

# Quantum-Mechanical Evaluation of $\pi$ – $\pi$ versus Substituent– $\pi$ Interactions in $\pi$ Stacking: Direct Evidence for the Wheeler–Houk Picture

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**S** Supporting Information

**ABSTRACT:** The influence of substituents on  $\pi$ -stacking interactions has previously been explained by two competing hypotheses: a nonlocal effect in which tuning of the  $\pi$  density by the substituent alters the interaction (the Hunter–Sanders picture) or a local effect in which the direct interaction of the added substituent and changed polarity of the phenyl-substituent  $\sigma$  bond alter the interaction (the Wheeler–Houk picture). In this work, we applied the recently developed functional-group partition of symmetry-adapted perturbation theory (F-SAPT) to directly quantify these two effects in situ. The results show that both pictures contribute to the change in interaction energy but that the Wheeler–Houk picture is usually dominant.

Noncovalent  $\pi$ -stacking interactions are ubiquitous in nature and have been found to play critical roles in the stabilization of DNA,<sup>1</sup> the strength and specificity of drug–protein interactions,<sup>2</sup> and myriad other areas of supramolecular chemistry.<sup>3</sup> These interactions are strongly modulated by the presence of substituents around the  $\pi$  ring,<sup>4,5</sup> leading to a powerful avenue for the rational design of noncovalent contacts. However, the physical mechanism by which the substituents tune the interaction energy has been a source of considerable exploration and debate in the literature.<sup>6</sup> The long-held hypothesis of Hunter and Sanders (HS) posits that the substituent principally serves to inductively add or withdraw density from the  $\pi$  system of the substituted benzene, thus changing the electrostatic interaction.<sup>4,7</sup> This effect is nonlocal and indirect, as the substituent affects the second benzene only through the  $\pi$  system of the substituted benzene. A second hypothesis proposed by Wheeler and Houk (WH) posits that the direct interaction between the substituent and the second benzene plus the change due to the altered polarity of the linking phenyl-substituent  $\sigma$  bond (which is of C–X topology in Ph–X vs C–H in Ph–H) wholly explains the influence of the substituent on the interaction energy.<sup>8</sup> This effect is local (confined to the substituent and the linking  $\sigma$  bond) and both direct (in the X $\cdots$ Bz interaction) and indirect (in the changed  $\sigma\cdots$ Bz interaction<sup>9</sup>). A markedly interesting consequence of the WH hypothesis is that the  $\pi$  system is not involved in the substituent effect.

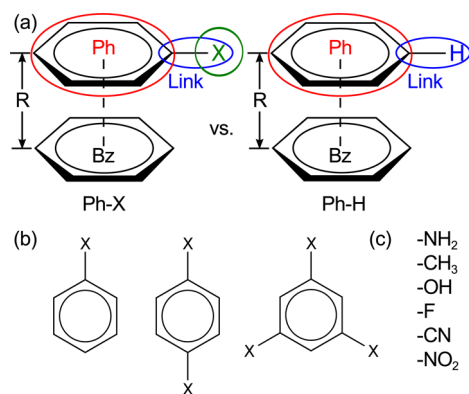
To this point, the evidence presented for these two hypotheses has been admirably thorough but ultimately circumstantial in

nature. The main evidence invoked for the HS picture is the correlation in several experiments<sup>5,10,11</sup> of the substituent effect with the Hammett  $\sigma_m$  constant (a loose quantification of the inductive adding- or withdrawing-power of a substituent vs hydrogen). However, high-level electronic structure computations definitively show that both electron-donating and electron-withdrawing substituents enhance the interaction energy for gas-phase cofacial benzene dimers.<sup>12,13</sup> Some more recent experiments also support this finding.<sup>14</sup> Additionally, symmetry-adapted perturbation theory<sup>15</sup> (SAPT) shows that significant contributions to the substituent effect are provided by enhanced dispersion interactions in substituted benzene dimers.<sup>13,16</sup> Another interesting consideration is additivity: theoretically<sup>9,17</sup> and, very recently, experimentally<sup>18</sup> it has been shown that substituent effects are almost wholly additive in benzene dimers with multiple substituents. This finding seems inconsistent with the HS model given the diminishing flexibility or polarizability expected of the  $\pi$  system as additional substituents are added. For the WH hypothesis, the primary evidence is the excellent and nearly one-to-one correlation between the substituent effect in Ph–X $\cdots$ Bz and the direct interaction energy in an analogous H–X $\cdots$ Bz model system that removes the  $\pi$  system of the substituted monomer completely.<sup>8,9</sup> However, it should be noted that this evidence, while compelling, is circumstantial: the H–X $\cdots$ Bz model has different physics than the true Ph–X $\cdots$ Bz system of interest. In particular, the invocation of the H–X $\cdots$ Bz model a priori precludes the HS contribution. In the real system, it is possible that the HS picture may play some role and that the WH contribution may be different than that observed in the H–X $\cdots$ Bz model system (due to the different electronic structure of the X functional group and linking  $\sigma$  bond in Ph–X vs H–X). Finally, it is noteworthy that the recent and thorough experimental study of Shimizu and co-workers<sup>18</sup> points strongly toward the direct interaction model of the WH picture but states in the conclusions that “due to the limitation in the number of substituents in our system and the measurement error, we cannot definitively exclude the indirect [substituent effect] model.” It is thus apparent that a theoretical tool with the capability to provide a robust and direct quantification of the substituent effects arising from these two pictures would provide a useful addition to this longstanding line of inquiry.

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In this study, we applied the newly developed functional-group SAPT (F-SAPT) analysis<sup>19</sup> to probe the origins of the substituent effect in situ (i.e., directly in the substituted benzene dimers, not in truncated model systems). F-SAPT begins from the formalism of SAPT, which provides an ab initio quantification of the electrostatics, exchange, induction/polarization, and dispersion contributions to the intermolecular interaction energy. F-SAPT asserts the picture that the constituent functional groups of weakly interacting monomers are composed of collections of protons and localized occupied electrons and then accumulates an effective two-body partition of the SAPT terms according to these groupings of particles. The result is a robust classification of the many-body SAPT interaction energy (and physical components) into effective interactions between pairs of functional groups. With F-SAPT, we can compute the SAPT interaction energy in Ph–X⋯Bz and obtain contributions from the Ph functional group, the X functional group, and the linking  $\sigma$  bond (Link). Likewise, we can compute the SAPT interaction energy in Ph–H⋯Bz and obtain contributions from the Ph functional group and the Link fragment (H is part of the Link fragment in this system, so the X functional group contains no particles in this system and its interaction energy contribution is zero). The difference in interaction energies between these two systems,  $\Delta E_{\text{int}} \equiv E_{\text{int}}(\text{Ph}-\text{X}) - E_{\text{int}}(\text{Ph}-\text{H})$ , is the substituent effect we seek, and it now can be partitioned into contributions from the Ph, X, and Link fragments, e.g.,  $\Delta E_{\text{int}}^{\text{Ph}} \equiv \Delta E_{\text{int}}^{\text{Ph}}(\text{Ph}-\text{X}) - \Delta E_{\text{int}}^{\text{Ph}}(\text{Ph}-\text{H})$ . The quantity  $\Delta E_{\text{int}}^{\text{Ph}}$  contains the difference in interaction energy due to the polarization of the Ph fragment by the substituent and is the indirect HS contribution to the substituent effect. The quantity  $\Delta E_{\text{int}}^{\text{X}}$  contains the direct interaction due to the substituent and is the direct WH contribution to the substituent effect. The quantity  $\Delta E_{\text{int}}^{\text{Link}}$  contains the difference in interaction energy due to the altered polarity of the linking  $\sigma$  bond and is the indirect WH contribution to the substituent effect. We refer to this process of partitioning a difference in interaction energies as “difference F-SAPT.” Figure 1 shows a schematic of this

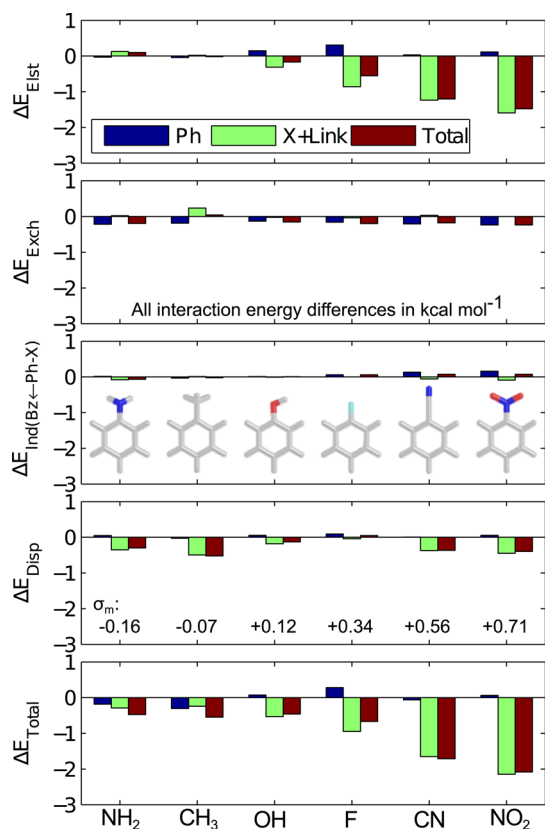


**Figure 1.** (a) Schematic of difference F-SAPT partitioning of Ph–X and Ph–H to provide Ph, Link, and X contributions. (b) Substituent placements used in this work. (c) Substituents used in this work, ordered by  $\sigma_m$  from most donating (top) to most withdrawing (bottom).

computational experiment. To simplify the analysis, in this study we did not permit any contribution to the substituent effect due to ring relaxation or intermolecular displacement: these effects are higher-order and not directly encapsulated within either the WH or HS picture.

For the computational methodology, we used F-SAPT0/jun-cc-pVDZ with density fitting accelerations in the PSI4 program,<sup>20</sup> as described in our previous papers.<sup>19,21</sup> The underlying SAPT0/jun-cc-pVDZ methodology has been found to be accurate relative to coupled-cluster complete-basis-set [CCSD(T)/CBS] benchmarks for interaction energies.<sup>22,23</sup> To provide the partition of the electrons into functional groups, we used the robust intrinsic bond orbital (IBO) localization methodology of Knizia.<sup>24</sup> To examine the origins of substituent effects across a broad range of withdrawing/donating substituents, we used substituted benzene dimers with –NH<sub>2</sub>, –CH<sub>3</sub>, –OH, –F, –CN, and –NO<sub>2</sub> substituents and studied singly, doubly, and triply substituted dimers, as shown in Figure 1. The Ph–X monomers were optimized at the DF-MP2/aug-cc-pVDZ level of theory, and the corresponding Ph–H monomers were obtained by removing X and placing a capping hydrogen at a distance of 1.094 Å along the linking C–X bond. The Ph–X⋯Bz and Ph–H⋯Bz dimers were obtained by aligning the rings of the monomers and then separating them by a distance R. For the results presented in the main text, a uniform R of 3.90 Å from the Bz⋯Bz DF-MP2/jun-cc-pVDZ equilibrium was used; additional results from the individual DF-MP2/jun-cc-pVDZ equilibrium separations of each substituted benzene dimer show the same quantitative trends. More details on the computational experiment, including explicit data, results for both choices of R, and sensitivity testing with the aug-cc-pVTZ basis set, are available in the Supporting Information (SI). The aug-cc-pVTZ analysis was performed only to validate that there was no significant contamination from basis set superposition error in the difference F-SAPT0/jun-cc-pVDZ analysis (e.g., due to the different atoms present in Ph–X vs Ph–H); F-SAPT0/jun-cc-pVDZ is expected to be much more accurate than F-SAPT0/aug-cc-pVTZ because of systematic error cancellation in the dispersion term<sup>22,23</sup> and was used for all chemical analysis in this work. Another point of interest is the possibility of multiple local minima in the IBO localization schemes on which all partitions rely. We investigated this and found that the partitions were all quite robust toward different localizations of the  $\pi$  orbitals of Ph–X (see section S6 in the SI).

The difference F-SAPT results for singly substituted monomers at R = 3.90 Å are shown in Figure 2. Here we will comment on only the singly substituted cases; the transferability to multiply substituted cases is discussed below. The first major finding from difference F-SAPT is that *both* the HS and WH pictures can contribute to the substituent effect, depending on the term and substituent. The second major finding is that the WH picture usually dominates the total. For electrostatics, the total contribution tracks well in sign and magnitude with  $\sigma_m$  but is dominated by WH contributions, suggesting that the local electrostatic environments of the X + Link groups govern this term. HS electrostatic contributions are present, but contrary to expectations, they are attractive for electron-donating substituents and repulsive for electron-withdrawing substituents, and the corresponding magnitudes do not track well with  $\sigma_m$ . This suggests that HS-type electrostatic contributions are not simple differential quadrupole–quadrupole interactions but are more likely related to differential charge penetration (as evidenced by the opposite sign vs that predicted by the quadrupole–quadrupole picture) and are quite susceptible to the exact polarization of the Ph unit by the substituent. For exchange, the total contribution is relatively constant across all of the substituents and is dominated by attractive HS contributions. Difference density analysis of the Ph unit (see the SI) indicates



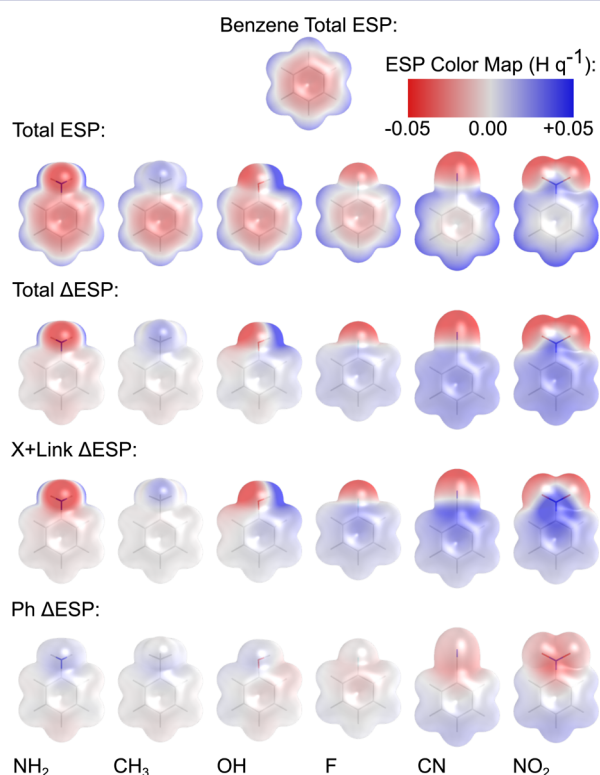
**Figure 2.** Difference F-SAPT analysis at the F-SAPT0/jun-cc-pVDZ level ( $R = 3.90 \text{ \AA}$  from the benzene dimer equilibrium) for singly substituted benzene dimers.  $\Delta E_{\text{ind}(\text{Ph} \leftarrow \text{Bz})}$  is negligible and therefore not shown.

that nonzero contraction of the  $\pi$  clouds occurs in some form for all of the substituents, leading to the attractive HS contributions seen here. However, the exact magnitude and topology of the Ph polarization varies markedly with the substituent considered, implying that the nearly constant magnitudes of the HS contributions to exchange are somewhat coincidental. The WH contributions to exchange are negligible, except for a repulsive contribution from  $-\text{CH}_3$  due to direct steric clash. For induction, only the Ph-X monomer polarizing the Bz monomer produces a non-negligible effect (for the other direction, the underlying  $E_{\text{ind}(\text{Bz} \leftarrow \text{Bz})}$  induction term is only on the order of  $0.1 \text{ kcal mol}^{-1}$  in magnitude to begin with and does not change much upon substitution). The strength and sign of this induction contribution varies with  $\sigma_m$  and is characterized by opposing HS and WH contributions. For dispersion, the total is generally attractive and uncorrelated with  $\sigma_m$ , and it is almost wholly dominated by the WH picture (i.e., direct dispersion between the substituent and the opposing benzene). Overall, electrostatics and then dispersion are the dominant terms, followed by much smaller contributions from exchange and induction. Since the WH contributions dominate the electrostatics and dispersion terms, the total substituent effect is usually governed by the WH picture. In fact, the only substituent for which the HS contribution is greater is  $-\text{CH}_3$ , for which the larger individual exchange and dispersion contributions from the WH picture nearly cancel.

Another consideration is transferability of the results to multiply substituted cases. The full difference F-SAPT0/jun-cc-pVDZ partitions for singly, doubly, and triply substituted cases

(Figures S2–S4 in the SI) demonstrate remarkable additivity of all nontrivial contributions, as shown succinctly in Figure S14. It is particularly interesting that *both* the WH and HS contributions are additive: this suggests that HS effects are possibly dominated by local polarizations of the phenyl density around added substituents (e.g., the accumulation of phenyl charge around the ring carbon to which the substituent is attached; see below) rather than large-scale changes of the phenyl density throughout the phenyl ring. In fact, the only term that shows noticeable nonadditivity is induction, which is expected for this nonlinear term.

Further insights are provided by plots of differences in the electrostatic potential (ESP) for substituted and unsubstituted benzene monomers, partitioned in the same manner as in F-SAPT. These results for Hartree-Fock/jun-cc-pVDZ methodology (corresponding to the treatment of electrostatics in SAPT0/jun-cc-pVDZ) are shown in Figure 3. As with the F-



**Figure 3.** Difference ESP analysis at the Hartree-Fock/jun-cc-pVDZ level for singly substituted benzene monomers. The ESP is mapped onto the isodensity surface of the substituted benzene monomer at  $0.002 \text{ electron bohr}^{-3}$ . For difference ESPs, red and blue indicate areas with enhanced and reduced nucleophilicity relative to benzene, respectively.

SAPT results, both WH and HS contributions occur, but the WH contributions usually dominate the change in the molecular ESP. The Ph contributions to the difference ESP track quite well in sign, strength, and magnitude with  $\sigma_m$  but are relatively weak overall. The X + Link contributions are much stronger and also quite localized, producing strong electric fields in the neighborhood of the substituent. Additional plots of partitioned differences in the density between substituted and unsubstituted benzene monomers are available in the SI. These show that the extra electrons of the substituent and the altered polarity of the linking  $\sigma$  bond are by far the dominant effects in the difference density, supporting the local interaction model. With



regard to the difference density of the Ph unit (much smaller than X + Link), a more complicated picture emerges than that predicted by  $\sigma_m$  alone. The principal effect for most of the substituents is a concentrated accumulation of density around the ring carbon involved the linking  $\sigma$  bond (especially in the  $\sigma$  network around this carbon), presumably to stabilize the withdrawal along the altered linking  $\sigma$  bond. This accumulation of density to cover the polarization of the linking  $\sigma$  bond is necessarily mirrored by a depletion of density elsewhere in the Ph system and usually comes from diffuse contributions from the  $\pi$  system, though there is a complicated and nonuniform nodal structure of the  $\pi$  difference density around the ring. The possible exception to these observations is the  $-\text{CH}_3$  substituent, which exhibits only very mild link-bond polarization and  $\pi$  withdrawal. With this exception identified, a very interesting picture emerges: essentially all of the substituents exhibit some contraction of the  $\pi$  system to cover the polarization of the linking  $\sigma$  bond. This supports the observation of always attractive HS contributions to the exchange terms above. The difference ESP for the Ph unit seems to track with the region of depletion in the ring (e.g., the  $\pi$  system above the linking carbon in  $\text{NH}_2$  or other carbons in the Ph unit for electron-withdrawing substituents), partially explaining both the trends in the Ph difference ESP and the complicated HS contributions to the electrostatics. The main conclusions from these analyses are (1) that the local changes caused by the addition of X and polarization of the linking  $\sigma$  bond dominate both the ESP and density differences and (2) that the minor Ph contributions to the difference ESP track well with the magnitude and sign of  $\sigma_m$  but the minor Ph contributions to the difference density do not (and are quite complicated overall), indicating that  $\sigma_m$  is not a good measure of  $\pi$ -electron donation or withdrawal caused by the substituent.

Overall, the difference F-SAPT, ESP, and density analyses indicate that the HS and WH pictures both contribute to the substituent effect in sandwich benzene dimers. The HS picture is usually dominant in the exchange term and also contributes to electrostatics and induction, but it is much more complicated than the simple picture of  $\pi$  donation or withdrawal usually advocated in discussing this picture. The WH picture dominates the larger electrostatics and dispersion terms and therefore is usually the dominant contributor to the total substituent effect. The only exception is if direct steric interactions from the WH term mask attractive WH contributions from electrostatics and/or dispersion, as occurs for  $-\text{CH}_3$ . Moreover, these conclusions transfer quite readily to doubly and triply substituted cases, indicating the additivity of both WH and HS effects as the number of substituents is increased. In any case, this in situ F-SAPT study of substituent effects clearly indicates the broad qualitative correctness of the WH model, albeit with the caveat that minor HS effects do occur.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

Molecular geometries; additional difference F-SAPT, ESP, and density analyses; and explicit data values. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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