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Beyond the Benzene Dimer: An Investigation of the Additivity of $\pi-\pi$ Interactions

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The benzene dimer is the simplest prototype of $\pi-\pi$ interactions and has been used to understand the fundamental physics of these interactions as they are observed in more complex systems. In biological systems, however, aromatic rings are rarely found in isolated pairs; thus, it is important to understand whether aromatic pairs remain a good model of $\pi-\pi$ interactions in clusters. In this study, ab initio methods are used to compute the binding energies of several benzene trimers and tetramers, most of them in 1D stacked configurations. The two-body terms change only slightly relative to the dimer, and except for the cyclic trimer, the three- and four-body terms are negligible. This indicates that aromatic clusters do not feature any large nonadditive effects in their binding energies, and polarization effects in benzene clusters do not greatly change the binding that would be anticipated from unperturbed benzene−benzene interactions, at least for the 1D stacked systems considered. Three-body effects are larger for the cyclic trimer, but for all systems considered, the computed binding energies are within 10% of what would be estimated from benzene dimer energies at the same geometries.

Noncovalent interactions are fundamental to supramolecular chemistry, drug design, protein folding, crystal engineering, and other areas of molecular science.[1] In particular, $\pi-\pi$ interactions between aromatic rings are ubiquitous in biochemistry and they govern the properties of many organic materials. Aromatic side chains in proteins are often found in pairs due to the favorable energetics of the $\pi-\pi$ interaction,[2,3] and certain drugs utilize $\pi-\pi$ interactions to intercalate into DNA.[4] The fundamental physics of individual $\pi-\pi$ interactions has been a subject of several high-level quantum mechanical studies,[5−9] but demonstrable convergence of the results even for the prototype benzene dimer has been achieved only recently[8] due to the extreme sensitivity of the results to electron correlation and basis set effects.

In many instances, an aromatic ring may be involved in more than one $\pi-\pi$ interaction at a time, such as the stacking of nucleic acid bases in the double-helical structure of DNA. In proteins as well, aromatic side chains can be found in clusters; for example, the carp parvalbumin protein (P3CPV) exhibits a cluster of seven phenylalanine residues. Burley and Petsko observed that 80% of the aromatic pairs they identified in a protein data bank (PDB) search were involved in “pair networks” as opposed to being isolated pairs.[2] Additionally, self-assembled stacks of aromatic macrocycles have been studied as possible molecular wires.[10] It is therefore critical to understand whether the properties of $\pi-\pi$ interactions, as understood from prototype studies of benzene dimers, change significantly when they occur in clusters, due to polarization or other many-body effects.

Some work along these lines was performed by Engkvist et al.,[11] who used simple potentials derived from CCSD(T) energies for benzene dimer to find and analyze local minimum structures on the trimer and tetramer potential energy surfaces. While their objective was to explore the potential energy surfaces and shed light on benzene cluster experiments, they did note that the two observed linear trimers (“H” and “double-T”, which we call T1 and T2, respectively; see Figure 1) had an interaction energy about twice that of the T-shaped dimer and that the cyclic trimer (C, Figure 1) had a total energy about 3 times that of the dimer. More recent ab initio results have been reported by Ye et al.,[12] who performed density functional theory (DFT) and second-order Møller−Plesset perturbation theory (MP2) computations for small benzene clusters in a parallel-displaced (PD) configuration as a model of π-stacks in polystyrene. In accord with other studies (see, e.g., ref 13), these authors found DFT unreliable for π-stacking. Their MP2 results indicated that the interaction energy for five benzenes (-7.09 kcal mol^{-1}) was somewhat larger than one might expect by thinking of the pentamer simply as four benzene dimers (-6.24 kcal mol^{-1} at the same level of theory). This implies that something other than nearest-neighbor two-body interactions (i.e., benzene dimers) is making a significant contribution to the total interaction.

To better understand and model clusters of aromatic systems, it is important to understand the nature and magnitude of these other contributions, and to determine the relative magnitude of the different kinds of contributions (two-body vs three-body, nearest-neighbor vs non-nearest-neighbor, etc.). Here, we consider these different contributions in benzene trimers and tetramers consisting of various combinations of the prototypical configurations of the benzene dimer: the sandwich (S), T-shaped (T), and parallel-displaced (PD) configurations (see Figures 1 and 2). These configurations are chosen as interesting prototypes,

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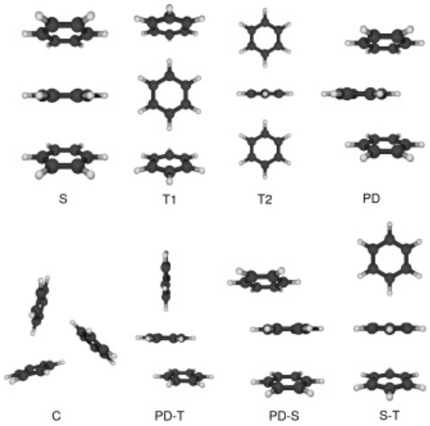

Figure 1. Eight benzene trimer configurations.

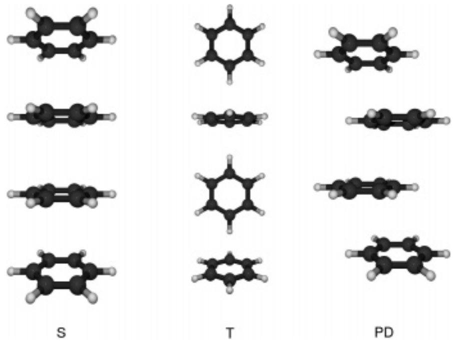

Figure 2. Three benzene tetramer configurations.

TABLE 1: Total and Many-Body Interaction Energies (kcal mol^{-1}) of Various Benzene Trimers at the MP2/cc-pVDZ+ Level of Theory

	S	PD	T1	T2	C	S/PD	S/T	PD/T
$\Delta^2E(12)$	−1.93	−2.91	−2.37	−2.38	−2.52	−1.95	−1.95	−2.90
$\Delta^2E(13)$	−0.01	−0.05	0.01	−0.03	−2.52	−0.04	−0.12	−0.14
$\Delta^2E(23)$	−1.93	−2.91	−2.37	−2.38	−2.52	−2.90	−2.39	−2.39
Δ^2E	−3.87	−5.88	−4.72	−4.80	−7.55	−4.88	−4.46	−5.42
Δ^3E	0.034	0.000	0.078	0.064	−0.33	0.023	−0.026	0.001
$\boldsymbol{E_{\mathrm{tot}}}$	**−3.83**	**−5.88**	**−4.64**	**−4.73**	**−7.88**	**−4.86**	**−4.49**	**−5.42**
E_{dimer}[a]	−3.74	−5.68	−4.70	−4.70	−7.32	−4.71	−4.22	−5.19

[a] E_{dimer} is the predicted interaction energy based on a simple sum of (nearest-neighbor) benzene dimer energies. The MP2/cc-pVDZ+ interaction energies of benzene dimer at these geometries are −1.87 (S), −2.84 (PD), −2.35 (T), and −2.44 kcal mol^{-1} (C).

but it is not our objective to survey and identify the lowest-energy configurations of the benzene trimer and tetramer. Nevertheless, we also consider the cyclic configuration of the trimer, which according to experiment should be the most stable.[14] In addition, our inclusion of diffuse functions, found to be critical in previous work[8] but neglected in the MP2 computations of Ye et al.,[12] allows us to examine their role in the additivity of these interactions.

Due to the large size of these systems, we were unable to apply the very high levels of theory we previously applied to the benzene dimer.[8] However, we have observed that MP2 in conjunction with small basis sets tends to exhibit a fortuitous cancellation of errors: small basis sets underestimate binding, while MP2 overestimates binding. We found that a modified aug-cc-pVDZ basis, which we will designate cc-pVDZ+, provides interaction energies within a few tenths of 1 kcal mol^{-1} of our previous estimates of the complete basis set coupled-cluster [CCSD(T)] limit for the geometries considered. The cc-pVDZ+ basis is the usual cc-pVDZ basis plus the diffuse s and p functions on carbon from the aug-cc-pVDZ basis. At the MP2/cc-pVDZ+ level of theory, using the geometries given below, we predict dimer interaction energies of −1.87 (sandwich), −2.84 (parallel-displaced), and −2.35 kcal mol^{-1} (T-shaped), while our previous estimates of the CCSD(T)/complete basis set values[8] were −1.81, −2.78, and −2.74 kcal mol^{-1}, respectively.

To compute the three- and four-body interaction terms between the monomers, we used a modified version of the Boys−Bernardi counterpoise correction[15] developed by Hankins, Moskowitz, and Stillinger,[16] which defines the many-body interactions in terms of the lower-order interaction energies. For a trimeric system, the total energy would be

$$E_{\mathrm{tot}} = \sum_i E(i) + \sum_{ij} \Delta^2 E(ij) + \Delta^3 E(123)$$

where

$$\Delta^2 E(ij) = E(ij) - E(i) - E(j)$$

$$\Delta^3 E(123) = E(123) - \sum_i E(i) - \sum_{ij} \Delta^2 E(ij)$$

and all computations are performed using the full basis of the trimer. The scheme can be extended for tetramers (denoting the four-body terms as Δ^4E) or larger clusters.

For simplicity, we use rigid monomers with parameters recommended by Gauss and Stanton[17] [r_e(C−C) = 1.4079 Å and r_e(C−H) = 1.0943 Å]; our previous work[8] indicates that there is almost no relaxation of monomer geometries when the dimers are fully optimized. We also used intermonomer parameters previously determined[8] at the MP2/aug-cc-pVDZ level of theory for the dimers [R_{S} = 3.8 Å, R_{T} = 5.0 Å, $R1_{\mathrm{PD}}$ = 3.4 Å, and $R2_{\mathrm{PD}}$ = 1.6 Å]. Tests of the sandwich trimer show that optimizing the intermonomer distances results in only a 0.05 Å increase from the dimer distance of 3.8 Å, a 0.03 kcal mol^{-1} change in the total energy, and changes on the order of 0.01 kcal mol^{-1} in the various many-body terms. With the assumption that all systems will exhibit the same magnitude of changes upon similar optimization, such optimization does not appear to be necessary for the purposes of this study. For the cyclic or C-trimer configuration, which experiment suggests is the lowest-energy configuration,[14] we were unable to find any geometric parameters in the literature. However, we found that the MP2/cc-pVDZ+ equilibrium geometry for this configuration (subject to C_{3h} symmetry) has a 4.8 Å intermonomer (center-to-center) separation with each monomer tilted 12° away from perpendicular.

Theoretical results for the trimers are summarized in Table 1. The reported values Δ^2E and Δ^3E are the sum of the individual two- and three-body interaction energies, respectively, for the given trimer. A few general trends are readily apparent from the table. One is that the nearest-neighbor two-body energies [$\Delta^2E(12)$ and $\Delta^2E(23)$] are in every case slightly larger than the corresponding benzene dimer energy. This is a result of the ghost functions from the additional monomers stabilizing the “dimer” systems when considered in the full basis of the trimer/tetramer. A second trend is that in all systems besides the C-trimer (which only has nearest-neighbor two-body interactions), the long-distance two-body interactions [$\Delta^2E(13)$] are generally small but stabilizing contributions to the overall interaction. On the other hand, the three-body interaction terms (Δ^3E) are mostly small but destabilizing. For the C-trimer, the three-body term is definitely significant—more than 0.3 kcal mol^{-1}—which might be expected because the C-trimer is a true three-body system, with each monomer having a close interac-

TABLE 2: Total and Many-Body Interaction Energies (kcal mol^{-1}) of Various Benzene Tetramers at the MP2/cc-pVDZ+ Level of Theory

	S	PD	T
$\Delta^2E(12)$	−1.94	−2.93	−2.37
$\Delta^2E(13)$	−0.01	−0.06	0.01
$\Delta^2E(14)$	0.01	0.01	−0.01
$\Delta^2E(23)$	−1.98	−2.97	−2.39
$\Delta^2E(24)$	−0.01	−0.06	−0.03
$\Delta^2E(34)$	−1.94	−2.93	−2.39
Δ^2E	−5.87	−8.94	−7.17
$\Delta^3E(123)$	0.035	0.000	0.077
$\Delta^3E(124)$	0.005	0.002	−0.006
$\Delta^3E(134)$	0.005	0.002	−0.005
$\Delta^3E(234)$	0.035	0.000	0.062
Δ^3E	0.079	0.004	0.127
Δ^4E	−0.0002	−0.0012	−0.0050
E_{tot}	**−5.80**	**−8.94**	**−7.05**
E_{dimer}[a]	−5.61	−8.52	−7.05

[a] E_{dimer} is the predicted interaction energy based on a simple sum of (nearest-neighbor) benzene dimer energies. The MP2/cc-pVDZ+ interaction energies of benzene dimer at these geometries are −1.87 (S), −2.84 (PD), and −2.35 kcal mol^{-1} (T).

tion with both of the other monomers. Because the three-body and long-distance two-body terms are small, one might expect that the binding energies of these trimers might be reasonably well estimated simply from the sum of (nearest-neighbor) benzene dimer energies at these geometries, a quantity we denote E_{dimer}. As shown in Table 1, this simple sum-of-dimers estimate is rather good, within 0.3 kcal mol^{-1} of the explicitly computed values for all but the C-trimer, where the difference is 0.6 kcal mol^{-1}.

In the tetramers, the results for which are summarized in Table 2, we see similar trends in regard to the two-body interactions: nearest-neighbor interactions are slightly more stabilizing than those in the isolated dimer, and long-distance interactions are, individually, relatively small. For the three-body interactions, the two all-nearest-neighbor terms $\Delta^3E(123)$ and $\Delta^3E(234)$ correspond very closely to the three-body term for the trimer, while the other two terms are essentially zero, such that the tetramer Δ^3E is essentially the sum of the two Δ^3E's from the trimers (123) and (234). The four-body terms are negligible for all cases, being no more than $^1/_{100}$ of 1 kcal mol^{-1}. Although the new types of interactions (four-body and non-nearest-neighbor three-body terms) are negligible, the larger number of long-distance two-body terms and all-nearest-neighbor three-body terms leads to larger deviations from the simple sum-of-dimers estimate than was observed for the trimers (except for the T-tetramer, which shows a fortuitous agreement with the sum-of-dimers estimate). The aggregate effects of long-distance two-body terms and all-nearest-neighbor three-body terms will become more significant on an absolute basis for larger clusters and would need to be included if accurate total binding energies are required. Fortunately, however, it should be possible to obtain good estimates of these effects simply from trimers. Overall, we observe deviations from the sum-of-dimers estimate of about 0.4 kcal mol^{-1} or less for the tetramer stacks considered. This is considerably smaller than the 0.85 kcal mol^{-1} deviation noted for the slightly larger PD pentamer system (with a somewhat different geometry) considered by Ye et al.[12] Given the similarity between the two- and three-body terms obtained for the trimers and tetramers, we can reasonably assume that they remain similar for the pentamer, allowing us to obtain a simple estimate of the interaction energy that would be obtained by adding one more benzene to our PD tetramer. This estimate yields −11.96 kcal mol^{-1}, giving a deviation of 0.6 kcal mol^{-1} from our sum-of-dimers estimate. The remaining 0.25 kcal mol^{-1} difference between our estimate of this deviation and that of Ye et al. may be ascribed to the different geometries and basis sets employed. We also note, however, that the lack of diffuse functions in the MP2 computations of Ye et al. leads to considerably smaller total interaction energies, making the discrepancy from the sum-of-dimers estimate larger on a percentage basis. Overall, the differences between our ab initio interaction energies and the simple sum-of-dimers estimates are 1−6% for the trimers (7% for the C-trimer), 0−5% for the tetramers, and 5% for the pentamer (estimated) versus 12% from the work of Ye et al.

TABLE 3: Total and Many-Body Interaction Energies (kcal mol^{-1}) of Benzene Trimers at the CCSD(T)/cc-pVDZ+ Level of Theory

	S	PD	T1	C
$\Delta^2E(12)$	−0.48	−0.92	−1.62	−1.61
$\Delta^2E(13)$	0.02	−0.01	0.02	−1.61
$\Delta^2E(23)$	−0.48	−0.92	−1.62	−1.61
Δ^2E	−0.94	−1.85	−3.22	−4.84
Δ^3E	0.038	0.014	0.072	−0.250
E_{tot}	**−0.90**	**−1.84**	**−3.14**	**−5.09**
E_{dimer}[a]	−0.86	−1.72	−3.20	−4.62

[a] E_{dimer} is the predicted interaction energy based on a simple sum of (nearest-neighbor) benzene dimer energies. The CCSD(T)/cc-pVDZ+ interaction energies of benzene dimer at these geometries are −0.43 (S), −0.86 (PD), −1.60 (T), and −1.54 kcal mol^{-1} (C).

It is important to determine whether the near-addivity of the interaction energies persists when higher-level treatments of electron correlation are employed. Therefore, we performed CCSD(T)/cc-pVDZ+ calculations on four of the trimers, the results of which are summarized in Table 3. While the total interaction energies and the nearest-neighbor two-body terms vary greatly from the MP2 energies in Table 1 (consistent with our previous work[8]), the magnitudes of the three-body terms are very similar to those computed via MP2, demonstrating that these three-body terms do not depend greatly on the computational method employed. On a percentage basis, the deviations from the sum-of-dimers estimates are 2−7% for the S, PD, and T1 configurations, and a somewhat larger 9% for the C-trimer. It is interesting to note that the total energies for the T1 and C systems here are quite similar to those reported by Engkvist et al.,[11] who, as noted above, used CCSD(T) results to calibrate their potential.

In conclusion, we have demonstrated that the interaction energies in larger benzene clusters are fairly close to what one might expect based simply on the sum of interaction energies for isolated benzene dimers, with an error of less than 10% for all systems considered. Two considerations keep this simple picture from being perfectly accurate:

(1) Nearest-neighbor two-body interactions are stabilized by up to $^1/_{10}$ of 1 kcal mol^{-1} when computed in the basis set of the full system as opposed to the dimer basis.

(2) Long-distance two-body interactions, as well as nearest-neighbor three-body terms, have an aggregate effect which will become increasingly important for the total binding energy of larger clusters (although these effects are readily estimated from trimers).

Fortunately, we find that four-body terms and three-body terms that include any non-nearest-neighbor monomer pairs are insignificant for the configurations considered and can be safely neglected.

Because the nearest-neighbor three-body terms are fairly insensitive to the electronic structure method, it seems worthwhile to use a less expensive method to determine these terms, while very accurate methods may be used to determine the dominating two-body terms. In this light, the recent multicenter model of Hopkins and Tschumper,[18] which employs high-level computations only on dimers and low-level computations on the entire cluster, is very promising.

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Supporting Information Available: Cartesian coordinates and total energies of the clusters. This material is available free of charge via the Internet at http://pubs.acs.org.

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