

Revised for *JCTC*
April 26, 2006

Assessment of Model Chemistries for Noncovalent Interactions

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Abstract.

In the present study, we report tests of 57 model chemistry methods for calculating binding energies of 31 diverse van der Waals molecules arranged in five databases of noncovalent interaction energies. The model chemistries studied include wave function theory (WFT), density functional theory (DFT), and combined wave-function-density-functional-theory (CWFDFT), and they include methods whose computational effort scales (for large systems) as N^7 , N^6 , N^5 , and N^4 , where N is the number of atoms. The model chemistries include two CWFDFT N^7 models, four multilevel WFT N^7 models, five single-level WFT N^7 models, four CWFDFT N^6 models, three multilevel WFT N^6 models, eleven single-level WFT N^6 models, five CWFDFT N^5 models, ten single-level WFT N^5 models, four multilevel WFT N^5 models, four single-level DFT N^4 models, and five single-level WFT N^4 models. We draw the following conclusions based on the mean absolute errors in 31 noncovalent binding energies: (1) MCG3-MPW gives the best performance for predicting the binding energies of these noncovalent complexes. (2) MCQCISD-MPWB and MCQCISD-MPW are the best two N^6 methods. (3) M05-2X is the best single-level method for these noncovalent complexes. These four methods should facilitate useful calculations on a wide variety of practical applications involving hydrogen bonding, charge transfer complexes, dipole interactions, weak (dispersion-like) interactions, and $\pi\cdots\pi$ stacking. If a user is interested in only a particular type of noncovalent interactions, though, some other methods, may be recommended for especially favorable performance/cost ratios. For example, BMC-CCSD has outstanding performance for hydrogen bonding, and PWB6K has outstanding cost-adjusted performance for dipole interaction calculations on very large systems. We also show that M05-2X has excellent performance for interactions of amino acid pair residues.

1. Introduction

Noncovalent interactions play very important roles in many areas of science such as molecular recognition, protein folding, stacking of nucleobases, crystal packing, vapor-liquid condensation, polymer packing, soft materials design, self-assembly, supramolecular chemistry, solvation, and molecular scattering. It is especially noteworthy that noncovalent interactions underlie many complex biological functions including cell-cell recognition, intracellular signaling, and the regulation of gene expression. Understanding various noncovalent interactions is a key to unraveling the mysteries of cellular function in health and disease and to developing new drugs as well as being a critical component in nanotechnological uses of soft materials.

A model chemistry is “an approximate but well defined mathematical procedure of simulation”¹ of chemical phenomena. As pointed out by Pople,¹ there is a wide range of possible empiricism; a model chemistry can even be *ab initio* (i.e, without parameters except for fundamental constants of physics). Several multilevel model chemistry methods, such as the Gaussian-*n* theories and their variants developed by Pople and coworkers,²⁻⁵ the related Weizmann-*n* methods,^{6,7} the complete basis set (CBS) family of methods by Petersson and coworkers,⁸⁻¹⁰ the single-coefficient¹¹⁻¹⁵ and multi-coefficient¹⁴⁻²⁴ correlation methods (MCCMs) of our group, and the recent multilevel methods of Hu and coworkers,^{25,26} have been developed and validated for covalent interactions as required for application to thermochemistry (heats of formation, atomization energies, etc.) and kinetics (barrier heights). Although some researches²⁷⁻³⁰ have employed these multilevel methods for hydrogen bonded clusters and ionic clusters, until now there has been only one systematic validation of multilevel methods for noncovalent interactions, and that study was limited to rare gas interactions.³¹ The lack of broader validation studies is partly due to the lack, until recently,³²⁻³⁴ of standard databases (analogous to the G3 database,^{5,35-37} Database/3,¹⁵ or a recent metal-ligand bond energy database³⁸) for nonbonded interactions. In a recent communication,³⁹ we

compared several multilevel methods for the calculation of the stacking interaction energies in benzene dimers, and we found that the empirical hybrid of density functional theory (DFT) and wave function theory (WFT), also called multi-coefficient extrapolated density functional theory,^{22,23} give the best results for benzene dimers. A key objective of the present article is to assess multilevel model chemistry methods against several recently developed databases^{32,33} for nonbonded interactions. We also present the results for several single-level methods for comparison. Both DFT and WFT are considered.

Section 2 describes the theories and databases used in the present work. Section 3 presents results and discussion, and Section 4 has concluding remarks. The appendix considers interaction energies of amino acid residues.

2. Theory and Databases

2.1 Theory

The levels of electron correlation used in the present paper include Møller-Plesset second, third, and fourth order perturbation theory (MP2,⁴⁰ MP3,⁴¹ MP4⁴¹), Møller-Plesset fourth order perturbation theory without singles and triples contributions⁴¹ (MP4DQ), Møller-Plesset fourth order perturbation theory without triples contributions⁴¹ (MP4(SDQ)), quadratic configuration interaction with single and double excitations⁴² (QCISD), QCISD with quasiperturbative connected triples⁴² (QCISD(T)), coupled cluster with single and double excitations (CCSD),⁴³ and CCSD with quasiperturbative connected triples (CCSD(T)).⁴⁴ In general, core orbitals are doubly occupied in all configurations except for some MP2 calculations, and those are denoted MP2(full). We also present results for two hybrid meta-DFT methods, PWB6K³³ and M05-2X.⁴⁵ We note that PWB6K was found in a previous study³³ to perform best out of 25 density functionals tested against the databases employed here, and readers interested in the performance of other density functionals are referred to that study. For example, PWB6K was found to have an error three times lower than the popular B3LYP⁴⁶ functional.

PWB6K was also found to have excellent performance for hydrogen bonds to π acceptor,⁴⁷ a type of interaction not present in the database. The M05-2X functional was not available (it had not yet been developed) at the time of those assessments, and so it is included here.

Multi-coefficient extrapolated DFT methods^{22,23} include both DFT and WFT components in the same calculation.²³ These calculations may be labeled as combined wave function density functional methods (abbreviated CWFDFT or WFT/DFT) or as fifth-rung methods on Jacob's ladder^{48,49} of density functionals. We compare the results obtained by multi-coefficient extrapolated DFT methods (MC3BB,²² MC3MPW,²² MC3MPWB,²³ MCCO-MPW and MPWB,²³ MCUT-MPW and MPWB,²³ MCQCISD-MPW and -MPWB,²³ and MCG3-MPW and -MPWB²³) to those obtained by pure-WFT-based multi-level methods, in particular, G3SX,⁵ CBS-QB3,⁹ G3SX(MP3),⁵ MCCM/3,¹⁵ and BMC-CCSD.²⁴ Within the MCCM/3 suite, we specifically consider MCG3/3, MC-QCISD/3, and MC-UT/3. We note that G3SX(MP3), MCG3/3, and MC-QCISD/3 were selected as particularly efficient methods in a previous systematic study of multilevel methods for thermochemistry.⁵⁰ Since then, though, the multi-coefficient extrapolated DFT methods^{22,23} have been developed, and they show even better performance. We note that the recently developed multilevel method BMC-CCSD²⁴ has similar cost to MC-QCISD/3 but improved performance for atomization energies, barrier heights, ionization potentials, and electron affinities. Thus it will be interesting to test BMC-CCSD for noncovalent interactions. BMC-CCSD and MC-QCISD/3 are considerably less expensive than G3SX and G3SX(MP3).

We also consider some examples of the older scaling-all-correlation (SAC) methods,^{12,14,15} which are single-coefficient correlation methods. Although previous tests of these methods for thermochemistry have shown worthwhile improvement over MP2 at essentially no additional cost, they are not as powerful as MCCMs, and the present tests

will show if they are useful for noncovalent interactions. The three scaling-all-correlation (SAC) methods tested in this study use version-3s scaling coefficients.¹⁵

Note that the zero-point corrections were excluded from the G3SX, G3SX(MP3), and CBS-QB3 calculations (and all other methods) in this article since, in the standard spectroscopic notation, we are interested in predicting D_e ,⁵¹ not D_0 .

2.2. Noncovalent Interaction Databases. We tested all 62 considered methods against five recently developed databases, in particular, HB6/04,³² CT7/04,³² DI6/04,³² WI7/05,³³ and PPS5/05,³³ for various kinds of noncovalent interactions. HB6/04 is a hydrogen bond database that consists of the equilibrium binding energies of six hydrogen bonding dimers, namely $(\text{NH}_3)_2$, $(\text{HF})_2$, $(\text{H}_2\text{O})_2$, $\text{NH}_3\cdots\text{H}_2\text{O}$, $(\text{HCONH}_2)_2$, and $(\text{HCOOH})_2$. The CT7/04 database consists of the binding energies of seven charge transfer complexes, in particular $\text{C}_2\text{H}_4\cdots\text{F}_2$, $\text{NH}_3\cdots\text{F}_2$, $\text{C}_2\text{H}_2\cdots\text{ClF}$, $\text{HCN}\cdots\text{ClF}$, $\text{NH}_3\cdots\text{Cl}_2$, $\text{H}_2\text{O}\cdots\text{ClF}$, and $\text{NH}_3\cdots\text{ClF}$. The DI6/04 database contains the binding energies of six dipole interaction complexes: $(\text{H}_2\text{S})_2$, $(\text{HCl})_2$, $\text{HCl}\cdots\text{H}_2\text{S}$, $\text{CH}_3\text{Cl}\cdots\text{HCl}$, $\text{CH}_3\text{SH}\cdots\text{HCN}$, and $\text{CH}_3\text{SH}\cdots\text{HCl}$. The WI7/05 database consists of the binding energies of seven weak interaction complexes, namely HeNe , HeAr , Ne_2 , NeAr , $\text{CH}_4\cdots\text{Ne}$, $\text{C}_6\text{H}_6\cdots\text{Ne}$, and $(\text{CH}_4)_2$, all of which are bound by dispersion interactions. The PPS5/05 database consists of binding energies of five π - π stacking complexes, namely $(\text{C}_2\text{H}_2)_2$, $(\text{C}_2\text{H}_4)_2$, sandwich $(\text{C}_6\text{H}_6)_2$, T-shaped $(\text{C}_6\text{H}_6)_2$, and parallel-displaced $(\text{C}_6\text{H}_6)_2$.

Figures 1 to 5 depict the geometries of the noncovalent complexes in the present study.

2.3. Computer Programs, Geometries, Basis Sets, Counterpoise Correction, and Full Models. All the calculations in the present study are performed by using the locally developed program *MLGAUSS*⁵² in conjunction with *Gaussian03*.⁵³ The *MLGAUSS* program is available from the Truhlar group's software webpage.⁵⁴

The geometries for the benzene dimers are taken from Sinnokrot and Sherrill.⁵⁵ The geometries of all other complexes are optimized at the MC-QCISD/3¹⁵ level of

theory. Note that these same geometries are used for all methods tested. For methods, namely G3SX(MP3), CBS-QB3, and G3SX, that are ordinarily *defined* to use other geometries, we added the suffix “//Q” to denote this choice of geometries, which is used for *all* methods in this article.

The basis sets used include the 6-31G(d),⁴¹ 6-31+G(d,p),⁴¹ 6-31G(2df,p),⁴¹ 6-31B(d),²⁴ G3Large,³ G3XLarge,⁵ modified Gaussian-3¹⁴ (MG3), and modified Gaussian-3 semi-diffuse⁵⁶ (MG3S) basis set. We note that the MG3 basis¹⁴ is also denoted G3LargeMP2.⁵⁷

For most of the tested methods, we perform calculations without the counterpoise corrections (CP)^{58,59} for basis set superposition error (BSSE). We do present, however, the CP-corrected results for the MP2/MG3S, M05-2X/MG3S, and PWB6K/MG3S levels of theory.

A comment on the distribution between all possible models and a “full theoretical model chemistry” is in order here. When particular procedure for particular models or particular symmetries are avoided, and a model is general and continuous, the model may be called a full theoretical model chemistry.¹ For this reason,^{17,18} we prefer SAC-,^{12,13} MCG3-,¹⁸ G3S-,⁴ and G3SX-type⁵ methods to G2-,² G3-,³ and G3X-type⁵ methods because the G2-, G3-, and G3X-type methods involve a discontinuous high-level correction, whereas scaling methods do not. Similarly, the use of CP corrections disqualifies a method as “full” because, for example, one needs special decisions such as whether to apply it only to van der Waals molecules, but not (for example) to the O-H bond in water. Similarly, should Ne₂Be be treated as a complex of Ne₂ with Be or NeBe with Ne? Should NH₄Cl be treated as NH₃ complexed to HCl or NH₄⁺ complexed to Cl⁻? Finally, it is essentially impossible to apply CP corrections to amorphous solids and many other cases. Nevertheless, CP corrections are often used for calculating van der Waals binding energies, so we do consider some non-“full” models employing CP corrections in this paper.

3. Results and Discussion

Results are given in Tables 1-3 and S1-S8, where tables with an S prefix are given in supporting information. In particular, the binding energies and mean errors of the tested multilevel methods are listed in Tables 1, S1, S3, S5, S7, and 3, and results for the tested single-level methods are presented in Tables 2, S2, S4, S6, S8, S10, and 3. In these tables we classify the methods according to their scaling properties⁶⁰ (N^7 , N^6 , N^5 , or N^4), where N is the number of atoms. The tables show the mean unsigned error (MUE, also called mean absolute deviation) and mean signed error (MSE). We use “CP” to denote calculations that do include the counterpoise correction for the BSSE.

In order to put the large number of results in this paper into perspective, we define an overall error quantity in Table 3, namely the mean MUE:

$$\text{MMUE} = [\text{MUE}(\text{HB}) + \text{MUE}(\text{CT}) + \text{MUE}(\text{DI}) + \text{MUE}(\text{WI}) + \text{MUE}(\text{PPS})]/5 \quad (1)$$

Our discussion will focus *mainly* on the highly averaged MUEs and MMUEs because they provide measures of the broad usefulness of the methods tested for various kinds of noncovalent interactions. The tables are arranged in such a way that users interested in one or another subsets of the results may make their own comparisons and draw their own conclusions.

3.1 Hydrogen Bonding. Tables 1 and 2 summarize the results for hydrogen bonding calculations. Among the tested multilevel methods, G3SX(MP3) gives the lowest MUE for binding energies in the HB6/04 database. BMC-CCSD is the best N^6 multilevel method, and it has an MUE only 10% larger than G3SX(MP3) with a cost more than five times lower, as well as having better scaling to large systems. MC3MPW is the best N^5 multilevel method, with an MUE much larger than BMC-CCSD and a cost only slightly smaller, but better scaling. Table 2 shows that the best of the tested single-level methods for hydrogen bonding calculations are M05-2X/MG3S and MP2/MG3. MP2/MG3S gives almost identical results to those obtained with MP2/MG3. Note that

the only difference between MG3 and MG3S is that MG3S does not have diffuse basis functions on hydrogen atom. The counterpoise correction improves the performance of the M05-2X/MG3S calculations, but it deteriorates the performance of the MP2/MG3S method by a large margin.

Evaluation of energies at a standard geometry to assess hydrogen bonding sometimes leads to significantly different conclusions than would be obtained if the level of theory used for the energy calculation is also used for geometry optimization. This is especially true for methods that are defined to use inappropriately low levels of geometry. For example G3SX is defined to use B3LYP/6-31G(2df,p) geometries, which are not very good for hydrogen bonding because of the lack of diffuse functions.³⁷ CBS-QB3 suffers in the same way. In the present study, though, we use MC-QCISD/3 geometries, which are quite accurate. We have previously³² validated that mean errors are only slightly changed for hydrogen bonding, dipole interactions, and weak interactions when MC-QCISD/3 geometries instead of using consistently optimized geometries.

3.2 Charge Transfer Complexes. Tables S1, S2, and 3 present the results for the charge transfer complexes. Among the multilevel methods, MCQCISD-MPWB and MCQCISD-MPW give the lowest MUE for calculating the binding energies in the CT7/04 database. MCG3-MPW and MCG3-TS are the two best N^7 methods, and MC3MPWB is the best N^5 multilevel method.

Tables S2 and 3 shows that the PWB6K/MG3S method is the best single level method for calculating interaction energies in charge transfer complexes.

3.3 Dipole Interaction. Tables S3, S4, and 3 summarize the results for the dipole interaction complexes. Among the multilevel methods, MCG3-MPW gives the lowest MUE for calculating the binding energies in the DI6/04 database. MCQCISD-MPW is the best N^6 multilevel method, and SAC-MP2/6-31+G(d,p) is the best N^5 method.

From Tables S4 and 3, we can see that MP2/6-31G(2df,p) is the best single-level method, but this good performance is due to the error cancellation between the BSSE and

the incomplete treatment of correlation, as can be ascertained by noticing that the MP2 method with larger basis sets gives worse results. PWB6K is the best N^4 methods for dipole interactions.

3.4 Weak Interaction. Tables S5, S6, and 3 present the results for the weak interaction complexes. These complexes are bound by dispersion-like forces. MCCO/3 is the best multilevel method, whereas MCG3-MPWB and MCQCISD-MPWB are the best N^7 and N^6 methods, respectively.

Tables S6 and 3 shows that M05-2X/MG3S (with CP correction) is the best single-level method for the calculations of binding energies of these weakly bound van der Waals complexes.

3.5 $\pi\cdots\pi$ Interaction. Tables S7, S8, and 3 summarize the results for the $\pi\cdots\pi$ stacking complexes. Among the multilevel methods, MCG3-MPWB gives the lowest MUE for calculating the binding energies in the PPS5/05 database. MCQCISD-MPWB is the best N^6 multilevel method, and MC3MPWB is the best N^5 multilevel method. Table S8 shows that MP2/6-31G(d) is the best single-level method, but this good performance is again due to error cancellation, since the MP2 method with larger basis sets give worse results. PWB6K was found to be the best density functional for stacking interactions in biological systems⁶¹ and tetramers⁶² of formic acid and formamide. Here we find that the new M05-2X functional is even better for $\pi\cdots\pi$ stacking.

3.6. Overall Results. Table 3 is a summary of the performance of the tested methods for noncovalent interactions. The rank order is according to the MMUE column, which is the average of the five database columns included in this table, as defined by eq 1. Clearly the exact position in the ranking is not as meaningful as the general trends, but the MMUE provides a way to organize the discussion. In Table 11, we also tabulate the “cost” for each method, which is measured by the computer time for a single-point energy calculation of the T-shaped benzene dimer (at the fixed geometry of Sinnokrot and Sherrill⁵⁵) divided by the computer time for an MP2/6-31+G(d,p) energy calculation

on the same dimer with the same computer program and same computer. Although we are aware of the danger of timing algorithms with specific programs on specific computers, these costs (if not interpreted too finely), nevertheless help place the methods in a perspective of affordability.

From Table 3, we can see that the best performer for these non-covalent databases is MCG3-MPW, and its cost is much less than the G3SX, MP4/6-31(2df,p), and CCSD(T)/6-311+G(d,p) methods. The best N^6 method is MCQCISD-MPWB. Note that three N^6 methods, namely MCQCISD-MPWB, MCQCISD-MPW, and MCQCISD-TS, outperform the CBS-QB3 and G3SX N^7 methods with much less cost. The best N^4 method, M05-2X, outperforms the best N^5 method, MC3MPWB. M05-2X is also the best single-level method. To obtain better performance than M05-2X one must go to a method four times as expensive and with much worse scaling.

4. Concluding Remarks

It is clear that even the best single-level WFT methods are not competitive with the single-level DFT methods, multilevel WFT methods, and multilevel DFT/WFT methods, either for the kind of accuracy (MMUE of 0.31 kcal/mol) attainable with the low-cost methods or for the much higher standard of about half that error (MMUE of 0.16 kcal/mol). Although model chemistries were originally developed for covalent interactions and have been widely applied to such interactions, several of the modern model chemistries are sufficiently robust that they also give excellent results for noncovalent interactions, and they should be very useful for many important applications that require accurate models for noncovalent interactions. It is encouraging that the best performing methods in the current tests (MCG3-MPW,²³ MCQCISD-MPWB,²³ MCQCISD-MPW,²³ and M05-2X³⁴) also show excellent performance^{22,23,34} for atomization energies, bond energies, barrier heights, ionization potentials, and electron affinities.

5. Software

M05-2X has been incorporated in *NWCHEM*⁶³ and *GAUSSIAN03*⁵³ and will soon be available in release versions of these programs. All multilevel methods tested in this paper except CBS-QB3 are available in MLGAUSS.⁵² CBS-QB3 is available in GAUSSIAN03.⁵³

Acknowledgment. This work was supported by the Office of Naval Research under grant no. N00012-05-01-0538 and the U. S. Department of Energy, Office of Basic Energy Sciences.

Supporting Information Available: The calculated binding energies and mean errors for the CT7/04, DI6/04, WI7/05, and PPS5/05 databases are given in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Appendix

As an adjunct to this study, as requested by a referee, we calculated the binding energies of five pairs of amino acid residues by ten different density functionals; the tested DFT methods are B3LYP,⁴⁶ PBE,⁶⁴ B97-1,⁶⁵ O3LYP,⁶⁶ TPSS,⁶⁷ MPW1B95,⁶⁸ MPWB1K,⁶⁸ PW6B95,³³ PWB6K,³³ and M05-2X.³⁴ The amino acid residues and the pair geometries are taken from Ref. 69, where a pair of residue was cut from a crystal structure, and each residue is modeled by an amino acid in which the –OH group is replaced by a –CH₃ group; see Figure 6. The results are given in Table 4. It is encouraging that the two best performing functionals are (in order) M05-2X because these two functionals (out of 14 tested) were also found³⁴ to be the two best functionals (in the same order) for both stacking and hydrogen bonding interactions in nucleobase pairs.

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Table 1. Binding energies (kcal/mol) and mean errors (kcal/mol) for the HB6/04 database by multilevel methods

	(NH ₃) ₂	(HF) ₂	(H ₂ O) ₂	NH ₃ ...H ₂ O	(HCONH ₂) ₂	(HCOOH) ₂	MSE	MUE
best estimate	3.16	4.57	4.97	6.41	14.94	16.15		
<i>N</i>⁷ methods								
G3SX(MP3)//Q	3.15	4.57	5.10	6.39	14.67	15.91	-0.07	0.11
MCG3	3.14	4.41	5.06	6.36	14.69	15.75	-0.13	0.16
CBS-QB3//Q	3.26	4.80	5.18	6.61	15.02	16.35	0.17	0.17
G3SX//Q	3.23	4.84	5.26	6.52	15.10	16.52	0.21	0.21
MCG3-MPW	2.91	4.48	4.86	6.09	14.39	15.72	-0.29	0.29
MCG3-MPWB	2.86	4.44	4.83	6.06	14.07	15.49	-0.41	0.41
<i>N</i>⁶ methods								
BMC-CCSD	3.25	4.87	5.22	6.43	14.94	16.08	0.10	0.12
MC-QCISD/3	3.16	4.48	5.07	6.34	14.25	15.22	-0.28	0.32
MCUT/3	3.22	4.60	5.14	6.41	14.20	15.12	-0.25	0.34
MCQCISD-MPW	2.87	4.45	4.83	6.07	13.98	15.35	-0.44	0.44
MCQCISD-MPWB	2.86	4.38	4.84	6.06	13.65	15.09	-0.55	0.55
MCUT-MPW	2.79	4.42	4.72	5.99	13.64	15.06	-0.59	0.59
MCUT-MPWB	2.80	4.41	4.79	6.02	13.37	14.95	-0.64	0.64
<i>N</i>⁵ methods								
SAC-MP2/MG3S	3.38	4.93	5.51	6.85	15.01	16.39	0.31	0.31
MC3MPW	3.26	4.76	5.52	7.04	14.17	16.21	0.13	0.39

Table 2. Binding energies (kcal/mol) and mean errors (kcal/mol) for the HB6/04 database by single-level methods

Method	(NH ₃) ₂	(HF) ₂	(H ₂ O) ₂	NH ₃ ...H ₂ O	(HCONH ₂) ₂	(HCOOH) ₂	MSE	MUE
best estimate	3.16	4.57	4.97	6.41	14.94	16.15		
N⁷ methods								
CCSD(T)/6-311+G(d,p)	3.66	4.66	5.91	7.17	13.48	14.51	-0.13	0.90
MP4/6-31G+(d)	4.25	5.51	6.90	8.31	14.89	15.80	0.91	1.05
MP4/6-31G(2df,p)	3.87	7.12	6.44	6.99	17.65	18.98	1.81	1.81
QCISD(T)/6-31G(d)	4.28	7.10	6.81	8.00	17.30	17.64	1.82	1.82
MP4/6-31G(d)	4.31	7.19	6.88	8.05	17.40	17.86	1.92	1.92
N⁶ methods								
MP3/6-311+G(d,p)	3.54	4.61	5.76	6.98	13.23	14.30	-0.30	0.89
MP3/6-31G+(d)	4.14	5.40	6.73	8.12	14.73	15.62	0.76	1.01
CCSD/6-311+G(d,p)	3.43	4.54	5.67	6.85	12.69	13.70	-0.55	1.03
MP4(SDQ)/6-311+G(d,p)	3.45	4.53	5.70	6.89	12.56	13.56	-0.58	1.09
MP4(DQ)/6-31B(d)	4.50	6.10	6.41	8.08	15.46	15.41	0.96	1.21
CCSD/6-31B(d)	4.51	6.14	6.43	8.06	15.82	15.77	1.09	1.21
MP4(SDQ)/6-31G(2df,p)	3.64	6.87	6.15	6.67	16.45	17.72	1.22	1.22
MP3/6-31G(2df,p)	3.74	6.83	6.20	6.82	16.85	18.09	1.39	1.39
QCISD/6-31G(d)	4.11	6.99	6.65	7.77	16.51	16.91	1.46	1.46
MP4(SDQ)/6-31G(d)	4.14	7.02	6.69	7.82	16.45	16.87	1.47	1.47
MP3/6-31G(d)	4.21	6.94	6.71	7.96	16.72	17.15	1.58	1.58
N⁵ methods								
MP2/MG3	3.32	4.92	5.43	6.74	14.87	16.29	0.23	0.25

MP2/MG3S	3.33	4.91	5.46	6.78	14.87	16.27	0.24	0.26
MP2(full)/G3Large	3.34	4.99	5.48	6.80	14.97	16.46	0.31	0.31
MP2/6-31+G(d,p)	4.02	4.91	6.37	7.89	14.40	15.51	0.48	0.88
MP2/MG3S-CP	2.87	3.94	4.53	5.96	13.22	14.10	-0.93	0.93
MP2/6-311+G(d,p)	3.73	4.66	5.99	7.35	13.31	14.45	-0.12	0.99
MP2/6-31G+(d)	4.27	5.51	7.00	8.49	14.87	15.96	0.98	1.07
MP2/6-31B(d)	4.73	6.35	6.78	8.59	16.57	16.89	1.62	1.62
MP2/6-31G(2df,p)	4.01	7.22	6.61	7.25	17.76	19.19	1.97	1.97
MP2/6-31G(d)	4.40	7.34	7.08	8.35	17.48	18.19	2.11	2.11
N⁴ methods								
M05-2X/MG3S-CP	3.01	4.78	5.13	6.40	14.33	16.22	-0.05	0.20
PWB6K/MG3S-CP	3.05	4.78	5.09	6.40	13.75	15.72	-0.23	0.34
M05-2X/MG3S	3.19	5.17	5.53	6.71	14.71	16.81	0.32	0.40
PWB6K/MG3S	3.23	5.19	5.51	6.73	14.13	16.43	0.17	0.44
HF/6-31G(d)	3.00	5.95	5.59	6.43	12.93	14.61	-0.28	0.95
HF/6-311+G(d,p)	2.25	4.17	4.75	5.42	10.41	12.17	-1.84	1.84
HF/MG3S	1.71	3.99	3.97	4.54	10.22	12.30	-2.24	2.24
HF/MG3	1.71	3.99	3.97	4.54	10.22	12.30	-2.24	2.24
HF/G3Large	1.71	3.99	3.96	4.54	10.21	12.29	-2.25	2.25
Average							0.37	1.21

Table 3. Overall results

Method	type ^a	HB6/05	CT7/05	DI6/05	WI7/05	PPS5/05	MMUE	Cost ^b
		MUE	MUE	MUE	MUE	MUE		
N⁷ methods								
MCG3-MPW	ML DFT/WFT	0.29	0.13	0.15	0.06	0.18	0.16	110
MCG3-MPWB	ML DFT/WFT	0.41	0.13	0.20	0.05	0.17	0.19	111
MCG3	ML WFT	0.16	0.19	0.29	0.05	0.80	0.30	104
G3SX(MP3)//Q	ML WFT	0.11	0.18	0.35	0.08	0.80	0.31	135
CBS-QB3//Q	ML WFT	0.17	0.38	0.36	0.11	0.57	0.32	204
G3SX//Q	ML WFT	0.21	0.26	0.39	0.11	0.84	0.36	1116
CCSD(T)/6-311+G(d,p)	SL WFT	0.90	0.62	0.47	0.07	0.95	0.60	409
MP4/6-31G(2df,p)	SL WFT	1.81	0.71	0.31	0.25	0.58	0.73	848
MP4/6-31G+(d)	SL WFT	1.05	0.96	0.50	0.14	1.06	0.74	150
MP4/6-31G(d)	SL WFT	1.92	0.75	0.69	0.10	0.28	0.75	61
QCISD(T)/6-31G(d)	SL WFT	1.82	0.83	0.74	0.10	0.46	0.79	71
N⁶ methods								
MCQCISD-MPWB	ML DFT/WFT	0.55	0.12	0.19	0.05	0.18	0.22	29
MCQCISD-MPW	ML DFT/WFT	0.44	0.12	0.18	0.07	0.33	0.23	29
MCUT-MPWB	ML DFT/WFT	0.64	0.14	0.25	0.06	0.52	0.32	22
MCUT/3	ML WFT	0.34	0.25	0.35	0.07	0.74	0.35	16
MCUT-MPW	ML DFT/WFT	0.59	0.18	0.22	0.09	0.75	0.37	22
MC-QCISD/3	ML WFT	0.32	0.23	0.37	0.07	0.85	0.37	23
BMC-CCSD	ML WFT	0.12	0.31	0.58	0.14	1.17	0.46	26
MP3/6-31G+(d)	SL WFT	1.01	0.86	0.56	0.12	0.47	0.60	5
MP3/6-311+G(d,p)	SL WFT	0.89	1.00	0.55	0.07	0.55	0.61	14
MP4(SDQ)/6-31G(2df,p)	SL WFT	1.22	0.80	0.66	0.24	0.24	0.63	18

MP4(SDQ)/6-311+G(d,p)	SL WFT	1.09	0.84	0.70	0.07	0.47	0.63	15
MP3/6-31G(2df,p)	SL WFT	1.39	0.85	0.45	0.23	0.26	0.63	17
CCSD/6-311+G(d,p)	SL WFT	1.03	0.99	0.74	0.07	0.46	0.66	68
MP3/6-31G(d)	SL WFT	1.58	0.90	0.73	0.09	0.69	0.80	2
MP4(SDQ)/6-31G(d)	SL WFT	1.47	0.85	0.87	0.10	0.76	0.81	1
QCISD/6-31G(d)	SL WFT	1.46	0.89	0.93	0.10	0.81	0.84	8
MP4(DQ)/6-31B(d)	SL WFT	1.21	1.99	0.86	0.14	0.69	0.98	1
CCSD/6-31B(d)	SL WFT	1.21	2.19	0.86	0.13	0.73	1.03	8
<i>N</i>⁵ methods								
MC3MPWB	ML DFT/WFT	0.46	0.46	0.38	0.07	0.48	0.37	7
MCCO-MPWB	ML DFT/WFT	0.70	0.27	0.33	0.07	0.69	0.41	21
MP2/MG3S-CP	SL WFT	0.93	0.26	0.25	0.18	0.48	0.42	22
MCCO-MPW	ML DFT/WFT	0.52	0.36	0.31	0.12	0.81	0.43	20
MC3MPW	ML DFT/WFT	0.39	0.52	0.36	0.13	0.93	0.47	6
MP2/MG3S	SL WFT	0.26	0.73	0.45	0.07	1.24	0.55	14
MP2/MG3	SL WFT	0.25	0.72	0.44	0.09	1.32	0.56	15
MC3BB	ML DFT/WFT	0.62	0.32	0.75	0.27	1.10	0.61	7
SAC-MP2/MG3S	ML WFT	0.31	0.86	0.53	0.08	1.38	0.63	14
MP2(full)/G3Large	SL WFT	0.31	0.80	0.57	0.10	1.40	0.63	36
MP2/6-31+G(d,p)	SL WFT	0.88	0.71	0.23	0.13	1.40	0.67	1
MP2/6-311+G(d,p)	SL WFT	0.99	0.47	0.29	0.08	1.69	0.70	5
MCCO/3	ML WFT	0.44	0.60	0.70	0.04	1.80	0.72	15
MP2/6-31G(d)	SL WFT	2.11	0.87	0.46	0.12	0.21	0.75	1
MP2/6-31G+(d)	SL WFT	1.07	1.01	0.29	0.14	1.37	0.78	1
SAC-MP2/6-31+G(d,p)	ML WFT	0.88	1.24	0.15	0.15	2.17	0.92	1
MP2/6-31G(2df,p)	SL WFT	1.97	1.18	0.18	0.26	1.16	0.95	3
SAC-MP2/6-31G(d)	ML WFT	2.83	1.67	0.17	0.14	1.04	1.17	1

MP2/6-31B(d)	SL WFT	1.62	3.35	1.13	0.13	0.31	1.31	1
<i>N</i>⁴ methods								
M05-2X/MG3S-CP	SL DFT	0.20	0.30	0.32	0.03	0.71	0.31	9
M05-2X/MG3S	SL DFT	0.40	0.46	0.27	0.09	0.49	0.34	6
PWB6K/MG3S	SL DFT	0.44	0.25	0.24	0.15	0.81	0.38	9
PWB6K/MG3S-CP	SL DFT	0.34	0.16	0.32	0.07	1.02	0.38	9
HF/6-31G(d)	SL WFT	0.95	2.39	2.12	0.23	2.69	1.68	0.1
HF/6-311+G(d,p)	SL WFT	1.84	3.09	2.17	0.31	3.42	2.17	1
HF/MG3S	SL WFT	2.24	3.77	2.40	0.30	3.39	2.42	5
HF/MG3	SL WFT	2.24	3.77	2.40	0.30	3.39	2.42	6
HF/G3Large	SL WFT	2.25	3.77	2.41	0.30	3.39	2.42	8
Average		0.95	0.93	0.62	0.13	1.01	0.73	

^a ML denotes multilevel; SL denotes single-level.

^b The cost for each method is measured by the computer time for a single-point energy calculation of the T-shaped benzene dimer (at the fixed geometry of Sinnokrot and Sherrill⁵⁵) divided by the computer time for an MP2/6-31+G(d,p) energy calculation on the same dimer with the same computer program and same computer.

Table 4. Binding energies (kcal/mol) and mean errors for amino acid residue pairs ^a

Methods	F30-K46	F30-L33	F30-Y13	F30-F49	F30-Y4	MSE	MUE
best estimate	3.10 ^b	5.00 ^b	3.90 ^b	2.70 ^c	5.30 ^c		
M05-2X	2.53	4.47	3.41	2.07	3.62	-0.78	0.78
PWB6K	2.20	3.87	2.87	1.49	2.80	-1.35	1.35
PW6B95	1.82	2.91	2.36	1.04	2.03	-1.97	1.97
MPWB1K	1.55	2.76	2.05	0.85	1.81	-2.20	2.20
MPW1B95	1.47	2.41	1.93	0.72	1.53	-2.39	2.39
B97-1	1.69	1.65	2.17	1.08	0.72	-2.54	2.54
PBE	1.47	1.17	1.87	0.83	0.22	-2.89	2.89
TPSS	0.81	-0.35 ^d	0.82	0.07	-1.17 ^d	-3.97	3.97
B3LYP	0.42	-0.66	0.49	-0.24 ^d	-1.81 ^d	-4.36	4.36
O3LYP	-0.30 ^d	-4.13 ^d	-1.00 ^d	-1.41 ^d	-4.73 ^d	-6.31	6.31

^a Basis set: 6-31+G(d,p); geometries from Ref. 69. No counterpoise correction was made.

^b MP2 /CBS+ Δ CCSD(T) from Ref. 69.

^c MP2/CBS + side chain Δ CCSD(T) from Ref. 69.

^d Negative number denotes that the interaction energy is repulsion at the geometry of Ref. 69.

Figure caption

Figure 1. Geometries of the dimers in the HB6/04 database

Figure 2. Geometries of the complexes in the CT7/04 database

Figure 3. Geometries of the dimers in the DI6/04 database

Figure 4. Geometries of selected dimers in the WI7/05 database

Figure 5. Geometries of the dimers in the PPS/05 database

Figure 6. Geometries of the pairs of amino acid residues

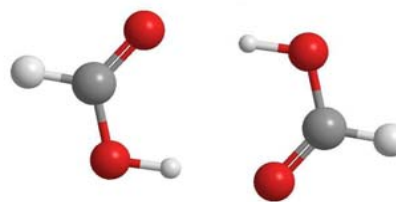
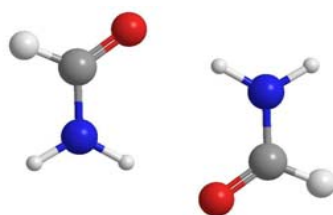
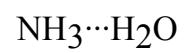
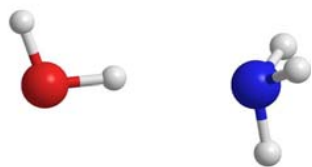
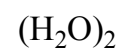
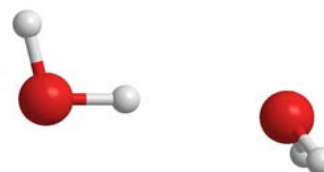
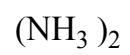


Figure 1

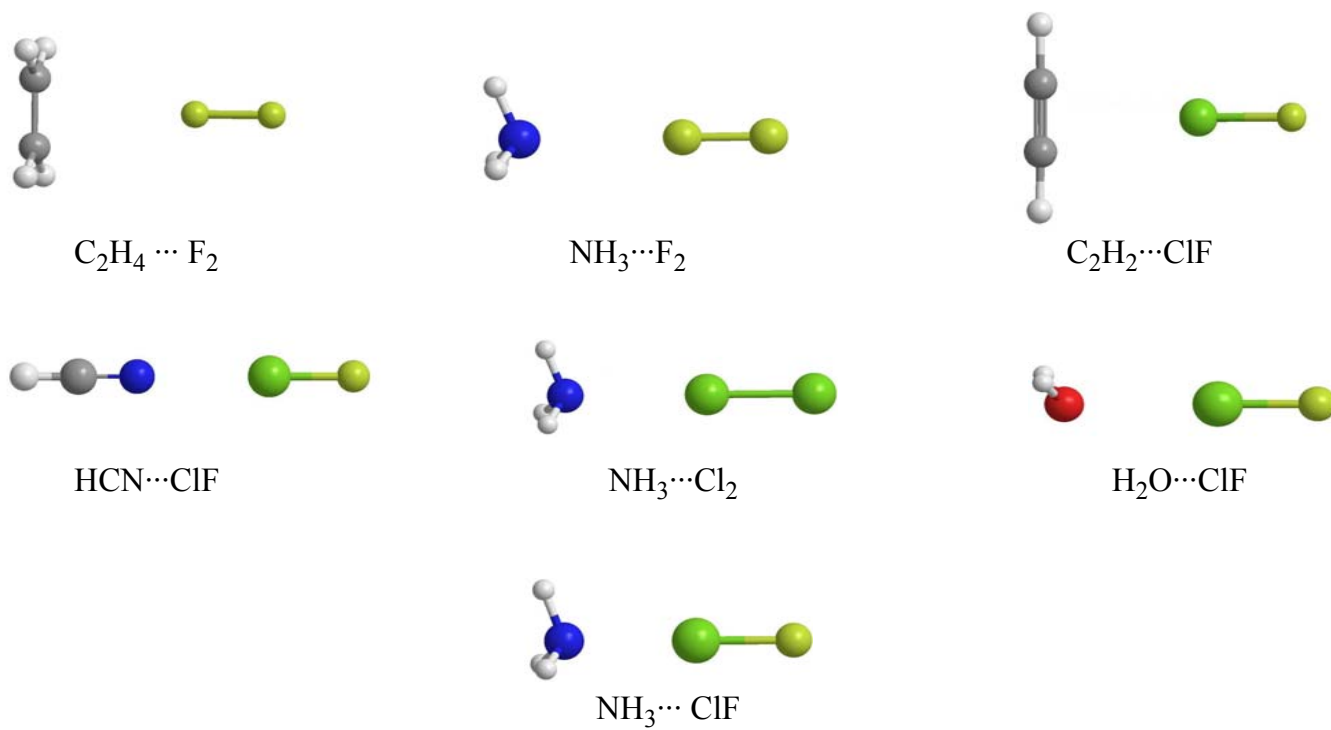


Figure 2

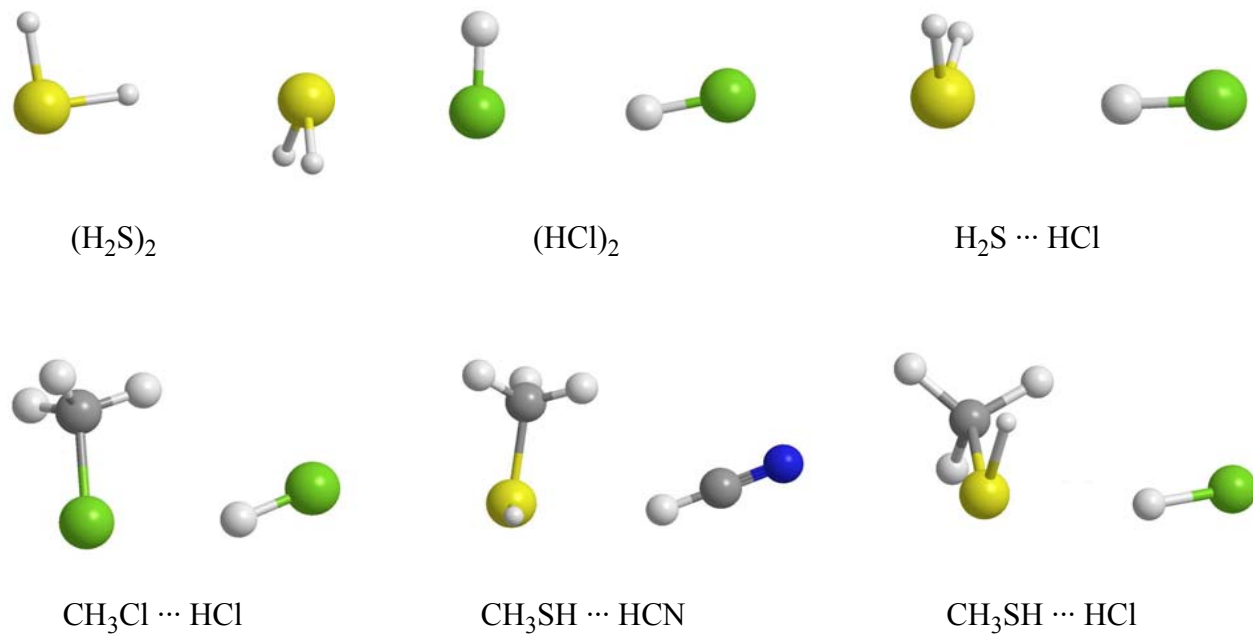


Figure 3

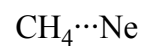
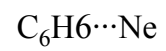
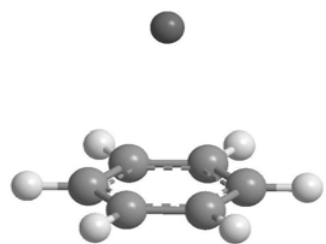


Figure 4

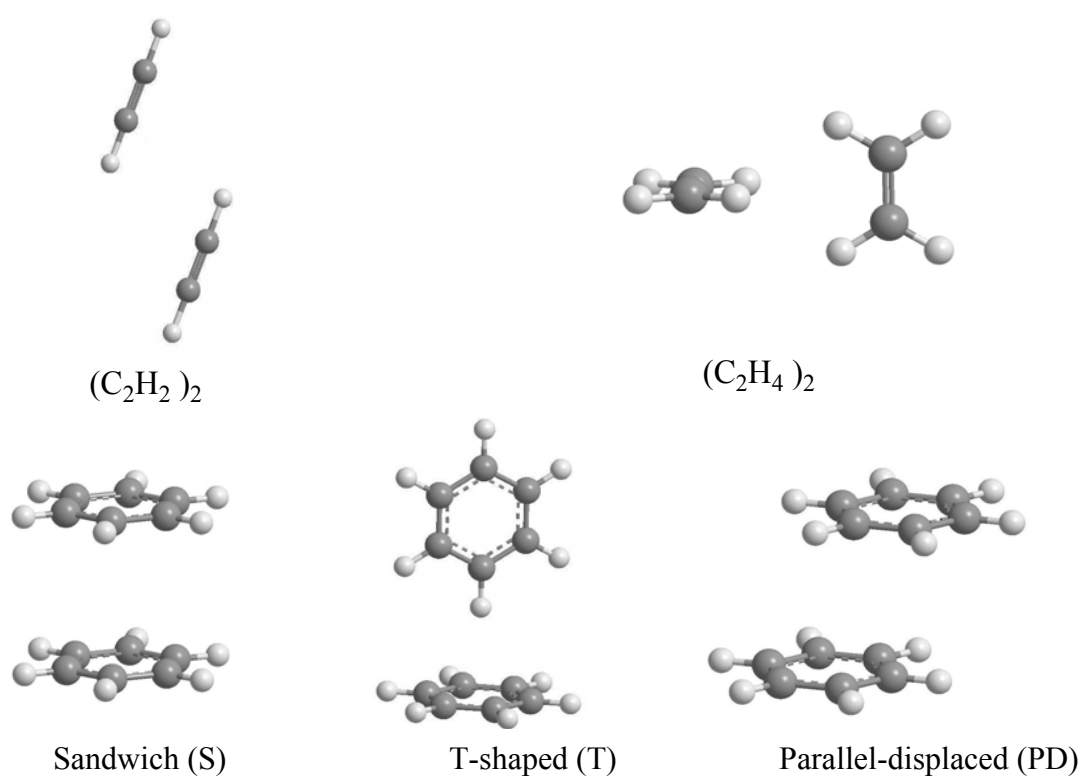


Figure 5

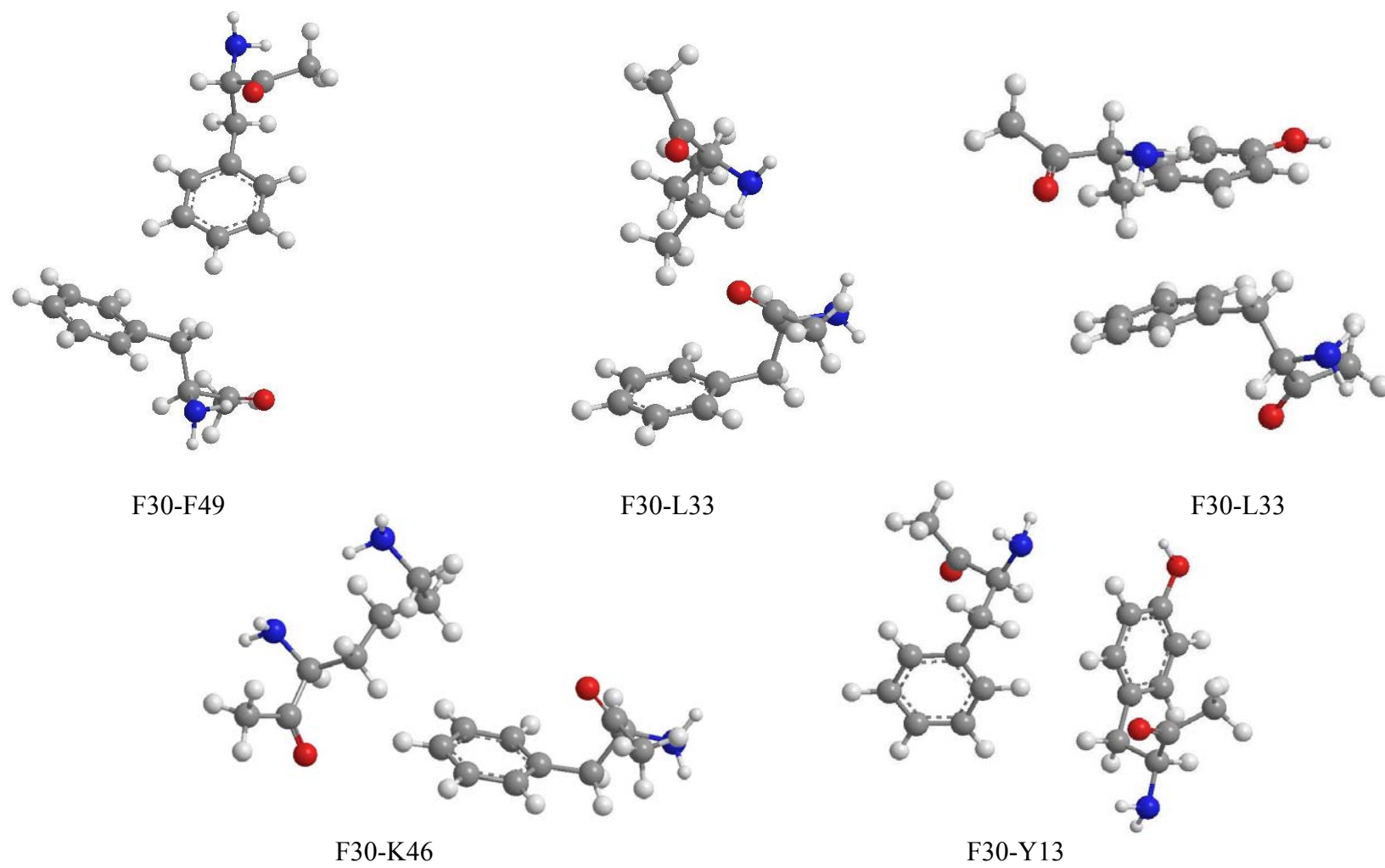


Figure 6