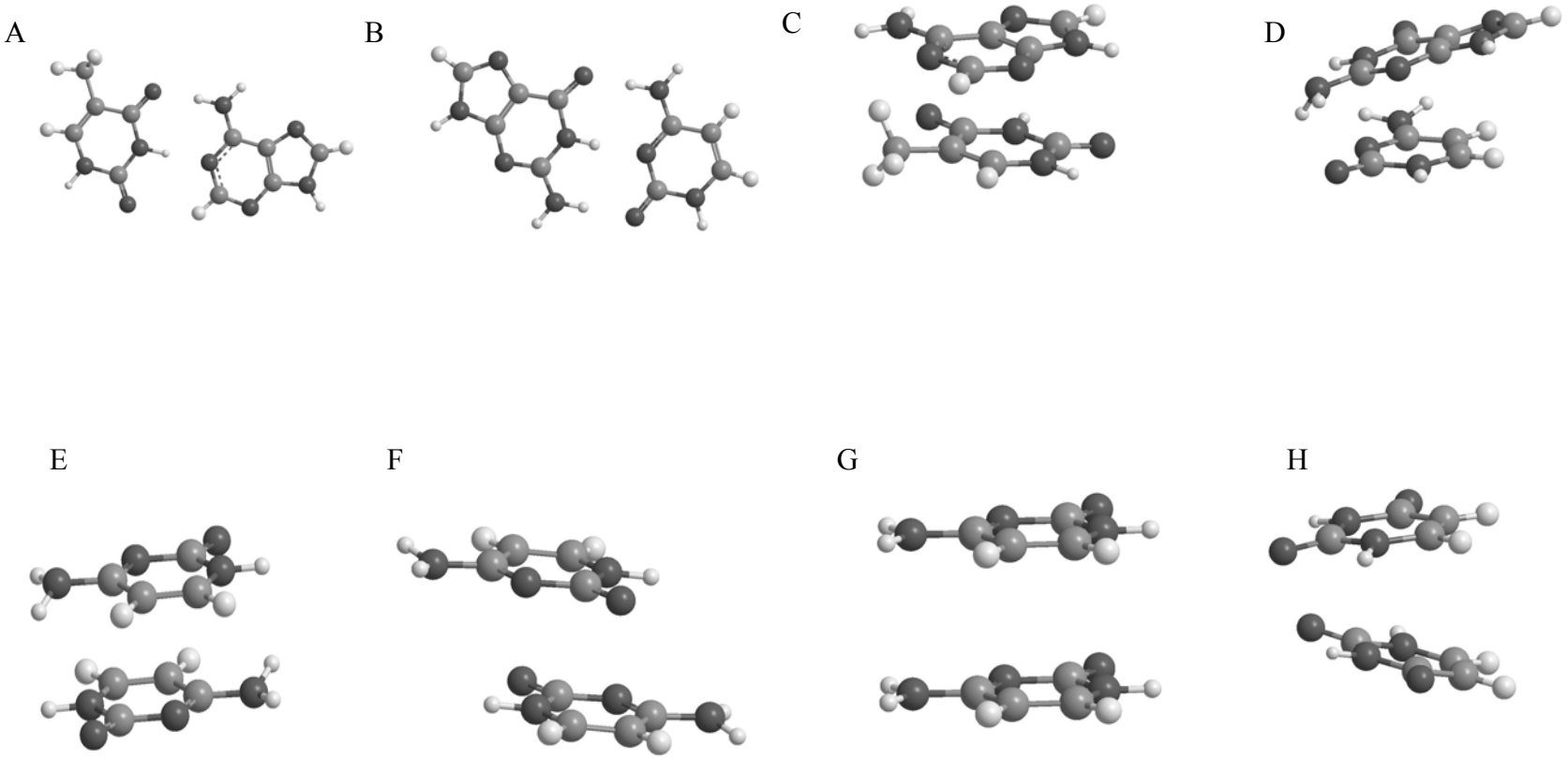


Figure 2

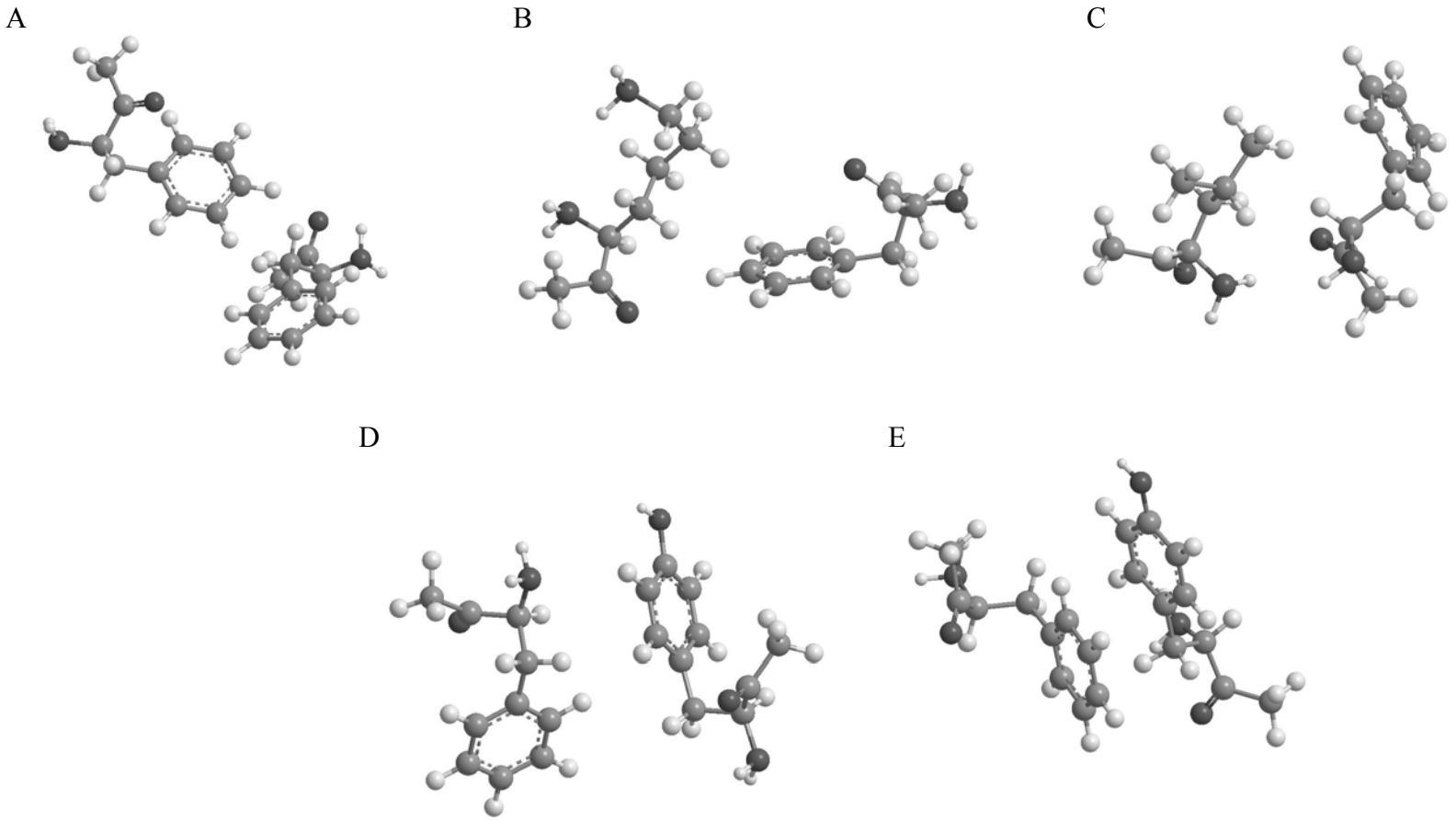
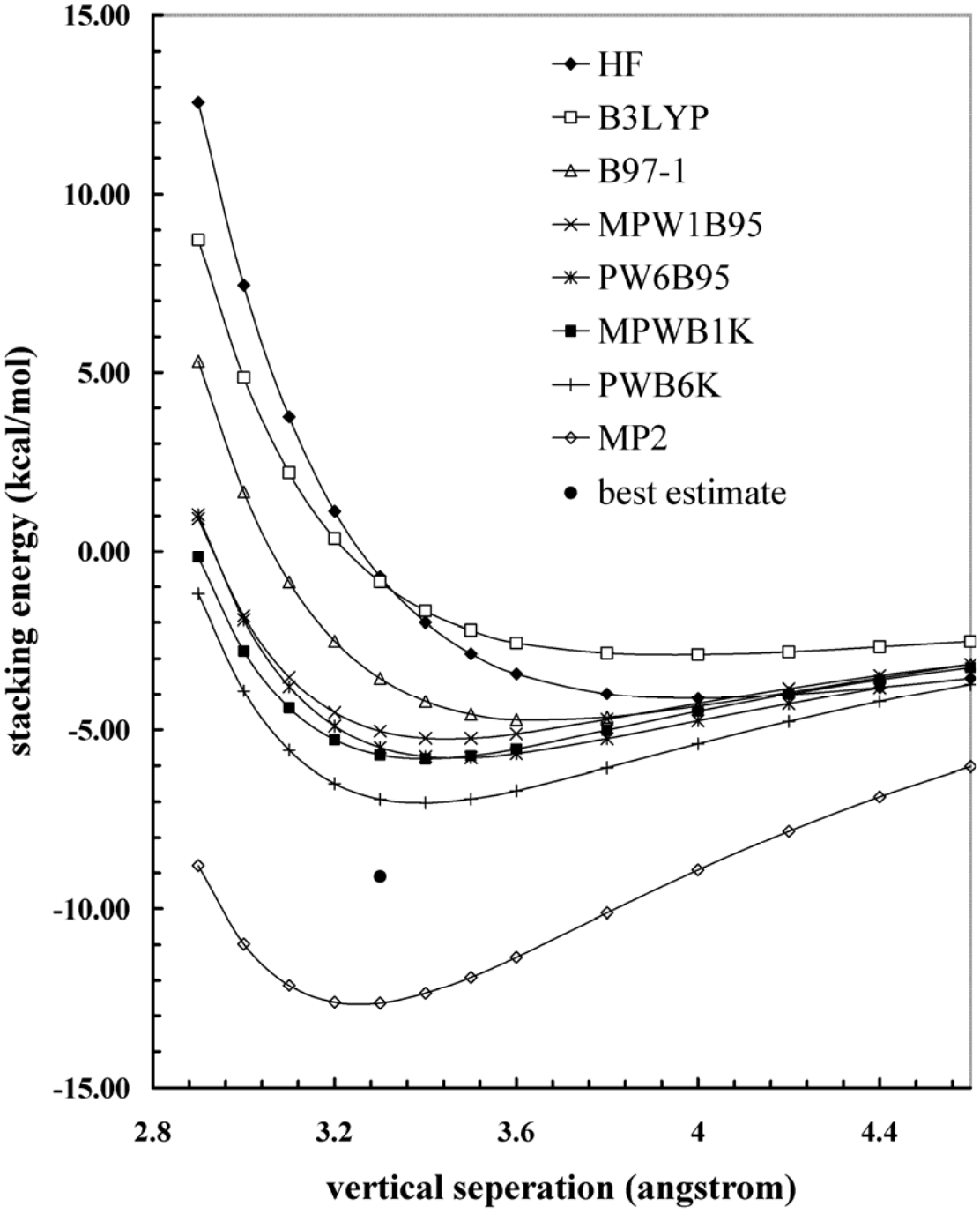


Figure 3


15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
stacking energy (kcal/mol)
2.8
3.2
3.6
4
4.4
vertical seperation (angstrom)
HF
B3LYP
B97-1
MPW1B95
PW6B95
MPWB1K
PWB6K
MP2
best estimate