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Density Functional and Semiempirical Molecular Orbital Methods Including Dispersion Corrections for the Accurate Description of Noncovalent Interactions Involving Sulfur-Containing Molecules

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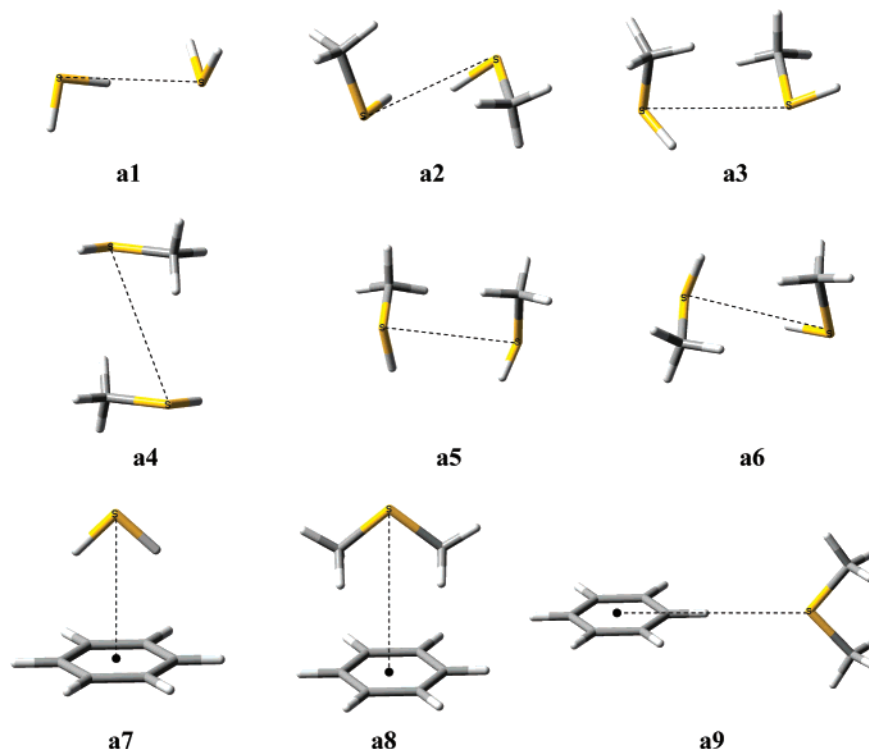
Abstract: We describe the use of density functional theory (DFT-D) and semiempirical (AM1-D and PM3-D) methods having an added empirical dispersion correction, to treat noncovalent interactions between molecules involving sulfur atoms. The DFT-D method, with the BLYP and B3LYP functionals, was judged against a small-molecule database involving sulfur-π, S–H···S, and C–H···S interactions for which high-level MP2 or CCSD(T) estimates of the structures and binding or interaction energies are available. This database was also used to develop appropriate AM1-D and PM3-D parameters for sulfur. The DFT-D, AM1-D, and PM3-D methods were further assessed by calculating the structures and binding energies for a set of eight sulfur-containing base pairs, for which high-level ab initio data are available. The mean absolute deviations (MAD) for both sets of structures shown by the DFT-D methods are 0.04 Å for the intermolecular distances and less than 0.7 kcal mol^{-1} for the binding and interaction energies. The corresponding values are 0.3 Å and 1.5 kcal mol^{-1} for the semiempirical methods. For the complexes studied, the dispersion contributions to the overall binding and interaction energies are shown to be important, particularly for the complexes involving sulfur-π interactions.

Introduction

It is now recognized that noncovalent interactions involving aromatic side chains play an important role in determining protein dynamics during folding and also protein–ligand recognition. A variety of interactions involving π-systems has been studied including π–π, cation-π, alkyl-π, amino-π, oxygen-π, and sulfur-π. Of these interactions, sulfur-π contacts have been the subject of only limited theoretical study in spite of the recognition of their importance in biological systems.[1–7] In the late 1970s frequent and close contacts between side chains of sulfur-containing amino acids (Met and Cys) and aromatic amino acids (Tyr, Trp, and Phe) were first recognized in crystal structures of globular proteins. Morgan et al.[8] identified proteins that contained one or more chains of alternating "sulfur and π-bonded atoms" and established a minimum distance of 5 Å for S···C(sp^2) van der Waals contacts. Sulfur-π interactions were found to occur more frequently than originally thought as exemplified by database searches carried out by Morgan et al.[9] and Reid et al.[10] In the statistical analysis of PDB data performed by Reid et al. a preference for the placement of divalent sulfur at the edge and slightly above the plane of aromatic rings was found. More recent structural analyses have considered the interaction of Met, Cys, and disulfide bridges separately with aromatic residues, and this work showed that although only a small number of examples of Met···aromatic interactions were found, Cys residues had a much stronger preference for facial contacts with aromatic residues.[11] A statistical analysis[12] of crystal structures[13] also provided evidence for interactions between disulfide units and aromatic residues.

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Figure 1. Small-molecule database structures showing interaction distances (dotted lines). Complexes **a1**: hydrogen sulfide dimer (C_s); **a2**–**a6**: methanethiol dimers (C_1, except for **a4** which possesses C_i symmetry); **a7** benzene with hydrogen sulfide (C_{2v}); **a8**, **a9**: benzene with dimethylsulfide (both C_{2v}). For **a7** and **a8** the intermolecular distance corresponds to the distance between the sulfur atom and the center of mass of the benzene ring.
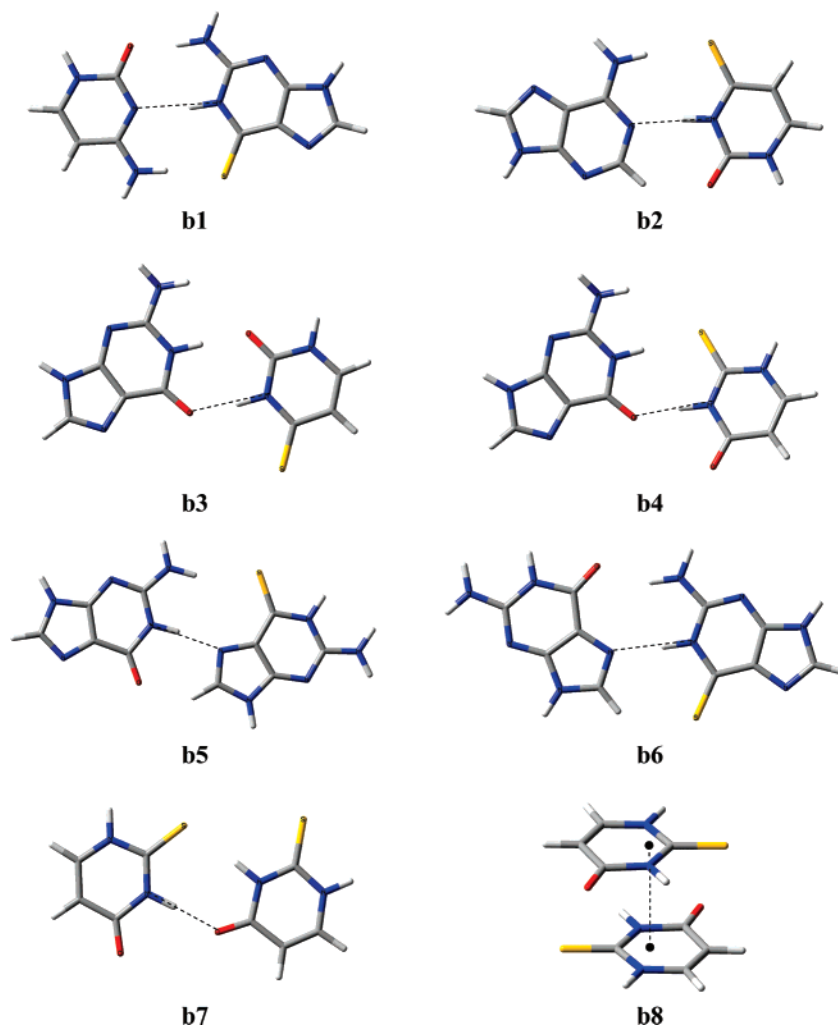
On the experimental side, Viguera and Serrano[14] investigated the contribution of sulfur-π interactions to the stability of α-helices employing spectroscopic techniques along with the AGADIR[15] algorithm. Phe$\cdots$Cys and Phe$\cdots$Met interactions were found to provide -2.0 kcal mol^{-1} and -0.65 kcal mol^{-1}, respectively, to helix stability. Tatko and Waters[16,17] studied Phe$\cdots$Met and Trp$\cdots$Met interactions and found that they were similar in magnitude to Phe$\cdots$Lys or Trp$\cdots$Lys interactions, with a value of -0.30 kcal mol^{-1}, and also found that the interaction of the Met side chain with the face of the aromatic residue was quite modest.

In view of the importance of π-stacking interactions in biological and other systems,[18] there have been an increasing number of studies to calculate these interactions which are often dominated by dispersive contributions. MP2 calculations with quite large basis sets are generally considered to be the minimum acceptable level for an ab initio study, although a higher level of electron correlation such as CCSD(T) is to be preferred.[18] In this respect, a number of studies at the post-Hartree–Fock level of the interaction of benzene with small sulfur containing molecules such as methanethiol,[3,4] dimethyl sulfide,[5] and H$_2$S have been reported,[6] including a recent CCSD(T) study of the C$_6$H$_6$$\cdots$H$_2$S complex.[7]

For the efficient study of large biomolecules the use of density functional theory (DFT) or perhaps a semiempirical method would be desirable, but here the accuracy of the predictions is of particular concern. There have been a number of investigations to determine how appropriate are different functionals for the study of π-stacking interactions, and the new functionals of Truhlar,[19] along with the older

half and half functional of Becke,[20] have shown promise. An alternative strategy is to add an empirical correction of the form R^{-6} to a density functional scheme to yield DFT-D models, rather than to tackle the difficult task of computing the dispersive term quantum mechanically.[21–23] Self-consistent-charge density functional tight-binding methods including such a dispersive correction (SCC DFTB-D) have also been developed.[24] DFT-D methods have been shown to be remarkably successful in predicting the binding energies of the *JSCH-2005* database[18] of 156 noncovalent biological complexes compiled by Hobza and co-workers.[25,26] For this same database, semiempirical models also including an empirical dispersive correction (AM1-D, PM3-D) have been developed which on average yield interaction energies to within $1-1.5$ kcal mol^{-1} of the high-level ab initio values [MP2 or CCSD(T)].[27]

In this paper we investigate the use of the DFT-D method[22,23,25,26] and semiempirical methods (AM1-D, PM3-D)[27] to describe a range of noncovalent sulfur interactions in a number of model systems and compare these with the results of high level ab initio calculations [MP2 or CCSD-(T)]. We have chosen to follow the approach of Jurečka et al.[18] in developing a small-molecule database to evaluate these more approximate methods. This database (Figure 1) contains different sulfur-π, S$-$H$\cdots$S, and C$-$H$\cdots$S interactions (**a1**–**a9**) for which high-level ab initio data (e.g., MP2 or CCSD(T)] have been reported (**a1**–**a7**)[7,23,28] or are calculated in this work (**a8**, **a9**). In our database hydrogen-bonded interactions have been considered in the H$_2$S dimer (**a1**) and in some of the CH$_3$SH dimers (**a2**, **a6**),

Figure 2. Biomolecule database structures showing interaction distances (dotted lines). Complexes **b1**: 6-thioG···C WC (C_s); **b2**: A···4-thioU WC (C_s); **b3**: G···4-thioU wobble (C_1); **b4**: G···2-thioU wobble (C_1); **b5**: G···6-thioG (C_s); **b6**: 6-thioG···G (C_s); **b7**: (2-thioU)$_2$ (C_s); **b8**: (2-thioU)$_2$ (C_1). In the **b8** complex the intermolecular distance is measured between the centers of mass of each monomer, and the monomers are parallel to each other.

whereas the other CH$_3$SH dimers (**a3**–**a5**) serve as models for C−H···S contacts, as does the C$_6$H$_6$···CH$_3$SCH$_3$ complex (**a9**). Sulfur-π interactions are considered in the complexes of benzene with H$_2$S (**a7**) and CH$_3$SCH$_3$ (**a8**). We use this same small molecule database to develop sulfur parameters for use in the AM1-D and PM3-D schemes and examine the strengths and weaknesses of these and the DFT-D method for treating important noncovalent interactions involving sulfur atoms, which are relevant for studying large biomolecules. We also examine the use of some alternative functionals for describing these interactions.

Computational Details

Empirical Dispersive Correction. In the approach developed by Grimme,[22,23] a pairwise additive potential of the form C_6/R^6 is used to account for long-range dispersion effects that can be particularly poorly described with some density functionals and with current semiempirical methods (AM1, PM3).[29,30] For each model, the dispersion corrected total energy is given by

$$E_{\text{Total}} = E + E_{\text{disp}} \tag{1}$$

where E is the normal self-consistent DFT or semiempirical energy (AM1, PM3) and E_{disp} is an empirical term containing the dispersion correction

$$E_{\text{disp}} = -s_6 \sum_i \sum_j \frac{C_6^{ij}}{R_{ij}^6} f_{\text{dmp}}(R_{ij}) \tag{2}$$

Here, the summation is over all atom pairs, C_6^{ij} is the dispersion coefficient for the pair of atoms i and j (calculated from the atomic C_6 coefficients), s_6 is a scaling factor that depends on the density functional or semiempirical method used, and R_{ij} is the interatomic distance between atoms i and j.[22] A damping function is used in order to avoid near singularities for small distances. This function is given by

$$f_{\text{dmp}}(R_{ij}) = \frac{1}{1 + e^{-\alpha(R_{ij}/R_0 - 1)}} \tag{3}$$

where R_0 is the sum of atomic van der Waals radii, and α is a parameter determining the steepness of the damping function. We note that initially the DFT-D method used the combination rule[22]

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$$C_6^{ij} = 2C_6^i C_6^j / (C_6^i + C_6^j) \tag{4}$$

whereas more recently the geometric mean was employed[23]

$$C_6^{ij} = \sqrt{C_6^i C_6^j} \tag{5}$$

DFT Calculations. In this work we have used both combination rules in the DFT-D calculations.[22,23] The values for the C_6, R_0, s_6, and α parameters were taken from the respective parametrizations, with one exception (Table 1). In the original DFT-D formalism, atomic C_6 coefficients were only quoted for the elements H, C, N, O, F, and Ne.[22] A corresponding C_6 coefficient for sulfur was determined following an algorithm proposed by Halgren[31] giving a C_6 value of 10.3 J nm^6 mol^{-1}, substantially larger than the value used for the geometric mean (5.57 J nm^6 mol^{-1}).[23] We also use a van der Waals radius of 1.87 Å for sulfur (Table 1).

The DFT-D calculations reported herein have been performed using a locally modified version of GAUSSIAN 03.[32] Although other functionals may be used within the DFT-D formalism, here all calculations have been performed with the dispersion corrected BLYP[33] and B3LYP[34] methods and the TZV(2d,2p) basis set.[35] Following Grimme we do not consider basis set superposition errors (BSSE) in view of the quite large basis sets employed. In this work the DFT-D method using the BLYP functional with the combination rule given in eq 4[22] is referred to as BLYP-D*. The BLYP-D and B3LYP-D notation refers to the use of the geometric mean, eq 5.[23] We have also compared some of the results of our DFT-D calculations with those using a number of alternative density functionals suggested to be appropriate for the description of π-stacking interactions. Thus, DFT calculations with the MPW1B95,[36] MPWB1K,[36] PW6B95,[19] and PWB6K[19] functionals were carried out using GAUSSIAN 03, with a local implementation of the PW6B95 and PWB6K functionals. Geometry optimizations using these four functionals were performed with the 6-31+G(d,p) basis set,[37] and the structures were optimized in the corresponding point group. We have not computed counterpoise-corrections to the binding energies, as the purpose of these calculations was to evaluate the performance of these functionals to describe sulfur-π interactions in the absence of such corrections, looking into their applicability to large molecular systems. As in the case of the DFT-D calculations, the numerical integration was performed employing the weighting scheme of Becke along with grids of ultrafine quality. Reported binding and interaction energies refer to electronic energies; zero-point vibrational as well as thermal corrections are not included.

Computational Results and Discussion

Small-Molecule Database. *DFT Calculations.* In Table 2 we report our calculations of the small-molecule database using the DFT-D (BLYP-D*, BLYP-D, B3LYP-D) method. We note that for the $(H_2S)_2$ (**a1**) and $(CH_3SH)_2$ complexes (**a2**−**a6**) we report binding energies (energy of the complex with respect to relaxed monomers), whereas for the complexes involving benzene (**a7**−**a9**) we report interaction energies (energy of the complex with respect to unrelaxed

Table 1. Atomic C_6 Coefficients (J nm^6 mol^{-1}) and van der Waals Radii, R_0 (Å)[a,b]

	C_6	R_0
H	0.16 (0.14)	1.11 (1.001)
C	1.65 (1.75)	1.61 (1.452)
N	1.11 (1.23)	1.55 (1.397)
O	0.70 (0.70)	1.49 (1.342)
S	10.30[c] (5.57)	1.87 (1.683)

[a] BLYP-D*, AM1-D, and PM3-D values and (in parentheses) BLYP-D and B3LYP-D values. [b] α and s_6 values are respectively as follows: 23, 1.4 (BLYP-D*, AM1-D, and PM3-D); 20, 1.2 (BLYP-D); and 20, 1.05 (B3LYP-D). [c] Determined using algorithm of Halgren.[31]

monomers). For the BLYP-D* method we also report the dispersion contribution (ΔE_{disp}) to the binding or interaction energy (ΔE).

We first consider our results for the hydrogen sulfide (**a1**) and methanethiol dimers (**a2**−**a6**). It is now generally accepted that strong hydrogen bonds can be accurately described using most standard density functionals.[38] In the case of a DFT-D approach the inclusion of an empirical C_6/R^6 correction may lead to some "double counting" of correlation effects,[22] which may be detrimental to the description of more strongly bound systems. However, in the case of the H_2S and the CH_3SH dimers, where the S−H···S interactions are weaker (and C−H···S interactions are even weaker), dispersion effects are expected to be important.

The binding energies and intermolecular separations obtained for the H_2S dimer agree well with the reference values,[23] showing a tendency of the DFT-D method to slightly overestimate the binding. In the case of the CH_3SH dimer, all three DFT-D schemes successfully identify the five stationary structures reported in the work of Cabalerio-Lago and Rodríguez-Otero,[28] with intermolecular orientations quite close to those obtained using the MP2 method. At this level, the binding energies of the different CH_3SH dimers span a narrow energy range of only 0.68 kcal mol^{-1}, and, as a result, it is not surprising that none of the dispersion corrected DFT methods reproduce the MP2 ordering of these energies. In fact, the DFT-D methods predict complex **a6** to have the largest binding, whereas at the MP2 level **a3** has the largest (Table 2). We also find that for the CH_3SH dimers, at the BLYP-D* level the dispersion contributions although relatively small (−1.60 to −2.68 kcal mol^{-1}) are important since they contribute between 60 and 92% to the overall binding energies (Table 2).

All the $(CH_3SH)_2$ structures show interactions between the sulfur atom in one molecule and a hydrogen atom in the methyl group of the second molecule. For the C−H···S contacts there is good agreement between the DFT-D calculations and the reference structures; the DFT-D calculations yield H···S distances close to 3.0 Å and C−H···S angles ranging from 130 to 150°. Regarding hydrogen-bonding, only structures **a2** and **a6** present interactions between a sulfur atom and a SH group, and only **a2** clearly exhibits this interaction, with an H···S distance and an S−H···S angle of 2.68 Å and 164.8° (BLYP-D*), respectively. At the BLYP-D and B3LYP-D levels these geometrical parameters are 2.69 Å, 164.7° and 2.69 Å, 164.4°, respectively. Overall, for the five $(CH_3SH)_2$ dimers alone, the

Table 2. Dispersion Corrected DFT Intermolecular Distances (Å) and Binding Energies and Interaction Energies (kcal mol^{-1}) for the Small-Molecule Database Complexes[a,b]

complex[c]		BLYP-D*			BLYP-D		B3LYP-D		reference[e]	
		R	ΔE_{disp}	ΔE	R	ΔE	R	ΔE	R	ΔE
$(H_2S)_2$ (C_s)	**a1**	4.13	−0.85	−1.91	4.12	−1.95	4.11	−1.97	4.10	−1.70
$(CH_3SH)_2$ (C_1)	**a2**	4.01	−1.63	−2.70	4.01	−2.86	4.00	−2.88	4.01	−2.28
$(CH_3SH)_2$ (C_1)	**a3**	3.87	−2.30	−2.52	3.78	−2.95	3.76	−3.27	3.76	−2.68
$(CH_3SH)_2$ (C_i)	**a4**	4.65	−1.60	−2.28	4.64	−2.68	4.63	−2.81	4.65	−2.00
$(CH_3SH)_2$ (C_1)	**a5**	4.17	−2.41	−2.66	4.10	−3.06	4.09	−3.30	4.11	−2.50
$(CH_3SH)_2$ (C_1)	**a6**	4.00	−2.68	−2.91	3.93	−3.33	3.93	−3.44	3.94	−2.46
$C_6H_6\cdots H_2S$ (C_{2v})	**a7**	3.83	−2.46	−2.14	3.69	−2.66	3.67	−2.93	3.80	−2.74
$C_6H_6\cdots CH_3SCH_3$ (C_{2v})	**a8**	4.92	−3.49	−1.96	4.81	−1.95	4.78	−2.27	4.94	−3.00
$C_6H_6\cdots CH_3SCH_3$ (C_{2v})	**a9**	5.53	−0.66	−0.83	5.40	−0.46	5.37	−0.61	5.46	−1.21
MAD[d]		0.04		0.41	0.04	0.57	0.05	0.62		

[a] TZV(2d,2p) basis set. [b] Binding energies for complexes **a1**−**a6**, interaction energies for complexes **a7**−**a9**. [c] Refer to Figure 1 for definition of interaction distance (R). [d] Mean absolute deviation. [e] Reference data: **a1**: RI-MP2/aug-cc-pVTZ;[23] **a2**−**a6**: MP2/aug-cc-pVDZ/cc-pVDZ (diffuse functions on hydrogen excluded);[28] **a7**: CCSD(T)/aug-cc-pVQZ;[7] **a8**, **a9**: MP2/aug-cc-pVDZ, this work.

BLYP-D*, BLYP-D, and B3LYP-D methods yield S⋯S distances with MAD (mean absolute deviation) values of 0.05, 0.01, and 0.01 Å, respectively, and give binding energies with corresponding MAD values of 0.29, 0.59, and 0.76 kcal mol^{-1}.

We next consider the $C_6H_6\cdots H_2S$ complex (**a7**), where we have chosen a C_{2v} structure with the sulfur atom located above the center ring (hydrogens-down configuration) since CCSD(T) data are available for this complex.[7] The BLYP-D* method predicts an intermolecular separation of 3.83 Å (refer to Figure 1) which differs by only 0.03 Å from the CCSD(T)/aug-cc-pVQZ value. At the BLYP-D and B3LYP-D levels the sulfur−benzene distances are a little short being 3.69 and 3.67 Å, respectively (Table 2). For this complex, compared to the CCSD(T) calculation, the interaction energy is underestimated by the BLYP-D* method by 0.60 kcal mol^{-1}, although this difference is still within the expected accuracy of the DFT-D model. On the other hand, the BLYP-D or B3LYP-D methods yield interaction energies (−2.66 and −2.93 kcal mol^{-1}) somewhat closer to the CCSD(T) value (−2.74 kcal mol^{-1}) even though the interaction distances differ from the reference values by more than 0.1 Å (Table 2). Importantly, for the $C_6H_6\cdots H_2S$ complex the BLYP-D* calculations indicate that in the absence of the dispersion correction the interaction between the respective monomers is repulsive (Table 2). Overall, for the $C_6H_6\cdots H_2S$ complex, the BLYP-D* method best describes the geometry of sulfur-π interactions with an interaction energy close to the ab initio value.[7]

We have used the MP2/aug-cc-pVDZ level of theory to obtain reference data for the $C_6H_6\cdots CH_3SCH_3$ complexes (**a8** and **a9**, Table 2). At this level, the interaction distance for the $C_6H_6\cdots H_2S$ complex (**a7**, hydrogens-down C_{2v} configuration) is calculated to be the same as the value obtained from the CCSD(T)/aug-cc-pVQZ calculation,[7] although the MP2 interaction energy is a little larger [MP2, −3.06 kcal mol^{-1}; CCSD(T), −2.74 kcal mol^{-1}]. In view of the excellent agreement between the MP2 and CCSD(T) calculations, we have also calculated two different C_{2v} configurations of the $C_6H_6\cdots CH_3SCH_3$ complex (**a8**, **a9**) at the MP2/aug-cc-pVDZ level of theory (Table 2).

Comparing to data obtained at the MP2/aug-cc-pVDZ level

for the $C_6H_6\cdots CH_3SCH_3$ complex (**a8**, **a9**) only, BLYP-D* exhibits intermonomer distances closest to the reference structures with a MAD value of 0.05 Å, whereas BLYP-D and B3LYP-D predict intermolecular distances with slightly larger deviations, underestimating these quantities in both cases (MADs: 0.10 and 0.13 Å, Table 2). Most importantly, for the orientation involving a sulfur-π interaction (**a8**), the dispersion energy (−3.49 kcal mol^{-1}, Table 2) contributes significantly to the overall interaction energy (−1.96 kcal mol^{-1}), in the absence of dispersion, the interaction being repulsive.

The calculations reported herein indicate that the BLYP-D* method is a little better than BLYP-D and B3LYP-D models for describing the intermolecular geometries of van der Waals complexes involving sulfur-π interactions especially when the sulfur atom is located above the π-surface, as indicated by the interaction distances and interaction energy MADs for the complexes **a7** and **a8** alone: 0.03 and 0.82 (BLYP-D*), 0.12 and 0.57 (BLYP-D), and 0.15 Å and 0.46 kcal mol^{-1} (B3LYP-D).

Finally, to compare the BLYP-D* method to other density functionals we have also carried out calculations with the MPW1B95,[36] MPWB1K,[36] PW6B95,[19] and PWB6K[19] functionals on those complexes involving benzene from our small-molecule database. The results are summarized in Table 3. It can be seen that all of the functionals describe the complex **a7** well but give intermolecular distances that are too great for complexes **a8** and **a9**. The best results are obtained with the PWB6K functional, particularly for complex **a7**, where the intermolecular distance and interaction energies differ from the reference CCSD(T) data[7] by only 0.02 Å and 0.23 kcal mol^{-1}, respectively. Compared to the reference MP2 calculations, PWB6K overestimates the equilibrium distances in complex **a8** by 0.13 Å but yields the same intermolecular separation as does BLYP-D* for complex **a9** (Table 2).

We turn now to calculations of these complexes using the dispersion corrected semiempirical methods.

Parametrization of Semiempirical Methods. The semiempirical calculations reported herein were performed using our own local semiempirical program.[39] As in our previous work[27] these calculations (AM1-D, PM3-D) use the combi-

Table 3. DFT Intermolecular Distances (Å) and Interaction Energies (kcal mol^{-1}) for Selected Small-Molecule Database Complexes[a]

complex[b]		MPW1B95		MPWB1K		PW6B95		PWB6K		reference[d]	
		R	ΔE	R	ΔE	R	ΔE	R	ΔE	R	ΔE
$C_6H_6\cdots H_2S$	**a7**	3.85	−2.30	3.83	−2.49	3.87	−2.46	3.82	−2.97	3.80	−2.74
$C_6H_6\cdots CH_3SCH_3$	**a8**	5.33	−1.02	5.29	−1.08	5.31	−1.32	5.07	−1.78	4.94	−3.00
$C_6H_6\cdots CH_3SCH_3$	**a9**	5.59	−0.73	5.58	−0.74	5.57	−0.88	5.53	−1.03	5.46	−1.21
MAD[c]		0.19	0.97	0.17	0.88	0.18	0.76	0.07	0.54		

[a] 6-31+G(d,p) basis set. [b] Refer to Figure 1 for definition of interaction distance (R). [c] Mean absolute deviation. Corresponding MAD values for these complexes only, at the various DFT-D levels are ($R,\Delta E$): BLYP-D*: 0.04, 0.67; BLYP-D: 0.10, 0.63; B3LYP-D: 0.13 Å, 0.51 kcal mol^{-1}. [d] Reference data: **a7**: CCSD(T)/aug-cc-pVQZ;[7] **a8**, **a9**: MP2/aug-cc-pVDZ, this work.

Table 4. Sulfur Parameters[a]

parameter[b]	AM1-D		PM3-D	
U_{ss} (eV)	−57.235044	(−56.694056)	−50.249536	(−49.895371)
U_{pp} (eV)	−48.307513	(−48.717049)	−43.968965	(−44.392583)
β_s (eV)	−3.311308	(−3.920566)	−8.397415	(−8.827465)
β_p (eV)	−7.256468	(−7.905278)	−7.594232	(−8.091415)
α (Å^{-1})	2.309315	(2.461648)	2.234331	(2.269706)

[a] (In parentheses) published AM1 and PM3 parameters.[29,30] All other parameters remain unchanged. [b] (In parentheses) units.

nation rule given in eq 4 and the associated C_6, R_0, s_6, and α parameters (Table 1), along with our modified semiempirical parameters for H, C, N, and O.[27]

In their development of the PM3$_{BP}$ Hamiltonian (for the treatment of hydrogen-bonding in nucleobase pairs), Giese et al.[40] found that the most appropriate parametrization scheme involved allowing the PM3$_{BP}$ parameters to vary only a little from the default values so that the final parameter set would be transferable to other chemical systems. This is the approach adopted herein, and we chose to modify only the U_{ss}, U_{pp}, β_s, β_p, and α parameters of sulfur (for both AM1[29] and PM3[30] methods); all the remaining parameters for sulfur are unchanged. Given the lack of complete structural data from the high level ab initio studies and the very good agreement between the BLYP-D* calculations and the ab initio reference data for the interaction distances in the small-molecule database (Table 2), we chose as our reference data (for the parametrization), the BLYP-D* structures (Table 2), in conjunction with the interaction energies taken from the ab initio data (Table 2).[7,23,28] The sulfur parameters were optimized using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) algorithm, details of which are available elsewhere.[41] Since we require the new semiempirical methods to be capable of accurately predicting interaction energies for structures extracted from experiment, we chose quite large weighting factors for the energy contributions to our fitting function, in line with our previous work.[27] The initial values of the parameters were set equal to the standard AM1[29] or PM3[30] values.

In Table 4 we report our modified AM1-D and PM3-D parameters for sulfur. We see that the final parameters only deviate a little from the standard AM1 or PM3 values. For the AM1-D model, the largest change is found for the β_s parameter which decreases in magnitude by 15.5%, while for the PM3-D method the largest change is found for the β_p parameter which also decreases in magnitude by 6.1%. These relatively small changes are not unexpected given that suitable AM1 SRP values for the calculation of thermal rate constants have been reported by allowing a variation in the standard values of only ±5%.[42]

In Table 5 we report the structures and binding (**a1**−**a6**) or interaction energies (**a7**−**a9**) for the complexes in the small-molecule database (Figure 1) calculated using the corrected semiempirical methods (AM1-D, PM3-D). In line with the DFT-D calculations for the $(H_2S)_2$ (**a1**) and $(CH_3SH)_2$ complexes (**a2**−**a6**) we report binding energies, whereas for the complexes involving benzene (**a7**−**a9**) we report interaction energies. In addition for the AM1-D and PM3-D methods we report the dispersion contribution (ΔE_{disp}) to the overall binding or interaction energies (ΔE). For comparison we have also calculated these complexes using the current semiempirical methods, AM1[29] and PM3.[30]

We see that compared to the AM1 and PM3 methods, the inclusion of a dispersive correction (AM1-D, PM3-D) leads to essentially a halving of the average error in the binding and interaction energies [MADs: 1.24 (AM1); 1.28 (PM3); 0.85 (AM1-D); 0.66 (PM3-D) kcal mol^{-1}, Table 5]. Interestingly, both the AM1 and PM3 methods predict all the complexes to be bound including those with sulfur-π interactions (**a7**, **a8**). We see that as far as the binding and interaction energies are concerned, our new semiempirical methods perform almost as well as the BLYP-D* method (MAD: 0.41 kcal mol^{-1}, Table 2), although the excellent agreement is not surprising given that these methods were parametrized using the BLYP-D* structures.

For the dispersion corrected methods, the largest difference between the semiempirical and reference interaction energies occurs for the $C_6H_6\cdots CH_3SCH_3$ complex (**a8**) with deviations of 2.83 (AM1-D) and 3.11 (PM3-D) kcal mol^{-1}, respectively. In spite of this large discrepancy, all other binding and interaction energies only differ from the reference value by less than 1 kcal mol^{-1} at the PM3-D level. Excluding complex **a8**, the AM1-D and PM3-D MADs for the binding/interaction energies (0.60 and 0.32 kcal mol^{-1}, respectively) are essentially comparable to the BLYP-D* values (Table 2). For the five $(CH_3SH)_2$ dimers, the relative ordering of the reference ab initio binding energies (**a3** > **a5** > **a6** > **a2** > **a4**) is not well reproduced at the AM1-D and PM3-D levels, in line with our DFT-D results (Table 2). However, unlike the DFT-D calculations (Table 2), the PM3-D method does in fact correctly predict **a3** to be the most stable arrangement of $(CH_3SH)_2$.[28] We note that at the AM1 and PM3 levels we were unable to locate all of the methanethiol stationary structures (Table 5). For the complexes involving benzene, the interaction energies at the AM1 and PM3 levels

Table 5. Semiempirical Intermolecular Distances (Å) and Binding Energies and Interaction Energies (kcal mol⁻¹) for the Small-Molecule Database Complexes[a]

complex[b]		AM1		PM3		AM1-D			PM3-D			reference[d]	
		R	ΔE	R	ΔE	R	ΔE_{disp}	ΔE	R	ΔE_{disp}	ΔE	R	ΔE
$(H_2S)_2$ (C_s)	**a1**	3.05	−3.84	3.23	−5.56	3.85	−0.93	−1.62	3.87	−0.87	−1.99	4.10	−1.70
$(CH_3SH)_2$ (C_1)	**a2**	3.67	−2.00	3.72	−2.12	3.92	−1.95	−2.34	3.97	−1.69	−2.31	4.01	−2.28
$(CH_3SH)_2$ (C_1)	**a3**	4.09[e]	−1.69[e]	4.27	−1.90	4.11	−3.07	−3.38	4.35	−2.56	−2.96	3.76	−2.68
$(CH_3SH)_2$ (C_i)	**a4**	4.30	−1.28	4.43	−1.55	4.61	−2.75	−3.11	4.58	−2.35	−2.91	4.65	−2.00
$(CH_3SH)_2$ (C_1)	**a5**	4.26	−1.21	4.38	−1.56	4.83	−2.87	−3.59	4.46	−2.33	−2.94	4.11	−2.50
$(CH_3SH)_2$ (C_1)	**a6**	3.66[f]	−2.06[f]	3.66[f]	−2.13[f]	4.17	−4.07	−3.89	4.51	−2.78	−2.67	3.94	−2.46
$C_6H_6{\cdots}H_2S$ (C_{2v})	**a7**	4.61	−0.55	4.57	−0.41	3.54	−3.26	−2.66	3.74	−2.73	−2.16	3.80	−2.74
$C_6H_6{\cdots}CH_3SCH_3$ (C_{2v})	**a8**	6.12	−0.18	4.86	−0.55	4.37	−6.20	−5.83	4.45	−5.83	−6.11	4.94	−3.00
$C_6H_6{\cdots}CH_3SCH_3$ (C_{2v})	**a9**	4.95	−0.85	5.02	−1.02	5.04	−0.96	−0.95	5.08	−0.95	−1.32	5.46	−1.21
MAD[c]		0.55	1.24	0.41	1.28	0.31		0.85	0.30		0.66		

[a] Binding energies for complexes **a1**−**a6**, interaction energies for complexes **a7**−**a9**. [b] Refer to Figure 1 for definition of interaction distance (R). [c] Mean absolute deviation. [d] Reference data: **a1**: RI-MP2/aug-cc-pVTZ;[23] **a2**−**a6**: MP2/aug-cc-pVDZ/cc-pVDZ (diffuse functions on hydrogen excluded);[28] **a7**: CCSD(T)/aug-cc-pVQZ;[7] **a8**, **a9**: MP2/aug-cc-pVDZ, this work. [e] Close to the **a5** structure. [f] Close to the **a2** structure.

Table 6. Dispersion Corrected DFT Intermolecular Distances (Å) and Binding Energies (kcal mol⁻¹) for the Sulfur-Containing Base Pairs in the Biomolecule Database[a]

complex[b]		BLYP-D*			BLYP-D		B3LYP-D		reference[c]	
		R	ΔE_{disp}	ΔE	R	ΔE	R	ΔE	R	ΔE
6-thioG${\cdots}$C WC pl (C_s)	**b1**	3.15	−4.03	−25.78	3.12	−27.35	3.11	−28.10	3.11	−25.50
A${\cdots}$4-thioU WC (C_s)	**b2**	2.94	−3.84	−13.78	2.87	−15.18	2.87	−15.36	3.04	−13.20
G${\cdots}$4-thioU (C_1)	**b3**	2.84	−3.83	−14.79	2.82	−15.92	2.80	−16.74	2.81	−15.90
G${\cdots}$2-thioU (C_1)	**b4**	2.80	−3.21	−13.27	2.79	−14.39	2.77	−14.99	2.77	−14.60
G${\cdots}$6-thioG pl (C_s)	**b5**	2.94	−3.68	−18.18	2.91	−19.71	2.90	−20.82	2.89	−19.00
6-thioG${\cdots}$G pl (C_s)	**b6**	2.97	−3.96	−18.84	2.93	−20.40	2.91	−21.49	2.92	−19.60
$(2\text{-thioU})_2$ pl (C_s)	**b7**	2.86	−3.20	−10.47	2.84	−10.95	2.82	−11.37	2.80	−11.60
$(2\text{-thioU})_2$ (C_1)	**b8**	3.6	−6.90	−4.23	3.5	−4.59	3.5	−4.99	3.6	−5.85
MAD[d]		0.05		0.95	0.05	0.94	0.04	1.35		

[a] TZV(2d,2p) basis set. [b] Refer to Figure 2 for definition of interaction distance (R). Abbreviations used: G (guanine), C (cytosine), A (adenine), U (uracil), WC (Watson−Crick), pl (planar). [c] Reference data: **b1**−**b7**: RI-MP2/CBS//RI-MP2/cc-pVTZ;[18] **b8**: MP2/6-31G*.[43] [d] Mean absolute deviation.

are all underestimated such that the inclusion of the dispersive correction leads to an improvement in the interaction energies. For example interaction energies for the complex involving H_2S are now −2.66 (AM1-D) and −2.16 (PM3-D) kcal mol⁻¹, close to the CCSD(T) value (−2.74 kcal mol⁻¹).[7] We see that for each of the complexes involving benzene (**a7**−**a9**) the dispersion contribution to the interaction energy at both the AM1-D and PM3-D levels is significant, in some cases being greater than the interaction energy (ΔE) itself (Table 5). However, despite the good agreement for the $C_6H_6{\cdots}H_2S$ complex, as previously noted, the interaction energy for the complex of benzene with dimethylsulfide (**a8**) is predicted to be almost twice that given by ab initio calculation at both the AM1-D and PM3-D levels [−5.83 (AM1-D); −6.11 (PM3-D); −3.00 kcal mol⁻¹ (MP2)].

As far as the structures of the various complexes are concerned, the inclusion of the dispersive correction leads to an improvement in the intermolecular distances (Figure 1, Table 5), the MADs being reduced from 0.71 (AM1) and 0.41 (PM3) to 0.31 (AM1-D) and 0.30 Å (PM3-D). We note that although the AM1-D and PM3-D methods yield binding and interaction energies of comparable accuracy to the DFT-D values, the DFT-D geometries for these complexes are in fact much closer to the reference ones [MAD: 0.04

(BLYP-D*); 0.04 (BLYP-D); 0.05 Å (B3LYP-D)]. The MADs for the interaction distances at both the AM1-D and PM3-D levels are still quite large (Table 5), even though these methods have been parametrized using the structures from our BLYP-D* calculations (Table 2).

Biomolecule Database. We have calculated the structures and binding energies of a number of sulfur-containing base pairs taken from the *JSCH-2005* database of Jurečka et al.[18] and also from the work of Šponer et al.[43] to further test the DFT-D and the semiempirical AM1-D and PM3-D methods. For the semiempirical methods, this represents an important step in examining the transferability of our new modeling schemes to the study of a series of complexes *not* included in the reference parametrization data. The hydrogen-bonded sulfur-containing complexes were taken from the *JSCH-2005* database (complexes **b1**−**b7**);[18] the stacked base pair (2-thioU)₂, orientation **b8** is taken from the work of Šponer et al.[43] The results are presented in Tables 6 and 7.

DFT Calculations. At the BLYP-D*/TZV(2d,2p) level, the binding energies of all the thiobase complexes are in very good agreement with the reference data (Table 6). The largest difference for a hydrogen-bonded base pair is just 1.33 kcal mol⁻¹ (**b4**), while in the case of the stacked (2-thioU)₂ complex (**b8**) the difference amounts to only 1.62 kcal mol⁻¹. Intermolecular distances are within the expected accuracy

Table 7. Semiempirical Intermolecular Distances (Å) and Binding Energies (kcal mol^{-1}) for the Sulfur-Containing Base Pairs in the Biomolecule Database

complex[a]		AM1		PM3		AM1-D			PM3-D			reference[b]	
		R	ΔE	R	ΔE	R	ΔE_{disp}	ΔE	R	ΔE_{disp}	ΔE	R	ΔE
6-thioG⋯C WC pl (C_s)	**b1**	3.15	−16.10	2.83	−17.50	3.06	−4.33	−21.38	2.76	−5.32	−27.12	3.11	−25.50
A⋯4-thioU WC (C_s)	**b2**	2.95	−5.76	2.81	−8.56	2.78	−4.10	−10.54	2.69	−4.63	−16.48	3.04	−13.20
G⋯4-thioU (C_1)	**b3**	3.02	−7.40	2.81	−5.52	2.96	−3.69	−15.24	2.74	−3.59	−13.85	2.81	−15.90
G⋯2-thioU (C_1)	**b4**	3.07	−8.24	2.80	−7.96	2.87	−3.44	−10.82	2.74	−3.36	−11.87	2.77	−14.60
G⋯6-thioG pl (C_s)	**b5**	2.99	−10.12	2.86	−10.96	2.84	−3.74	−15.73	2.71	−4.23	−21.17	2.89	−19.00
6-thioG⋯G pl (C_s)	**b6**	2.99	−10.12	2.79	−11.23	2.85	−4.26	−17.34	2.71	−4.71	−23.00	2.92	−19.60
(2-thioU)$_2$ pl (C_s)	**b7**	3.08	−6.08	2.81	−6.13	2.88	−3.13	−8.30	2.75	−3.42	−9.16	2.80	−11.60
(2-thioU)$_2$ (C_1)	**b8**	7.42[d]	−4.81	6.11[e]	−1.64	3.84	−9.70	−6.85	4.25	−7.86	−6.88	3.6	−5.85
MAD[c]		0.57	7.05	0.42	6.94	0.12		2.61	0.26		2.36		

[a] Refer to Figure 2 for definition of interaction distance (R). Abbreviations used: G (guanine), C (cytosine), A (adenine), U (uracil), WC (Watson−Crick), pl (planar). [b] Reference data: **b1**−**b7**: RI-MP2/CBS//RI-MP2/cc-pVTZ;[18] **b8**: MP2/6-31G*.[43] [c] Mean absolute deviation. [d] Corresponds to a planar hydrogen-bonded arrangement. [e] Rings are parallel but significantly displaced compared to the reference structure.

of the DFT-D method, showing a tendency to overestimation.[22,23,25,26] Overall, the BLYP-D* method exhibits MAD values of 0.05 Å and 0.95 kcal mol^{-1} for intermolecular distances and binding energies, respectively. On average, the binding energies calculated with the BLYP-D and B3LYP-D methods show absolute deviations from the reference data of just 0.94 and 1.35 kcal mol^{-1}, respectively, and with the exception of complexes **b2** and **b8**, intermolecular distances obtained with these methods are in very good agreement with the reference data. Finally, in comparison with BLYP-D*, both BLYP-D and B3LYP-D give shorter stacking and hydrogen-bonding distances and also larger binding energies.

Semiempirical Calculations. The AM1-D and PM3-D methods have previously been used to calculate the entire *JSCH-2005* database of Jurečka et al.[18] (excluding those complexes involving sulfur) and gave MADs of 1.1 and 1.3 kcal mol^{-1}, respectively, compared to 9.0 and 8.6 kcal mol^{-1} for the AM1 and PM3 methods.[27] For the complexes in the biomolecule database herein, we find a similar improvement in the MADs for both binding energies and geometries (Table 7). Overall the MADs are 2.61 kcal mol^{-1} (AM1-D) and 2.36 kcal mol^{-1} (PM3-D), considerably smaller than the corresponding values for the AM1 and PM3 methods, respectively (7.05 and 6.94 kcal mol^{-1}). As with the DFT-D calculations, the presence of sulfur in these systems does not seem to affect the overall performance of the AM1-D and PM3-D methods. We find that optimization of the stacked (2-thioU)$_2$ complex (**b8**) at the AM1-D and PM3-D levels yields the desired stacked configuration. However, at the AM1 level this structure collapses to a planar hydrogen-bonded arrangement of the two rings, and at the PM3 level the two rings remain essentially parallel but are significantly displaced compared to the MP2 structure, as indicated by the interaction distance of 6.11 Å (Table 7).

Conclusions

These calculations have reinforced our previous finding that the DFT-D method is a very accurate and efficient scheme for calculating a wide range of intermolecular interactions where dispersive contributions are particularly important. The MAD values we find for sulfur containing molecules are similar to those found for molecules having only first row

atoms. The extension of this scheme to semiempirical wavefunctions is found to yield MAD values a little larger than the DFT-D ones but still within 2 kcal mol^{-1} of the high level ab initio values. Thus, as we found for molecules containing first row atoms, the PM3-D and AM1-D methods can be surprisingly accurate and computationally economic. In view of this, even though these DFT and semiempirical methods with a R^{-6} correction might be deemed to be more 'approximate' than DFT methods requiring a specific functional, they do represent a good compromise between high level ab initio methods and empirical force field schemes.

Supporting Information Available: Cartesian coordinates of the BLYP-D* optimized complexes **a1**−**a9** and **b1**−**b8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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