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Face-to-Face Arene−Arene Binding Energies: Dominated by Dispersion but Predicted by Electrostatic and Dispersion/Polarizability Substituent Constants

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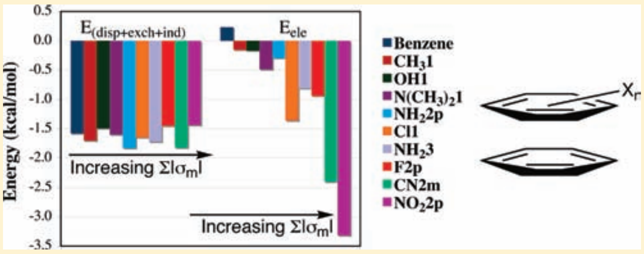
S *Supporting Information*



ABSTRACT: Parallel face-to-face arene−arene complexes between benzene and substituted benzenes have been investigated at the MP2(full)/6-311G** and M05-2X/6-311G** levels of theory. A reasonably good correlation was found between the binding energies and the $\Sigma|\sigma_m|$ values of the substituted aromatics. It is proposed that a substituent $|\sigma_m|$ value informs on both the aromatic substituent dispersion/polarizability and the effect the substituent has on the aromatic electrostatics. Supporting this hypothesis, a combination of electrostatic ($\Sigma\sigma_m$) and dispersion/polarizability (ΣM_r) substituent constant terms gives an excellent, and statistically significant, correlation with the benzene-substituted benzene binding energy. Symmetry adapted perturbation theory energy decomposition calculations show the dominant attractive force is dispersion; however, the sum of all nonelectrostatic forces is essentially a constant, while the electrostatic component varies significantly. This explains the importance of including an electrostatic term when predicting benzene-substituted benzene binding energies.

INTRODUCTION

Noncovalent interactions of aromatics are important in a wide range of chemical and biological processes.[1] Arene−arene interactions have been found to play key roles in enzyme−substrate recognition,[1d,2] protein structure and function,[3] DNA/RNA base-stacking[4] and intercalation,[5] organic reaction development,[6] and organic materials.[7] Significant experimental work has been done investigating the nature of arene−arene interactions,[1d,8] and there are three general conformations arene−arene dimers can assume: parallel face-to-face (**pff**), offset face-to-face (**osff**), and edge-to-face (**etf**), as demonstrated in Scheme 1 for the benzene−benzene dimer. For the benzene−benzene dimer, the **etf** and **osff** conformations are approximately the same in stability,[9] while for the benzene−nitrobenzene dimer, the **osff** geometry is much more stable than the **etf** or **pff** conformations.[10] Thus, there is no universally most stable benzene-substituted benzene dimer conformation. Computational studies have focused on **pff** arene−arene dimers to understand benzene-substituted benzene binding.[9−11] Sherrill and co-workers[9] and Tsuzuki and co-workers[11] have extensively investigated the nature of **pff** arene−arene interactions via high-level theoretical studies of benzene−benzene dimers and benzene-substituted benzene dimers and found the binding energy is primarily due to dispersion forces. It is noteworthy that this is in contrast to the seminal study of Hunter and Sanders,[12] where the attractive nature of arene−arene dimers was discussed in terms of electrostatics.

Recently, Houk and Wheeler reported a computational study of benzene-monosubstituted benzene **pff** dimers (Scheme 2a), and they found a reasonably good correlation between the binding energies and the Hammett σ_m values of the monosubstituted aromatics.[13] This result was interpreted as supporting the view of arene−arene binding being guided by electrostatics, similar to the Hunter−Sanders model.[12] Furthermore, it was not the only recent computational study showing a correlation between benzene-substituted benzene binding energies and Hammett constants.[14] Soon after the Houk and Wheeler publication, Sherrill and co-workers reported a study of **pff** arene−arene dimers where benzene was held constant and the other aromatic was either a mono- or a multisubstituted aromatic (Scheme 2b) with the substituents CH_3, F, OH, NH_2, CH_2OH, and CN.[15] An important difference between the Sherrill and co-workers' study and the Houk and Wheeler study is the substituents considered by Sherrill and co-workers had an approximately equal number of electron-withdrawing and electron-donating groups, whereas of the 24 substituents considered by Houk and Wheeler only five were electron-donating in nature. Because Sherrill and co-workers considered multisubstituted aromatics, a plot of the binding energies versus the aromatic $\Sigma\sigma_m$ values was reported, and there was no correlation. Furthermore, the study by Sherrill and co-workers reconfirmed their previous work showing the **pff** benzene−benzene dimer binding energy is weaker than the binding energy for any **pff** benzene-substituted benzene dimer, regardless of whether the substituent is electron-withdrawing or electron-donating.[9f]

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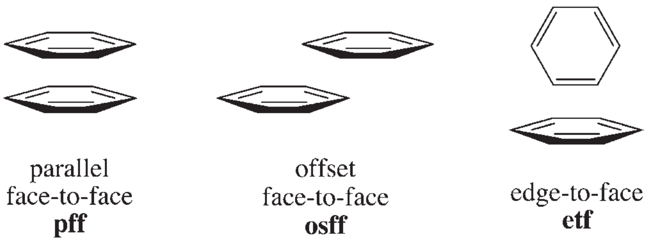
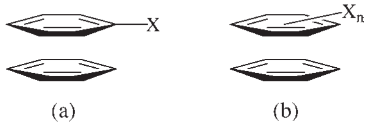
Scheme 1. Three General Conformations for Arene−Arene Dimers



Scheme 2. The General pff Arene−Arene Dimers Investigated by (a) Houk and Wheeler[13] and (b) Sherrill and Co-workers (n = 1, 3, 6)[15]



The Houk and Wheeler study also suggested the binding in benzene-substituted benzene dimers is guided by an interaction between the substituted aromatic substituents and the benzene π cloud, and more recent work from their group, studying the effect of aromatic substitution via Diels−Alder cycloaddition reactions, further supports this view.[16] The idea that an interaction between aromatic substituents and a benzene ring is important in benzene-substituted benzene binding has also been proposed for **osff**[17] arene−arene dimers and for **etf**[9c] dimers. Furthermore, it has been suggested that the interaction between aromatic substituents and anions is important in anion−π binding.[18]

The work presented here addresses many of the conflicting ideas regarding **pff** arene−arene dimers by computationally investigating a very large number of benzene-substituted benzene dimers. There is no denying that Sherrill and co-workers and Tsuzuki and co-workers are correct in stating **pff** arene−arene binding is dominated by dispersion forces;[9,11,15] however, it will be shown that the prediction of benzene-substituted benzene binding energies (E_{bind}) requires the consideration of electrostatic forces, as suggested by Houk and Wheeler.[13,16] Still, the Hammett constant σ_{m}, or $\Sigma\sigma_{\text{m}}$ for multisubstituted aromatics, is shown to not be sufficient for predicting E_{bind}, as made obvious in the recent paper by Sherrill and co-workers,[15] and instead it is proposed that a two variable equation with a combination of electrostatic ($\Sigma\sigma_{\text{m}}$) and dispersion/polarizability (ΣM_{r}) terms is best for predicting **pff** E_{bind} values. SAPT energy decomposition calculations are presented to further support the notion that variation in the attraction due to electrostatics must be accounted for to predict E_{bind}. Finally, a reasonably good correlation between E_{bind} and $\Sigma|\sigma_{\text{m}}|$ is presented, and a possible meaning for an aromatic $|\sigma_{\text{m}}|$ value is proposed.

METHODS

Benzene-substituted benzene dimers, C_6H_6:$C_6X_nH_{(6-n)}$, in a **pff** conformation were investigated where the substituted aromatics have X = F, Cl, Br, I, CN, NO_2, CH_3, OH, NH_2, OCH_3, and $N(CH_3)_2$ substituents with mono-, ortho-di-, meta-di-, para-di-, 1,3,5-tri-, and 1,2,4,5,-tetra-substitution patterns. Each dimer is referred to by its substituted aromatic using the shorthand **X1**, **X2o**, **X2m**, **X2p**, **X3**, and **X4** where X is the substituent, the numbers 1−4 are the number of substituents, and the letters "o", "m", and "p" indicate whether the disubstituted aromatics are ortho-, meta-, or para-substituted. The parent benzene−benzene dimer is referred to as **Benzene**. The **$N(CH_3)_2$4** dimer binding energy was not calculated because of the steric problems associated with having two large groups ortho to each other, and this is described in greater detail below. All aromatics were optimized, and frequency calculations were performed, at the MP2-(full)/6-311G** and M05-2X/6-311G** levels of theory. At the MP2-(full)/6-311G** level of theory, all aromatics were characterized as minima by the absence of imaginary frequencies except for **Br4**, which had one imaginary frequency from an out-of-plane distortion. The tendency for the MP2 method to give anomalous imaginary frequencies for aromatics has been explained as arising from a two-electron basis set incompleteness error (BSIE),[19] and when **Br4** is calculated at the M05-2X/6-311G** level of theory there are no imaginary frequencies. The rest of the aromatics were also minima at the M05-2X/6-311G** level of theory, except for **$CH_3$2m** and **$CH_3$3**. These two aromatics have imaginary frequencies corresponding to $C_{\text{ipso}}-C_{\text{methyl}}$ bond rotation, and a similar issue has been reported for the M06 method.[20] Given that the structures are almost identical to the MP2(full)/6-311G** calculated structures, which are minima, we are confident the M05-2X structures are also minima. For the substituted aromatics containing iodine atoms, the MIDI-X basis set was employed for I, while the 6-311G** basis set was used for all other atoms.

To calculate benzene-substituted benzene binding energies, the two aromatics were placed in a perfect **pff** conformation (Scheme 1) such that the geometric centers of the two aromatic were directly on top of each other, and the distance between the monomers was varied while keeping the monomer geometries constant. At each arene−arene distance, the binding energy was calculated by subtracting the combined energy of the two separate monomers from the energy of the dimer. For each dimer, the arene−arene distance was initially varied by 0.5 Å to find the general location of the energy minima. On each side of the resulting minimum energy point, the distance was varied by 0.1 Å to get a more exact value of the energy minimum, and this was taken as the benzene-substituted benzene binding energy. This was done at both levels of theory, and the MP2(full)/6-311G** calculated binding energies were corrected for basis set superposition error (BSSE) using the counterpoise method.[21] All reference to MP2(full)/6-311G** calculated binding energies throughout the remaining text refers to the BSSE corrected values, unless otherwise noted. The M05-2X/6-311G** method was developed for noncovalent complexes,[22] and it has been shown that the resulting binding energies have very small basis set superposition errors.[23] Thus, BSSE calculations were not performed for the M05-2X binding energies. Symmetry adapted perturbation theory (SAPT)[24] binding energy decomposition calculations were performed to determine the contributions from electrostatics, dispersion, induction, and exchange to the overall benzene-substituted benzene binding energies. The geometries for the SAPT calculations were the lowest energy BSSE corrected MP2(full)/6-311G** structures. The SAPT dimer and monomer wave functions were calculated using the CCSD/6-311G** theoretical method, and the wave functions of each monomer were calculated using the basis functions for the full dimer. This is the counter-poise approach to determining BSSE-corrected binding energies, and thus the SAPT binding energies reported in this Article should be considered BSSE-corrected. All optimization and binding energy calculations were performed using the Gaussian 03 suite of programs.[25] The SAPT calculations were done via SAPT2008[26] using ATMOL1024[27] as the front end for computing integrals.

The MP2(full)/6-311G** level of theory with BSSE correction performs very well in calculating **pff** arene−arene binding energies, as can

Table 1. Benzene-Substituted Benzene Binding Energies (E_{bind}) and Optimal Arene−Arene Distances (d) Calculated at the MP2(full)/6-311G** Level of Theory[a]

	MP2(full)/6-311G**			MP2(full)/6-311G**	
substituted benzene	E_{bind}	d	substituted benzene	E_{bind}	d
C_6H_6	−1.32	3.9	**$NO_2$2m**	−4.39	3.6
F1	−1.80	3.8	**$NO_2$2p**	−4.49	3.6
F2o	−2.30	3.8	**$NO_2$3**	−6.01	3.6
F2m	−2.29	3.8	**$NO_2$4**	−7.56	3.6
F2p	−2.32	3.8	**$CH_3$1**	−1.81	3.8
F3	−2.84	3.7	**$CH_3$2o**	−2.21	3.8
F4	−3.44	3.7	**$CH_3$2m**	−2.20	3.8
Cl1	−2.20	3.8	**$CH_3$2p**	−2.18	3.8
Cl2o	−3.05	3.7	**$CH_3$3**	−2.75	3.7
Cl2m	−3.13	3.7	**$CH_3$4**	−3.22	3.7
Cl2p	−3.12	3.7	**OH1**	−1.60	3.8
Cl3	−4.10	3.6	**OH2o**	−1.94	3.8
Cl4	−4.90	3.6	**OH2m**	−1.86	3.8
Br1	−2.34	3.8	**OH2p**	−1.93	3.8
Br2o	−3.32	3.7	**OH3**	−2.15	3.7
Br2m	−3.41	3.7	**OH4**	−2.75	3.6
Br2p	−3.40	3.7	**$NH_2$1**	−1.60	3.8
Br3	−4.51	3.6	**$NH_2$2o**	−1.92	3.7
Br4	−5.40	3.6	**$NH_2$2m**	−1.95	3.7
I1	−2.30	3.8	**$NH_2$2p**	−2.03	3.7
I2o	−3.24	3.7	**$NH_2$3**	−2.41	3.6
I2m	−3.31	3.7	**$NH_2$4**	−2.76	3.6
I2p	−3.30	3.7	**$OCH_3$1**	−1.77	3.8
I3	−4.29	3.6	**$OCH_3$2o**	−2.24	3.7
I4	−5.15	3.6	**$OCH_3$2m**	−2.14	3.7
CN1	−2.67	3.8	**$OCH_3$2p**	−2.31	3.7
CN2o	−4.08	3.7	**$OCH_3$3**	−2.72	3.7
CN2m	−4.09	3.7	**$OCH_3$4**	−3.48	3.6
CN2p	−4.13	3.7	**$N(CH_3)_2$1**	−1.82	3.8
CN3	−5.52	3.6	**$N(CH_3)_2$2o**	−1.49	4.3
CN4	−7.04	3.5	**$N(CH_3)_2$2m**	−2.53	3.7
$NO_2$1	−2.82	3.7	**$N(CH_3)_2$2p**	−2.52	3.7
$NO_2$2o	−4.43	3.7	**$N(CH_3)_2$3**	−3.36	3.6

[a] Binding energies (E_{bind}) are in kcal/mol and have been corrected for BSSE. The center of the substituted aromatic is directly on top of the center of the benzene monomer in each dimer, and the distance between the two centers corresponds to the benzene-substituted benzene distances (d) in angstroms.

be seen by comparing the C_6H_6−C_6H_6 and C_6F_6−C_6H_6 dimer binding energies calculated at the MP2(full)/6-311G** level of theory with BSSE correction with those calculated at the CCSD(T) level of theory with estimated basis set.[14a] The MP2(full)/6-311G** level of theory with BSSE correction gives reasonable agreement with very high levels of theory in terms of absolute arene−arene binding energies; however, in terms of predicting the difference in arene−arene binding energies, the agreement is excellent.[14a] The absolute benzene−benzene binding energy at the CCSD(T) level of theory with estimated basis set limit is −1.48 kcal/mol,[11c] and this is very similar to more recent CCSD(T) values with very large basis sets where the E_{bind} value ranges from −1.42 to −1.51 depending on the basis set.[9a] The values reported in Table 1 and the Supporting Information are −1.32 and −0.88 kcal/mol at the MP2(full)/6-311G** and M05-2X/6-311G** levels of theory, respectively, and these are 11% and 41% more positive that the −1.48 kcal/mol value of the very high-level ab initio calculation. Thus, the MP2(full)/6-311G** benzene−benzene binding energy is 11% more positive than the high-level ab initio calculations, and the M05-2X/6-311G** benzene−benzene binding energy is too positive by 41%. However, because the work here describes differences between arene−arene binding energies, absolute arene−arene binding energies are not the best way to evaluate the theoretical methods. The C_6F_6−C_6H_6 binding energy at the CCSD(T) level of theory with estimated basis set limit is −5.07 kcal/mol,[11a] and the difference between this and the benzene−benzene binding energy is 3.59 kcal/mol. The MP2(full)/6-311G** and M05-2X/6-311G** C_6F_6−C_6H_6 binding energies are −4.74 and −5.66 kcal/mol, respectively, and the differences between these and the respective benzene−benzene binding energies are 3.42 and 4.78 kcal/mol. Thus, the MP2(full)/6-311G** calculated difference between the C_6F_6−C_6H_6 binding energy and the benzene−benzene binding energy is 5% less than the value at the CCSD(T) level of theory with estimated basis set limit, and the M05-2X/6-311G** value is 33% greater. The absolute deviations are 0.17 kcal/mol for the MP2(full)/6-311G** level of theory and 1.19 kcal/mol for the M05-2X/6-311G** level of theory.

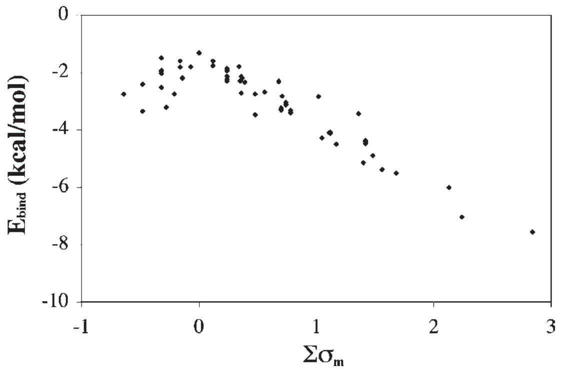


Figure 1. MP2(full)/6-311G** calculated benzene-substituted benzene binding energy (E_{bind}) versus the sum of the Hammett substituent constants σ_m ($\Sigma\sigma_m$).

The agreement with the very high level of theory for the MP2(full)/6-311G** values is excellent, and although the M05-2X/6-311G** value still deviates significantly from the value obtained at the CCSD(T) level of theory with estimated basis set limit, the method still reveals the same trends as the MP2(full)/6-311G** method and is thus an appropriate method for investigating differences in arene−arene binding energies.

■ RESULTS AND DISCUSSION

Comparison of the MP2(full) and M05-2X Methods. Before interpreting the results, it is worth noting up front that the non-BSSE corrected M05-2X E_{bind} values compare extraordinarily well to the BSSE corrected MP2(full) E_{bind} values. In the Methods section, the relative arene−arene binding energies of C_6H_6−C_6H_6 and C_6H_6−C_6F_6 were used to benchmark the M05-2X/6-311G** and MP2(full)/6-311G** methods against the CCSD(T) level of theory with estimated basis set limit, and the M05-2X method did not perform nearly as well as the MP2(full) method. However, a comparison of the MP2(full)/6-311G** and M05-2X/6-311G** E_{bind} values (Table 1 for the MP2(full) method and Supporting Information for the M05-2X method) shows there is very little difference. Furthermore, the figures relating the E_{bind} values to $\Sigma\sigma_m$ or $\Sigma|\sigma_m|$ (Figures 1−3 for the MP2(full) method and Supporting Information for the M05-2X method) are almost identical both in relative trends and in the magnitude of the binding energies. In fact, the reason the M05-2X results are in the Supporting Information is because they give essentially the same results as the MP2(full) method. It is also worth noting that the two methods also give almost identical arene−arene intermolecular distances (*d*). The performance of the M05-2X method is noteworthy because the calculations require significantly less computational resources and time than the MP2(full) calculations. The noncorrected MP2(full)/6-311G** E_{bind} and *d* values are also provided in the Supporting Information, and they help illustrate how well the M05-2X method performs. The noncorrected MP2(full)/6-311G** E_{bind} values are more binding than the BSSE corrected values by between −1.8 and −7.4 kcal/mol with a mean absolute deviation of 3.2 kcal/mol. In contrast, the mean absolute deviation between the M05-2X/6-311G** and the BSSE corrected MP2(full)/6-311G** E_{bind} values is 0.49 kcal/mol. The mean absolute deviation between the noncorrected and BSSE corrected MP2(full)/6-311G** arene−arene intermolecular distances, *d*, is 0.26 Å with the noncorrected arene−arene dimers always being closer than the BSSE corrected dimers. The mean absolute deviation between the M05-2X and the BSSE corrected MP2(full) *d* values is 0.07 Å. Thus, whether comparing the E_{bind} or *d* values, the M05-2X method performs extraordinarily well in reproducing the results of the significantly more computationally intensive BSSE corrected MP2(full)/6-311G** method.

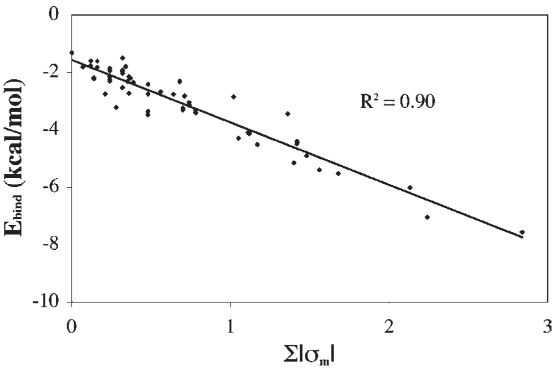


Figure 2. MP2(full)/6-311G** calculated benzene-substituted benzene binding energy (E_{bind}) versus the sum of the absolute value of the Hammett substituent constants σ_m ($\Sigma|\sigma_m|$).

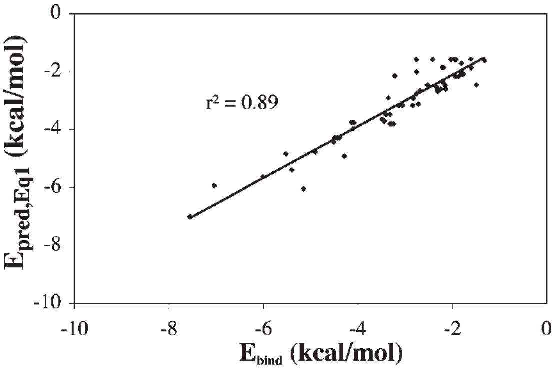


Figure 3. Correlation between the calculated E_{bind} values and the predicted benzene-substituted benzene binding energies obtained via eq 1 ($E_{\text{pred,eq1}}$).

Predicting Benzene-Substituted Benzene Binding Energies. One trend that is immediately clear from Table 1 is that the more substituents there are, the greater are the E_{bind} values and the closer are the two aromatics. This reinforces the finding of Sherrill and co-workers[9d,15] that any benzene-substituted benzene dimer, regardless of whether the substituents are electron-donating or electron-withdrawing, will have a greater E_{bind} value than the **Benzene** dimer. The only instance where this trend is broken is for the benzene-dimethylamino-substituted dimers. As shown in Table 1, the **$N(CH_3)_2$2o** dimer has a binding energy that is less attractive than the **$N(CH_3)_2$1** dimer. Furthermore, the **$N(CH_3)_2$2o** dimer is also significantly less binding than the **$N(CH_3)_2$2m** and **$N(CH_3)_2$2p** dimers, whereas for all of the other substituents, the ortho-, meta-, and para-disubstituted dimers have approximately the same E_{bind} values. The reason for the lower than expected **$N(CH_3)_2$2o** E_{bind} is because one of the two dimethylamino substituents is rotated significantly out of the plane of the aromatic, for steric reasons, thus impeding the binding with the benzene. The anomalously large arene−arene distance for the **$N(CH_3)_2$2o** dimer further highlights the issue. For all of the other substituents in Table 1, an increase in the number of substituents results in a shorter arene−arene distance. The **N(CH$_3$)$_2$2o** dimer does not follow the trend because of the sterics of the out-of-plane dimethylamino group. The steric factors complicating the interpretation of the **N(CH$_3$)$_2$2o** dimer would only be magnified for the **N(CH$_3$)$_2$4** dimer, and thus it was not investigated. However, the **N(CH$_3$)$_2$2o** dimer results remain in the analysis; one point in 66 does not appreciably alter a correlation.

Plotting E_{bind} against the substituted aromatic $\Sigma\sigma_{\text{m}}$ values, where the σ_{m} values were obtained from a standard reference,[28] gives the graph shown in Figure 1. This graph looks very similar to the graph reported by Sherrill and co-workers to illustrate the lack of correlation between benzene-substituted benzene binding energies and Hammett σ_{m} values.[15] The **Benzene** dimer has the smallest E_{bind} value, and adding any substituent, be they electron-withdrawing or electron-donating, increases E_{bind}.[9d,15] Thus, a linear correlation does not exist. This is the opposite of the findings by Houk and Wheeler; however, of the 24 monosubstituted aromatics in their study, only five contained an electron-donating group.[13] If only the substituted aromatics in Table 1 with electron-withdrawing substituents are considered, the correlation between E_{bind} and the $\Sigma\sigma_{\text{m}}$ values is reasonably good, with an r^2 value of 0.92 (the graph is in the Supporting Information), and this essentially reproduces the findings of the Houk and Wheeler study.[13]

Previous work by our group on substituted Cp−cation binding showed a reasonably good correlation between the charge on the cation and the sum of the absolute value of the Hammett substituent constant σ_{m} ($\Sigma|\sigma_{\text{m}}|$) of the substituted Cp anion.[29] Working from the hypothesis that there might be a similar relationship with benzene-substituted benzene dimers, the E_{bind} values in Table 1 were plotted against the $\Sigma|\sigma_{\text{m}}|$ values of the substituted aromatics (Figure 2). The r^2 value of 0.90 for the resulting graph is reasonably good (Figure 2), signifying a strong correlation between E_{bind} and the $\Sigma|\sigma_{\text{m}}|$ values. While this is certainly a very encouraging result when it comes to predicting benzene-substituted benzene binding energies, the physical significance of an aromatic $\Sigma|\sigma_{\text{m}}|$ value is not immediately clear, nor is it obvious why it performs so well in predicting E_{bind}. In fact, the latter point could be expanded to ask why any Hammett constant, or sum of Hammett constants, should predict E_{bind} values. While the literature is replete with both experimental[8a−c,e] and computational[13,14] studies correlating arene−arene binding energies with various types of Hammett constants, or sums of Hammett constants, it is not immediately clear why this endeavor has proven successful. Hammett substituent constants, of course, were developed by determining the effect a certain substituent had on the ionization of substituted benzoic acids.[28] However, the authors are unaware of any convincing argument relating the relative acidity of substituted benzoic acids with arene−arene binding energies. The genesis of employing Hammett constants to predict arene−arene attraction is in the numerous experimental studies using model systems to determine arene−arene binding energies.[8a−c,e] The assumption in this body of work seems to be that the attraction is electrostatic in nature, largely due to the model of Hunter and Sanders,[12] and that a parameter that describes the electronic effects a substituent has on benzoic acid acidity, the Hammett constant, should work to model the electronic/electrostatic arene−arene interaction. Of course, the work of Sherrill and co-workers[15] and the results in Figure 1 show this assumption to be incorrect.

Without any reasonable explanation as to why Hammett constants, or the sum of Hammett constants, should have ever been used to predict E_{bind} values in the first place, it is difficult to give an explanation as to why $\Sigma|\sigma_{\text{m}}|$ values work so well in predicting E_{bind} values (Figure 2). Still, the lack of a concrete explanation as to why $\Sigma|\sigma_{\text{m}}|$ values work so well does not preclude a comparison between $\Sigma\sigma_{\text{m}}$ and $\Sigma|\sigma_{\text{m}}|$ from being valuable. It is clear from Figures 1 and 2 that the $\Sigma|\sigma_{\text{m}}|$ values contain some information that the $\Sigma\sigma_{\text{m}}$ values lack, thus enabling the $\Sigma|\sigma_{\text{m}}|$ values to predict E_{bind} values. Specifically, the $\Sigma|\sigma_{\text{m}}|$ values allow for prediction of the E_{bind} values of the benzene-substituted benzene dimers where the substituted benzenes have electron-donating substituents. The obvious hypothesis, given the state of the field, is that the $\Sigma|\sigma_{\text{m}}|$ values contain information about how substituents affect both the electrostatic and the dispersion contributions to the overall binding. One way to test this hypothesis is to determine if a combination of the electrostatic substituent constant σ_{m} and the dispersion/polarizability substituent constant M_{r} (molar refractivity) predicts the E_{bind} values in Table 1. The molar refractivity substituent constant M_{r} was chosen because in quantitative structure activity relationship (QSAR) studies the M_{r} values are generally accepted to describe substituent polarizability.[30] Of course, $\Sigma\sigma_{\text{m}}$ and ΣM_{r} values were used because multiply substituted aromatics were investigated. The M_{r} values were obtained from a standard reference.[31] The resulting two parameter equation correlating the E_{bind} values in Table 1 with the substituted benzene $\Sigma\sigma_{\text{m}}$ and ΣM_{r} values gave eq 1, with an excellent correlation (r^2 = 0.98).

$$\begin{aligned} E_{\text{bind}} &= -1.46\sum\sigma_{\text{m}}(\pm 0.08) - 0.044\sum M_{\text{r}}(\pm 0.005) \\ &\quad - 1.57(\pm 0.10);\ n = 66, r^2 = 0.98, F = 1220 \end{aligned} \tag{1}$$

An F statistic greater than 124 signifies the correlation is statistically significant at the 99.9% confidence level, and eq 1 has an F value of 1220. Using the M05-2X/6-311G** E_{bind} values gives similar correlation equation coefficients and statistics (Supporting Information). Previous work by Sherrill and co-workers on **etf** benzene-substituted benzene dimers showed the binding energy correlated with a combination of $\Sigma\sigma_{\text{m}}$, the molecular polarizability, and a term accounting for the interaction between the aromatic substituents and the benzene hydrogen atoms.[9c] The work presented here extends this approach to **pff** dimers, although with different parameters and significantly more dimers.

Although the r^2 and F statistic values for eq 1 are impressive, a much more rigorous test of any correlation equation is how well it reproduces the values it is meant to predict. Equation 1 was used to predict E_{bind} for the dimers in Table 1, and the resulting values ($E_{\text{pred,eq1}}$) were plotted against the analogous E_{bind} values. The results of this analysis are shown in Figure 3, and the reasonably good r^2 value of 0.89 shows that eq 1 does a very good job of predicting E_{bind}. Multiparameter correlations with other electrostatic and dispersion substituent constants were also analyzed; the Hammett constant σ_{p} was used instead of σ_{m}, and the lipophilicity constant π was used instead of M_{r}. Thus, the combinations of $\Sigma\sigma_{\text{p}}$ and ΣM_{r}, $\Sigma\sigma_{\text{p}}$ and $\Sigma\pi$, or $\Sigma\sigma_{\text{m}}$ and $\Sigma\pi$ were investigated, and the resulting equations and graphs plotting the predicted binding energy (E_{pred}) versus the calculated binding energy (E_{bind}) are provided in the Supporting Information. While the r^2 and F statistic values for these equations are quite good, although not as good as they are for eq 1, the r^2 values for the plots of E_{pred} versus E_{bind} are significantly worse than the r^2 value in Figure 3, and thus the combination of $\Sigma\sigma_{\text{m}}$ and ΣM_{r} gives the best equations for predicting E_{bind}.

It is worth noting here the pitfall of relying solely on the statistics of a correlation equation to determine its validity. Using the $\Sigma\sigma_p$ and $\Sigma\pi$ values to determine a correlation equation for predicting E_{bind} gives $r^2 = 0.93$ and $F = 298$ with the MP2(full)/6-311G** E_{bind} values (eq S6 in the Supporting Information) and $r^2 = 0.87$ and $F = 147$ with the M05-2X/6-311G** E_{bind} values (eq S7 in the Supporting Information). These r^2 values are quite good, and the F statistic values are above the 124 cutoff for 99.9% confidence-level statistical significance. However, when eqs S6 and S7 are used to calculate benzene-substituted benzene binding energies and the resulting $E_{pred,EqS6}$ and $E_{pred,EqS7}$ values are plotted against the respective E_{bind} values, the r^2 values are 0.56 and 0.51, respectively (Figure S7 in the Supporting Information). Thus, even though the correlation eqs S6 and S7 have what appear to be impressive statistics, they do a very poor job predicting the E_{bind} values.

Energy Decomposition Calculations: The Sum of the Dispersion, Exchange, and Induction Energies Is a Constant. The results presented above show that benzene-substituted benzene binding energies can be predicted via a combination of electronic ($\Sigma\sigma_m$) and dispersion/polarizability (ΣM_r) terms, and this needs to be reconciled with the work of both Sherrill and co-workers and Tsuzuki and co-workers showing the dominant force in arene−arene binding is dispersion.[9,11] SAPT energy decomposition calculations were performed on 10 of the benzene-substituted benzene dimers in Table 1 using the lowest energy BSSE corrected MP2(full)/6-311G** conformers, and the results are presented in Table 2 and Figure 4. SAPT calculations partition the total binding energy (E_{SAPT}) into the electrostatic (E_{ele}), dispersion (E_{disp}), exchange (E_{exch}), and induction (E_{ind}) terms. The benzene-substituted benzene dimers were chosen to include a representative number of electron-donating and electron-withdrawing substituents, and, as shown in Table 2, there are four of the former and five of the latter, along with the parent **Benzene** dimer. As importantly as choosing an approximately equal number of electron-donating and electron-withdrawing substituents, it was also important to span as broad of a $\Sigma\sigma_m$ range as possible. The substituted aromatics in Table 2 have a $\Sigma\sigma_m$ range of −0.48 to +1.42, and this accounts for most of the $\Sigma\sigma_m$ range for the dimers reported in Table 1; of the 66 substituted aromatics in Table 1, only **Cl4**, **Br4**, **CN3**, **CN4**, **$NO_2$3**, **$NO_2$4**, and **$NH_2$4** fall outside of this range, and four of these seven (**Cl4**, $\Sigma\sigma_m = 1.48$; **Br4**, $\Sigma\sigma_m = 1.56$; **CN3**, $\Sigma\sigma_m = 1.68$; **$NH_2$4**, $\Sigma\sigma_m = -0.64$) are just barely outside the range. The benzene-substituted benzene total binding energies calculated using the SAPT method are termed E_{SAPT} in Table 2 and Figure 4a, and this is analogous to the E_{bind} values in Table 1 and Figures 1−3. The E_{SAPT} values are equal to $E_{ele} + E_{disp} + E_{exch} + E_{ind}$. The SAPT calculations employed the CCSD/6-311G** level of theory and are BSSE corrected. Thus, the E_{SAPT} values for the 10 dimers in Table 2 are slightly different than the respective E_{bind} values in Table 1. The E_{SAPT} values are always greater than the respective E_{bind} values, and the mean absolute deviation between the two sets of data is 0.23 kcal/mol. The relatively small difference between the E_{bind} and E_{SAPT} values of the 10 benzene-substituted benzene dimers in Table 2 suggests that using E_{SAPT} to discuss the total binding energies would yield the same conclusions as a discussion based on E_{bind} values. Furthermore, this suggests the trends observed for the energy decomposition values in Table 2 and Figure 4 should be general to the full set of benzene-substituted benzene dimers in Table 1.

In agreement with the work of Sherrill and co-workers and Tsuzuki and co-workers,[9,11] E_{disp} is the major attractive component of the overall binding energy, and E_{disp} varies considerably

Table 2. SAPT Calculated Binding Energy Decomposition Values for Selected Benzene-Substituted Benzene Dimers[a]

substituted benzene	$\Sigma\sigma_m$	E_{ele}	E_{disp}	E_{exch}	E_{ind}	$E_{(disp+exch+ind)}$	E_{SAPT}
$NH_2$3	−0.48	−0.81	−8.02	+6.97	−0.67	−1.72	−2.52
$NH_2$2p	−0.32	−0.29	−6.64	+5.27	−0.46	−1.83	−2.13
$N(CH_3)_2$1	−0.16	−0.49	−6.86	+5.72	−0.46	−1.60	−2.09
$CH_3$1	−0.07	−0.15	−5.74	+4.37	−0.28	−1.70	−1.86
Benzene	0.0	+0.23	−4.49	+3.14	−0.23	−1.58	−1.35
OH1	+0.12	−0.17	−5.31	+4.10	−0.28	−1.49	−2.09
Cl1	+0.37	−1.36	−5.73	+4.30	−0.22	−1.65	−3.01
F2p	+0.68	−0.94	−5.07	+3.82	−0.20	−1.45	−2.39
CN2m	+1.12	−2.40	−6.77	+5.27	−0.32	−1.82	−4.22
$NO_2$2p	+1.42	−3.32	−7.87	+6.84	−0.41	−1.44	−4.77

[a] SAPT calculations employed the CCSD/6-311G** level of theory. All energies are in kcal/mol. E_{ele}, E_{disp}, E_{exch}, and E_{ind} are the contribution to the total binding energy of electrostatics, dispersion, exchange, and induction. E_{SAPT} is the SAPT calculated total binding energy.

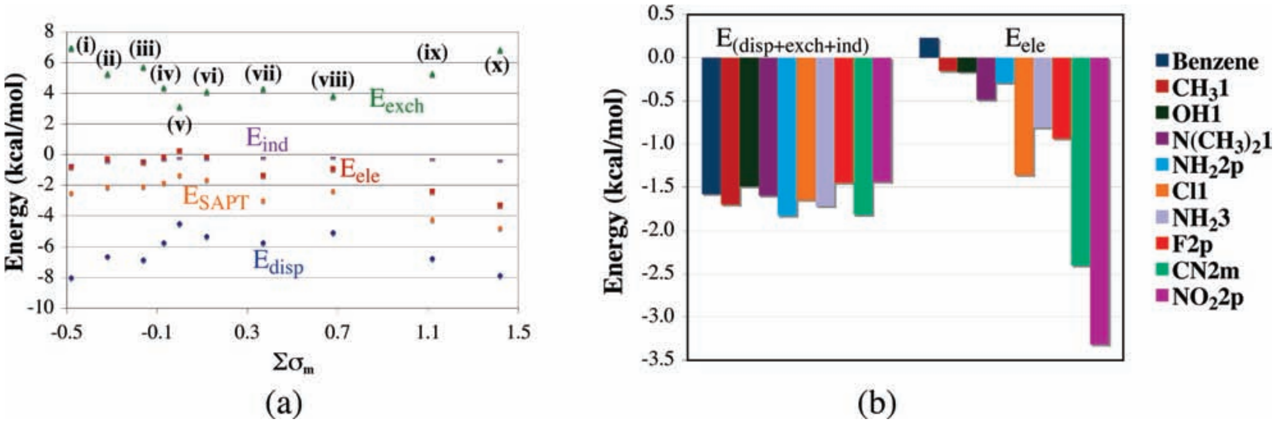


Figure 4. (a) Plots of SAPT calculated E_{exch}, E_{ind}, E_{ele}, E_{disp}, and E_{SAPT} values versus the substituent $\Sigma\sigma_m$ for the benzene-substituted benzene dimers (i) **$NH_2$3**; (ii) **$NH_2$2p**; (iii) **$N(CH_3)_2$1**; (iv) **$CH_3$1**; (v) **Benzene**; (vi) **OH1**; (vii) **Cl1**; (viii) **F2p**; (ix) **CN2m**; and (x) **$NO_2$2p**. (b) Graph comparing the $E_{(disp+exch+ind)}$ and E_{ele} values. The dimers are ordered, from left to right, by increasing $\Sigma|\sigma_m|$ values.

with aromatic substitution as shown in Figure 4a; E_{disp} is −4.49 kcal/mol for the benzene−benzene dimer and −8.02 kcal/mol for the **NH** dimer.

This is more variability in E_{disp} than has been previously reported;[9b,e,15] however, previous studies have investigated the difference in E_{disp} among benzene-monosubstituted benzene dimers. Given the greater surface area of multisubstituted aromatics, the E_{disp} variability among the benzene-substituted benzenes in Table 2 is not surprising. Another important point demonstrated by Table 2 and Figure 4a is that substituted aromatics where the substituents have vastly different electrostatic effects on the arene can have almost identical E_{disp} values. For instance, the **$NH_2$3** and **$NO_2$2p** dimers have almost identical E_{disp} values despite the former being the most electron-rich aromatic and the latter being the most electron-poor aromatic. Finally, all of the benzene-substituted benzene dimers in Table 2 have greater E_{disp} values than the parent **Benzene** dimer. All of the points made here regarding the relative E_{disp} values confirm the same point regarding dispersion energies: the greater is the surface area of the substituted aromatic, the greater is the contribution of dispersion to the overall binding energy.

Equally important to the E_{disp} values in Table 2 and Figure 4a are the E_{exch} values, which are always repulsive. In addition, the E_{exch} trend is opposite to the E_{disp} trend; the more attractive is the E_{disp} value, the more repulsive is the E_{exch} value. The opposing E_{disp} and E_{exch} trends are expected: the greater is the surface area, the more attractive is the dispersion energy, yet the greater is the orbital overlap, the more repulsive is the energy due to exchange.[32] Given E_{ind} is negligible in magnitude as compared to E_{disp} and E_{exch}, the sum of the energies due to dispersion, exchange, and induction ($E_{(disp+exch+ind)}$) is almost constant, as shown in Table 2 and Figure 4b. The E_{disp} values are generally between −1.0 and −1.5 kcal/mol more attractive than the E_{exch} values are repulsive, and the E_{ind} values range from about −0.2 to −0.7 kcal/mol. This results in $E_{(disp+exch+ind)}$ values of −1.4 to −1.8 kcal/mol, and, as shown in Figure 4b, there is no correlation between the substitution pattern and the $E_{(disp+exch+ind)}$ values. In contrast to the relatively constant $E_{(disp+exch+ind)}$ values, Figure 4b shows E_{ele} varies quite substantially with substitution, from +0.2 kcal/mol repulsive for the **Benzene** dimer to −3.3 kcal/mol attractive for the **$NO_2$2p** dimer. Furthermore, Figure 4b shows that the observed trend, although not perfect, is the greater are the substituted benzene $\Sigma|\sigma_m|$ values, the greater are the E_{ele} values. Perhaps the most surprising trend in Figure 4 is that the E_{ele} values for the benzene-substituted benzene dimers are always more binding than the parent **Benzene** dimer E_{ele}. Whether the substituted benzene has electron-donating groups ((i) **$NH_2$3**; (ii) **$NH_2$2p**; (iii) **N-$(CH_3)_2$1**; (iv) **$CH_3$1** in Figure 4a) or electron-withdrawing groups ((vi) **OH1**; (vii) **Cl1**; (viii) **F2p**; (ix) **CN2m**; (x) **$NO_2$2p** in Figure 4a), the contribution of E_{ele} to the overall binding energy is always net attractive as compared to the **Benzene** dimer. Thus, the E_{ele} trend in Figure 4a mirrors the trend in the overall binding energy (E_{SAPT}), the difference between the two being the −1.4 to −1.8 kcal/mol from the combined E_{disp}, E_{exch}, and E_{ind} terms ($E_{(disp+exch+ind)}$). Previous work by Sherrill and co-workers showed that the E_{ele} values for the toluene−benzene, phenol−benzene, fluorobenzene−benzene, and benzonitrile−benzene dimers are more binding than for the parent benzene−benzene dimer,[9b,e] and this demonstrated the surprising result shown here; adding an electron-donating substituent to a **pff** benzene−benzene dimer results in a more binding E_{ele} value. The Sherrill and co-workers work had the methyl group as the only electron-donating substituent, at least using σ_m values as a definition of electron donation, and the results in Table 2 show this is general to a broader group of electron-donating substituents.

The fact that $E_{(disp+exch+ind)}$ is a constant might initially give hope that a term describing the electrostatics of substituted aromatics, such as one of the Hammett constants, would correlate with E_{bind}. Of course, as has been demonstrated here, and previously by Sherrill and co-workers,[15] the Hammett constants σ_m (or $\Sigma\sigma_m$) and σ_p (or $\Sigma\sigma_p$) do not correlate with benzene-substituted benzene E_{bind} values. The primary reason for this, as shown in Table 2 and Figure 4, is that E_{ele} increases in binding both for strongly electron-withdrawing and for strongly electron-donating substituents. Thus, as we have shown above, a combination of $\Sigma\sigma_m$ and ΣM_r terms is required to predict E_{bind}. In recent experimental work investigating arene−arene interactions in organic solvents, Cockfroft and Hunter conclude that electrostatic effects are dominant and propose that the computational studies suggesting the dominance of dispersion only apply to the gas phase.[33] While dispersion may be dominant in terms of absolute contribution to E_{bind} in the gas phase, the work here shows that both electrostatics ($\Sigma\sigma_m$) and dispersion/polarizability (ΣM_r) terms are required to achieve a linear correlation with E_{bind} in the gas phase.

The SAPT results presented in Table 2 and Figure 4 explain why Houk and Wheeler found a reasonably good correlation between benzene-monosubstituted benzene binding energies and the σ_m values of the substituted aromatics where only five of the aromatics had electron-donating substituents.[13] The total binding energies they reported would have been primarily dependent on variations in E_{ele}, and the $E_{(disp+exch+ind)}$ term would have been relatively constant. The highly disproportionate number of electron-withdrawing groups obscured the fact that electron-donating groups would have also increased the overall binding energy, and this too would have been due to an increased contribution from the E_{ele} term. The results in Table 2 and Figure 4 also explain the recent results by Sherrill and co-workers showing there is no correlation between benzene-substituted benzene binding energies and the $\Sigma\sigma_m$ values of the multisubstituted aromatics where an approximately equal number of electron-withdrawing and electron-donating substituents were considered.[15] The work by Sherrill and co-workers included enough substituted aromatics with electron-donating groups to make clear the fact that the E_{bind} for dimers with a substituted aromatic was always more attractive than the **Benzene** dimer E_{bind}, regardless of whether the substituents were electron-withdrawing or electron-donating. Figures 1 and 4 further enforce this view. However, Figure 4 allows for the additional insight that the more attractive E_{bind} value is due solely to the increased contribution from E_{ele} because $E_{(disp+exch+ind)}$ remains relatively constant.

One of the primary findings in the SAPT calculations is that $E_{(disp+exch+ind)}$ values remain constant regardless of the substituted benzene substitution pattern; however, it is important to note that this conclusion only holds for **pff** benzene-substituted benzene dimers. Energy decomposition calculations by Tsuzuki and co-workers comparing the toluene−toluene dimer with the benzene−benzene dimer show that the lowest energy conformation of the toluene−toluene dimer is more stable than the lowest energy conformation of the benzene−benzene dimer by ~1.6 kcal/mol, yet the contribution from the electrostatic component is essentially equal.[11b] In this Tsuzuki and co-workers study, the lowest energy toluene—toluene dimer has the aromatics parallel, but with the molecular axes perpendicular to each other, in a conformation the authors term "cross". The lowest energy benzene—benzene dimer in the Tsuzuki and co-workers study is **osff**. While sweeping generalizations cannot be made by comparing toluene—toluene and benzene—benzene dimers, the results of the Tsuzuki and co-workers work[11b] certainly make it premature to make any predictions as to how $E_{(\text{disp+exch+ind})}$ values vary for arene—arene conformations other than **pff**, or for substituted benzene-substituted benzene dimers.

CONCLUSIONS

Previous work by Houk and Wheeler suggested that Hammett substituent constants alone could predict benzene-substituted benzene binding energies, E_{bind}.[13] Subsequent work by Sherrill and co-workers showed this not to be the case,[15] leaving open the question of how best to predict benzene-substituted benzene binding energies. The work presented here shows that the sum of the absolute value of the Hammett constants σ_m ($\Sigma|\sigma_m|$) does a reasonably good job predicting E_{bind} values, and the $\Sigma|\sigma_m|$ values are proposed to contain information about the substituent dispersion/polarizability, along with information about how the substituent effects the aromatic electrostatics. This view is supported by the excellent correlation between E_{bind} and a combination of $\Sigma\sigma_m$ and ΣM_r values. The fact that the energy due to electrostatics needs to be considered in predicting E_{bind} values is further supported by SAPT energy decomposition calculations showing the sum of dispersion, exchange, and induction energies ($E_{(\text{disp+exch+ind})}$) remains almost constant while the electrostatic component to E_{bind}, E_{ele}, varies approximately based on the substituted aromatic $\Sigma|\sigma_m|$ value. Certainly the most curious result of the reported work is the fact that E_{ele} is more binding regardless of whether electron-withdrawing or electron-donating substituents are added to a benzene ring, and current work in our group is aimed at explaining this finding. It is worth pointing out that the E_{ele} trend is largely dependent on two points, **CN2m** and **NO$_2$2p**. Although we are confident the trend is general for all highly electron-poor aromatics, part of our efforts to explain the E_{ele} trend involves performing more calculations of substituted aromatics with large positive or negative $\Sigma\sigma_m$ values to further support the result. In addition, future work may also involve calculating substituted aromatic polarizabilities, and using them in multiparameter equations instead of M_r values, to predict E_{bind}. As stated above, the conclusion that ($E_{(\text{disp+exch+ind})}$) remains constant regardless of substituted aromatic substitution pattern only holds for benzene-substituted benzene dimers. Finally, the work presented here shows the non-BSSE corrected M05-2X/6-311G** E_{bind} values are almost identical to the BSSE corrected MP2(full)/6-311G** values. Although the data analysis primarily relied on the MP2(full)/6-311G** results, the M05-2X/6-311G** level of theory gave essentially the same results, both qualitatively and in terms of absolute benzene-substituted benzene binding energies and distances; yet the M05-2X calculations required significantly less time and computational resources.

ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Arene monomer and benzene-substituted benzene dimer total energies and geometries, M05-2X data, equations and figures relating how well $\Sigma\sigma_p$ and ΣM_r, $\Sigma\sigma_p$ and $\Sigma\pi$, or $\Sigma\sigma_m$ and $\Sigma\pi$ predict E_{bind}, and complete citations for refs 25 and 26. This material is available free of charge via the Internet at http://pubs.acs.org.

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