

CHAPTER 1

Modern Computational Approaches to Understanding Interactions of Aromatics

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1.1 Introduction and Background

Two of the most common, and widely studied, interactions of aromatics are arene–arene and cation–arene interactions¹ and this chapter will focus on modern computational approaches aimed at understanding them. Two aromatic molecules generally interact to form one of the conformations shown in Figure 1.1(a): parallel face-to-face (**pff**), offset face-to-face (**osff**), edge-to-face (**etf**), or t-shaped (**tsh**).^{2,3} Of course, each one of these conformations has an infinite number of possible structures, largely dependent on the angle between the planes of the aromatic rings, and the degree to which the molecules are offset. Cation–arene interaction⁴ normally assume a conformation where the cation is over the π -density of the aromatic ring, as shown in Figure 1.1(b), and this has led to the interaction being termed cation– π . Depending on the nature of the aromatic, the cation may assume a position not directly

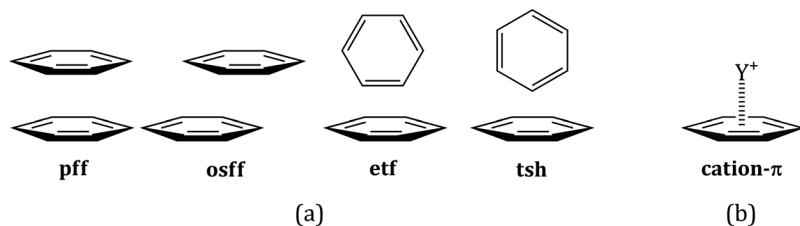


Figure 1.1 General conformations of: (a) arene–arene interactions; (b) cation–arene interactions.

above the center of the aromatic, and for certain polar aromatics the most stable cation–arene conformation has the cation binding to the negative end of the molecular dipole.⁵

A brief historical background on each of these interactions, largely focused on computational investigations, is given below, and this is followed by a review of current computational work aimed at understanding the nature of the interactions and predicting the strength of the interactions.

1.1.1 Arene–Arene Interactions

In the mid-1980s, Burley and Petsko reported one of the seminal studies showing that arene–arene interactions were distinct from typical hydrophobic interactions, showing that aromatic amino acid residues are predominantly found in the vicinity of other aromatic amino acid residues, and that the residues interact in an energetically favorable manner.⁶ Subsequently, non-covalent interactions of aromatics have been shown to play a significant role in a wide range of biologically and chemically relevant systems and processes. Face-to-face arene–arene interactions are important in nucleic acid structure^{1,7} and aromatic interactions are important in carbohydrate interactions^{8,9} the structure of helical peptides¹⁰ aromatic amino acid interactions,¹¹ DNA/RNA protein complexes¹² biological receptor interactions¹³ and peptide formation.¹⁴ In addition, due to the ubiquity of aromatics in biological systems, aromatic interactions are often a focus in drug development, and many pharmaceuticals contain an aromatic moiety.¹⁵ In terms of chemical systems, a few areas where aromatic interactions have been shown to be important include molecular recognition^{1,16} supramolecular complexes¹⁷ molecular self-assembly¹⁸ nanomaterials¹⁹ and organic catalysis.^{20,21}

Early computational investigations aimed at understanding arene–arene interactions focused on the aromatic quadrupole moment.²² Figure 1.2(a) presents a pictorial view of the quadrupole moments of benzene and hexafluorobenzene. Benzene has a negative quadrupole moment²³ and this can be viewed as the π -electron density region being more electron-rich than the hydrocarbon σ -framework region. Conversely, hexafluorobenzene has a positive quadrupole moment²³ and the hydrocarbon σ -framework region with the fluorine atoms is more electron-rich than the π -electron region. Hunter

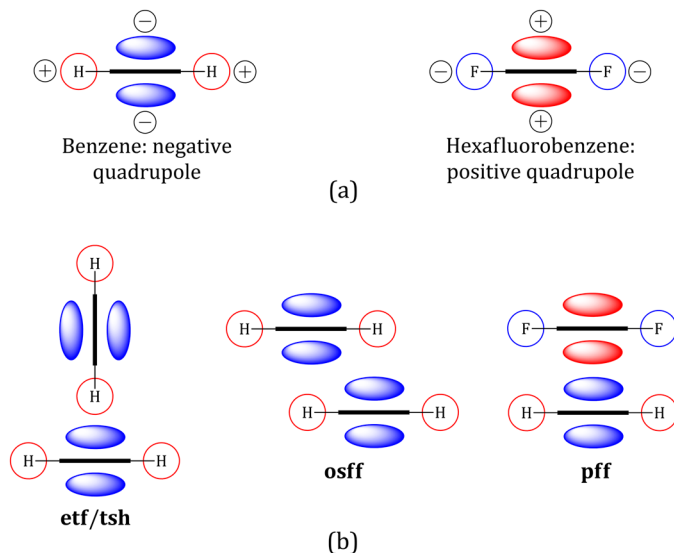


Figure 1.2 (a) The quadrupole moments of benzene (negative; $-8.7 \pm 0.5 \text{ D}\text{\AA}$) and hexafluorobenzene (positive; $+9.5 \pm 0.5 \text{ D}\text{\AA}$) are opposite in sign.²³ (b) The preferred **etf** and **osff** conformations of $\text{C}_6\text{H}_6\text{-C}_6\text{H}_6$ complexes, and the preferred **pff** conformations of $\text{C}_6\text{H}_6\text{-C}_6\text{F}_6$ complexes, can be explained *via* the aromatic quadrupole moments.

and Sanders discussed the nature of $\pi\text{-}\pi$ interactions through a charge distribution model² the results of which dictate that two aromatics with the same quadrupole moment, such as benzene, would interact most favorably either by adopting an **etf** or **tsh** conformation or by having the negative ends of their quadrupole moments get out of each other's way *via* an **osff** conformation (Figure 1.2(b)). Conversely, aromatics that have quadrupole moments opposite in sign, such as benzene and hexafluorobenzene, would be expected to prefer the **pff** conformation (Figure 1.2(b)), and this was demonstrated in the solid state²⁴ and *via* computations.²⁵

1.1.2 Cation–Arene Interactions

Kebarle and coworkers first reported the importance of the cation–arene interaction when they showed that the $\text{K}^+\text{-benzene}$ dimer had slightly more binding ΔH and ΔG° values than the $\text{K}^+\text{-water}$ dimer in the gas phase.²⁶ The result was quite surprising at the time, as it suggests a cation would prefer to bind to a nonpolar molecule, benzene, rather than the highly polar water molecule. Kebarle and coworkers suggested the cation– π conformation shown in Figure 1.1(b) to explain why the cation would be attracted to an aromatic ring. Subsequently, cation– π interactions have been shown to be important in a wide range of chemistry and biology¹ with significant early work being performed by the Dougherty group.²⁷

Similar to their work on the importance of arene–arene interactions in protein structures, Burley and Petsko also showed that amino acid residues with cationic side chains are preferentially found in the vicinity of aromatic amino acids.²⁸ In addition to being important in protein stability, notable areas where cation– π interactions have been shown to be important in biology include enzyme/protein-substrate recognition^{29,30} and ion-transport processes.³¹ In chemistry, cation– π interactions have been reported to play a role in organic reaction development³² and in nanomaterials.¹⁹

As was the case for arene–arene interactions, early computational work aimed at understanding cation– π interactions focused on the aromatic quadrupole moment.³³ In general, cation–arene interactions were generally investigated for electron-rich aromatics, which have negative quadrupole moments (*i.e.*, benzene²³), and the interaction can be described as a positive charge being attracted to the negative region of the arene quadrupole. Figure 1.3 shows this for Na^+ -benzene. Related to understanding the cation– π interaction *via* the aromatic quadrupole moment, early computational studies also aimed to understand the interactions *via* the aromatic electrostatic potential, as reported by Dougherty and coworkers.^{27,34}

1.1.3 Beyond the Aromatic Quadrupole Moment

The aromatic quadrupole moment proved useful as a model for predicting some aspects of the interactions of aromatics. As discussed above, it can be used to understand the preferred conformations for benzene–benzene and benzene–hexafluorobenzene dimers. In addition, it provides a good approach for understanding the cation–arene interactions of electron-rich aromatics such as benzene. However, the quadrupole moment describes the aromatic electron density distribution, and using it to describe arene–arene and cation–arene interactions suggests they can be understood in purely electronic/electrostatic terms. Recent computational approaches to understanding interactions of aromatics have highlighted the importance of aromatic polarizability, the importance of forces other than electrostatics such as induction, dispersion, and exchange, as well as substituent–substituent and ion–substituent effects. The findings of these modern computational approaches are discussed below, both in terms of understanding the interactions and in terms of predicting the relative strength of the interactions.

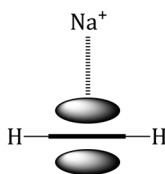


Figure 1.3 Prototypical cation– π complex of an aromatic: Na^+ - C_6H_6 . The attraction can be understood as the cation binding to the negative region of the aromatic quadrupole moment.

1.2 Computational Approaches to Understanding Arene–Arene Interactions

1.2.1 The Nature of Arene–Arene Interactions

Following the early computational work of Hunter and Sanders focusing on the importance of the aromatic quadrupole moment in arene–arene interactions² many small-molecule models were experimentally investigated to determine the forces important in arene–arene interactions^{35–39}. The small-molecule models generally focused on the interactions between substituted benzenes, and one such example is the 1,8-diarylnaphthalenes investigated by Cozzi and Siegel (Figure 1.4).^{38,39} A common theme among this body of work is the reported relationship between the experimentally determined arene–arene binding energies and Hammett substituent constants, and the interpretation that this correlation suggested the interactions were due to polar/ π electronic effects.

At the same time as experimental work showing correlations between arene–arene binding energies and Hammett constants continued to be reported¹ some experimental results began to appear suggesting forces other than electronic/electrostatic effects were important in understanding the nature of arene–arene interactions. Gung and coworkers showed that when one aromatic was electron-rich and the other aromatic was electron-poor (*i.e.*, hexafluorobenzene), the experimentally measured arene–arene binding energies did not correlate with the Hammett constants, and they suggested charge-transfer effects may be important in such arene–arene interactions.⁴⁰ In addition to these results, the early 2000s saw the beginning of a wealth of computational results showing there was no general relationship between arene–arene binding energies and Hammett constants, and suggesting that forces other than electronic/electrostatic effects were important in understanding the nature of these interactions. Primary among these studies was the work of Sherrill and coworkers employing the energy decomposition method symmetry adapted perturbation theory (SAPT). The SAPT method^{41,42}

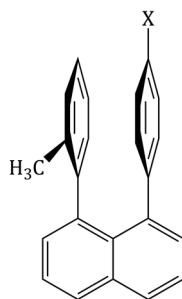


Figure 1.4 The 1,8-diarylnaphthalenes system is an example of a small-molecule model used to experimentally investigate arene–arene binding energies.^{38,39}

allows for the overall non-covalent binding energy E_{bind} to be broken down to the energies due to electrostatics (E_{ele}), induction (E_{ind}), dispersion (E_{disp}), and exchange (E_{exch}). Using the SAPT method to investigate mono-substituted benzene–benzene dimers, Sherrill’s research group showed the energy due to dispersion (E_{disp}) is a greater contributor to the overall E_{bind} value than E_{ele} for both **pff** and **etf** conformations.⁴³ This result was also reported by Tsuzuki and coworker⁴⁴ using a different computational approach to determine E_{ele} , E_{ind} , and E_{disp} ; they calculated E_{ele} and E_{ind} using the program ORIENT,⁴⁵ while E_{disp} was approximated as the energy contribution from electron correlation (E_{corr}) on E_{bind} . Tsuzuki and coworkers determined the E_{corr} value as the difference between the interaction energies calculated with electron-correlated levels and at the HF levels.⁴⁴ The Tsuzuki group computationally investigated arene–arene interactions in **pff**, and various **etf**, **tsh**, and **osff** conformations when two electron-rich aromatics were interacting (toluene–toluene, toluene–benzene)⁴⁶ when two electron-poor aromatics were interacting (nitrobenzene–nitrobenzene)⁴⁷ and when an electron-rich and electron-poor aromatic were interacting (nitrobenzene–benzene⁴⁷ and hexafluorobenzene–benzene⁴⁸), and in all cases they found E_{disp} was the greatest contributor to E_{bind} . Kim and coworkers studied **tsh** mono-substituted benzene–benzene dimers where the substituted benzene could be either the vertical (Figure 1.5(a)) or horizontal (Figure 1.5(b)) aromatic in the dimer conformation.⁴⁹ Using SAPT calculations they showed that E_{disp} was the greatest contributor to E_{bind} regardless of the substituent or conformation. The examples from the Sherrill, Tsuzuki, and Kim research groups capture the beginning of using energy decomposition methods in computational chemistry to understand interactions of aromatics broadly, and arene–arene interactions in particular. The work provided the important insight that the energy due to electrostatics (E_{ele}) is not the major contributor to arene–arene binding energies (E_{bind}), and the use of energy decomposition methods continues to be important in modern computational approaches to understanding arene–arene interactions.

The fact that SAPT calculations showed E_{disp} to be the major contributor to E_{bind} values for arene–arene interactions suggested that Hammett constants

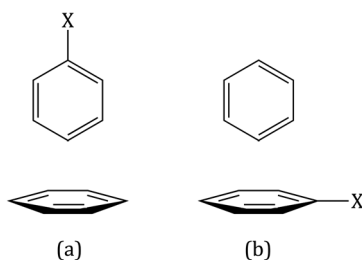


Figure 1.5 Arene–arene dimers between a substituted benzene and benzene, and in the t-shaped (**tsh**) conformation, can adopt two general conformations: (a) the substituted aromatic vertical; (b) the substituted aromatic horizontal.

should not correlate to arene–arene binding energies, as was reported in most of the experimental work. Consistent with the emerging view from computational work that E_{disp} was important to understanding arene–arene interactions, Sherrill and coworkers showed that adding any substituent to one of the aromatics in a **pff** benzene–benzene dimer, regardless of whether the substituent is electron-withdrawing or electron-donating, led to the dimer having a stronger binding energy.^{43,50} A natural outcome of this result is that E_{bind} values for substituted benzene–benzene dimers cannot correlate with Hammett substituent constants, and Sherrill and coworkers explicitly demonstrated this by computationally investigating **pff** substituted benzene–benzene dimers with an approximately equal number of electron-withdrawing (positive Hammett value) or electron-donating (negative Hammett value) groups.⁵¹ The resulting graph of E_{bind} versus $\Sigma\sigma_{\text{m}}$ (multi-substituted benzenes were investigated, and thus $\Sigma\sigma_{\text{m}}$ was used) yielded a parabola; there was no linear correlation. Work by the Sherrill group⁴³ and Kim group⁴⁹ showed the same trend is not apparent for **tsh** substituted benzene–benzene dimers, and adding a substituent may make such a complex more or less binding than the parent **tsh** benzene–benzene dimer, depending on the conformation.

Further investigating **pff** substituted benzene–benzene dimers using SAPT calculations, Lewis and coworkers reported that adding any substituent to the substituted aromatic results in a more binding E_{ele} value.⁵² This surprising result was explained by the Sherrill group as being the result of charge penetration.⁵³ The equilibrium distances for most arene–arene dimers, approximately 3.5–4.0 Å, brings the two aromatic monomers close enough such that the electron density of one aromatic monomer electrostatically interacts with the nuclei of the other aromatic monomer, and this is termed charge penetration. Replacing a hydrogen atom with any substituent results in a more electropositive nuclei, and increased electron density, thus increasing the electrostatic attraction due to charge penetration.

Just prior to the reports from the Sherrill and Lewis groups, Houk and Wheeler reported that the difference in substituted benzene–benzene **pff** dimer binding energies was due to the substituent of the substituted benzene interacting with the adjacent benzene ring, and not due to the substituent tuning the electrostatics of the substituted benzene.⁵⁴ Houk and Wheeler computationally demonstrated this important finding by comparing $\text{C}_6\text{H}_5\text{X}-\text{C}_6\text{H}_6$ E_{bind} values to the E_{bind} values of $\text{HX}-\text{C}_6\text{H}_6$ dimers where the X group in HX and the $\text{C}_6\text{H}_5\text{X}$ mono-substituted benzene are the same (Figure 1.6). This comparison showed that the difference in E_{bind} values between the $\text{C}_6\text{H}_5\text{X}-\text{C}_6\text{H}_6$ dimers for various substituted benzenes ($\text{C}_6\text{H}_5\text{X}$) was the same as the E_{bind} differences for $\text{HX}-\text{C}_6\text{H}_6$ dimers with various HX. This supports the notion that the strength of substituted benzene–benzene interactions is dictated by the interaction between the substituent and the adjacent (unsubstituted) benzene ring.⁵⁴ This finding aligns very well with the role of charge penetration in arene–arene interactions.⁵³ Houk and Wheeler expanded their work to **etf** dimers, computationally demonstrating the importance of substituents interacting directly with the adjacent ring in understanding the nature of the interactions.³

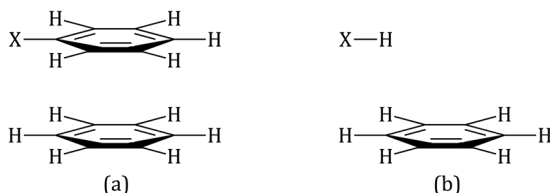


Figure 1.6 The E_{bind} values for $\text{C}_6\text{H}_5\text{X}-\text{C}_6\text{H}_6$ pff dimers (a) can be approximated very well as the E_{bind} values for $\text{HX}-\text{C}_6\text{H}_6$ complexes (b) where the X substituents in $\text{C}_6\text{H}_5\text{X}$ and HX are the same. This supports the notion that the strength of substituted benzene–benzene interactions are dictated by the interaction between the substituent and the adjacent benzene ring.⁵⁴

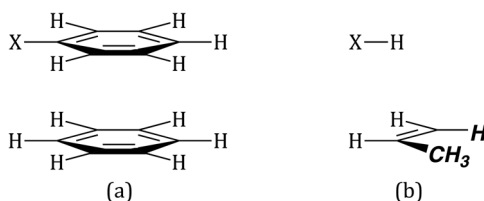


Figure 1.7 The E_{bind} values for $\text{C}_6\text{H}_5\text{X}-\text{C}_6\text{H}_6$ pff dimers (a) can be approximated very well as the E_{bind} values for $\text{HX}-\text{C}_3\text{H}_6$ complexes (b) where the X substituents in $\text{C}_6\text{H}_5\text{X}$ and HX are the same. This supports the hypothesis that arene–arene interactions are best understood as local, through-space, interactions between proximal regions of the adjacent aromatics.⁵⁵

Further computational work by Wheeler showed that arene–arene interactions can be understood *via* direct local interaction between the substituent and the region of the adjacent aromatic closest to the substituent (Figure 1.7).^{55,56} For instance, the E_{bind} values for $\text{C}_6\text{H}_5\text{X}-\text{C}_6\text{H}_6$ interactions correlated very well with the E_{bind} values for $\text{HX}-\text{C}_3\text{H}_6$ dimers⁵⁵ supporting the idea that arene–arene interactions are best understood as local, through-space, interactions between proximal regions of the adjacent aromatics. Wheeler has also looked at the interactions of substituted benzenes with aromatics other than benzene, such as borazine and 1,3,5-triazine, and computationally demonstrated more generally that arene–arene interactions are best understood as through-space interactions between the substituents of the substituted benzene with the proximal region of the neighboring aromatic, be it benzene, borazine or 1,3,5-triazine.⁵⁷

The recent advances in understanding arene–arene interactions underscore the notion that the term “ π -stacking” has become outdated, and Martinez and Iverson highlighted this point a few years ago in an important perspective.⁵⁸ In this work they point out the emerging importance of considering direct interactions between substituents on the interacting rings in understanding arene–arene complexes. In the four years since they published their perspective, work by the Sherrill group and by Houk and

Wheeler, among others, has cemented the idea that understanding arene–arene interactions should not be approached from the lens of π – π stacking. Rather, while arene–arene interactions were initially understood in terms of the aromatic quadrupole moment, according to the Hunter–Sanders model,² modern computational approaches have shown the nature of these interactions are best understood *via* the substituents on one aromatic monomer interacting, through-space, with the proximal region of the adjacent aromatic monomer.⁵⁶ Furthermore, the attractive nature of arene–arene dimers can be understood as arising from charge penetration.⁵³

1.2.2 Predicting the Strength of Arene–Arene Interactions

As described in various places throughout Section 1.2.1, a common theme in computational work aimed at understanding the nature of arene–arene interactions is correlating the E_{bind} values with physicochemical parameters, the most common being Hammett substituent constants.⁵⁹ While early experimental work showed that Hammett values, usually σ_{p} ^{38,39} correlated well with the E_{bind} values, computational work showed the correlations deteriorated when electron-donating substituents (with negative Hammett values) were included in the analysis.⁵¹ Recent computational work by the Sherrill and Wheeler groups, respectively noting the importance of charge penetration in arene–arene interactions, and how the proximally close regions of the aromatics in an arene–arene dimer interact in a local, through-space manner, demonstrates the complexity of the interactions and suggests the E_{bind} values should not correlate with an electronic parameter such as the Hammett substituent constant. Not surprisingly, Sherrill and coworkers found the best approach to correlating the E_{bind} values for **tsh** benzene-substituted benzene dimers was with a multi-variable equation.⁶⁰ The parameters included in the equation were the Hammett σ_{m} , the molecular polarizability, and a term accounting for the interaction between the substituents on one arene and the H-atoms on the adjacent aromatic.⁶⁰ Lewis and coworkers performed SAPT calculations on a large set of substituted benzene–benzene dimers in the **pff** conformation, and they found that most of the variability in E_{bind} was due to variability in the energy due to electrostatics; the E_{ele} term.⁵² The sum of the non-electrostatic terms ($E_{\text{ind}} + E_{\text{disp}} + E_{\text{exch}}$) was approximately constant regardless of the substitution pattern of the substituted aromatic. Still, the E_{bind} values did not correlate very well with the Hammett constants, and they too employed a multi-variable equation to best correlate the E_{bind} values; the terms in the equation were the Hammett constant σ_{m} and the molecular polarizability parameter M_{r} .⁵²

It is worth noting that modern approaches to predicting the strength of arene–arene interactions are in line with Iverson’s suggestion⁵⁸ that the terms “ π -stacking” and “ π – π interactions” do not convey the important forces at play in arene–arene binding. Both the Sherrill group⁶⁰ and Lewis group⁵² have shown the need for multi-parameter equations to accurately predict the strength of arene–arene interactions involving substituted benzenes, and the

Sherrill group explicitly uses a parameter that accounts for the interaction between the substituents on one arene and the H-atoms on the adjacent aromatic.⁶⁰ That the strength of arene–arene interactions involving substituted benzenes cannot simply be predicted *via* Hammett constants strongly suggests that the terms “ π -stacking” and “ π - π interactions” are, as Iverson suggests, outdated.⁵⁸

1.3 Computational Approaches to Understanding Cation–Arene Interactions

1.3.1 The Nature of Cation–Arene Interactions

As noted in the Introduction, Section 1.1.2, early work on understanding cation– π interactions of aromatics centered around the aromatic quadrupole moment³³ and the aromatic electrostatic potential (ESP).^{33,34} Dougherty and coworkers showed that the total cation-binding energy, E_{bind} , of a cation and negative quadrupole moment (Θ_{zz}) substituted aromatics correlates very well with the ESP of the substituted aromatic.³⁴ At about the beginning of the 2000s work by Cubero and coworkers⁶¹ and Tsuzuki and coworkers⁶² was disseminated showing the importance of π -electron polarizability in cation– π interactions. In both cases the groups demonstrated that cations induce polarization in the aromatic compound (Figure 1.8), and this induction contributes to the overall cation– π E_{bind} .

Shortly after the work illustrating the importance of π -electron polarizability in cation– π interactions, computational results were reported showing that positive Θ_{zz} aromatics bind cations⁶³ however, this was initially described as an anomaly due to the investigated aromatics having small positive Θ_{zz} values. Not long after, Lewis and Clements demonstrated that substituted aromatics with non-negligible positive Θ_{zz} values did bind cations.⁶⁴ This suggests that even though electrostatics is an important factor when describing the nature of cation– π interactions, other factors may also play important roles in the binding. The work of Cubero⁶¹ and Tsuzuki⁶² suggesting the importance of π -electron density polarizability in cation– π interactions of aromatics was offered as an explanation for why positive Θ_{zz} aromatics bind cations.

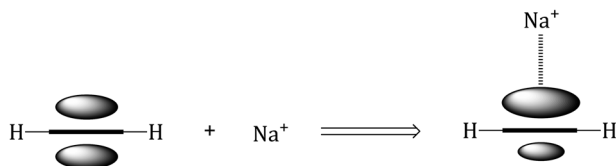


Figure 1.8 Work by Cubero and coworkers⁶¹ and Tsuzuki and coworkers⁶² suggested cations induce polarization in the aromatic compound, and this induction leads to an increase in the cation– π E_{bind} .

The results reported by Lewis and Clements suggested cation- π interactions may, at least partially, be guided by direct interactions between the cation and the aromatic ring substituents,⁶⁴ and this idea has been expanded by Wheeler and Houk. In a similar fashion to their work demonstrating the importance of through-space interactions on arene-arene complexes (Figures 1.6 and 1.7), Wheeler and Houk showed that the E_{bind} value for a cation interacting with a substituted aromatic was reasonably approximated by adding the E_{bind} values for a cation interacting with benzene and the E_{bind} value of the cation interacting with the appropriate H-X.⁶⁵ They also included the E_{bind} value for the cation interacting with the H atoms of the substituted benzene, and an equation illustrating the relationship is shown in Figure 1.9.⁶⁵ This strongly suggests the E_{bind} values for cation- π interactions of substituted aromatics are dictated by through-space interactions between the cation and aromatic substituents, rather than being dictated by the substituents tuning the π -density of the aromatic ring. Suresh and Sayyed, taking a somewhat similar approach to Wheeler and Houk, looked at how cations interacted with different fragments of substituted aromatics and found that through-space cation-substituent interactions were most important for electron-withdrawing substituents.⁶⁶

Recent computational work by Quinonero and coworkers suggests that cation- π interactions of aromatics are not entirely due to through-space interactions between the cation and the aromatic substituents.⁶⁷ Using the calculated quadrupole moment to approximate the energy due to electrostatics and the calculated dipole polarizabilities to approximate the energy due to polarizability, Quinonero and coworkers found the cation- π binding energies of 104 substituted benzenes and 67 heteroaromatics were best described by a combination of the electrostatic and polarizability parameters.⁶⁷ The dependence of the overall cation- π non-covalent binding energy on the aromatic dipole polarizabilities was interpreted by the authors as supporting the notion that π -electron cloud polarizability was important in cation- π binding energies, and the interactions weren't completely dictated by through-space interactions between the cation and the aromatic substituents. The authors concede that the polarizability term may reflect the polarizability

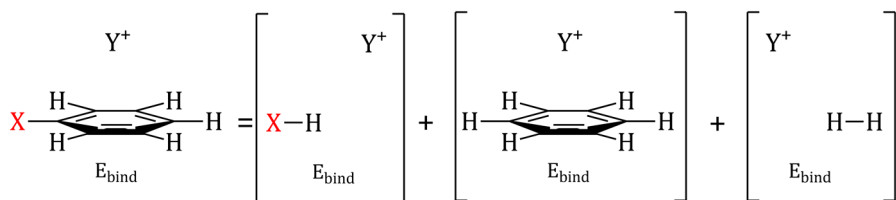


Figure 1.9 The E_{bind} value for a cation interacting with a substituted aromatic ($\text{C}_6\text{H}_5\text{X}$) can be reasonably approximated by adding the E_{bind} value for a cation interacting with benzene, the E_{bind} value of the cation interacting with the appropriate H-X, and the E_{bind} value for the cation interacting with the H atoms of the substituted benzene.⁶⁵

of the substituent in a through-space interaction; however, they show that the polarizability of the C atom at the *para* position of the mono-substituted benzenes correlates very well with the Hammett constant, σ_p , of the substituent, but not σ_m . Quinonero and coworkers suggest this supports the notion that the substituents are directly involved in the polarization of the aromatic ring, and that π -cloud polarizability and through-space interactions are both important in the cation– π interactions of aromatics.⁶⁷

Recent work by Lewis and coworkers⁶⁸ and by Sastry and coworkers⁶⁹ applied energy decomposition methods to understand the cation– π binding of aromatics. Lewis and coworkers employed the SAPT approach with the CCSD/6-311++G** method and basis set to investigate the cation– π binding of substituted benzenes⁶⁸ and Sastry and coworkers employed both the reduced variational space (RVS) and the DFT-SAPT approaches to investigate the energy decomposition of cation– π complexes involving benzene, phenol, and a variety of heteroaromatics.⁶⁹ As noted above in the arene–arene section, the SAPT calculations allow for the total non-covalent binding energy to be decomposed into E_{ele} , E_{disp} , E_{ind} , and E_{exch} , and the results reported by Lewis and coworkers show that E_{ele} is the largest contributor to the overall cation– π binding of substituted benzenes. Furthermore, among the component energy terms, E_{ele} is most sensitive to the distance between the cation and aromatic ring.⁶⁸ The RVS method decomposes the overall non-covalent binding energy into E_{ele} , E_{exch} , E_{pol} , and E_{CT} , where E_{ele} and E_{exch} are the same as for the SAPT method, E_{pol} is the energy due to polarization, and E_{CT} is the energy due to charge transfer. The DFT-SAPT method decomposes the overall non-covalent binding energy into E_{ele} , E_{disp} , E_{ind} , and E_{exch} , $E_{\text{exch-disp}}$, $E_{\text{exch-ind}}$ and $\delta(\text{HF})$, and this allows the polarization component of the overall binding energy to be determined *via* the equation $E_{\text{pol}}(\text{DFT-SAPT}) = E_{\text{ind}} + E_{\text{exch-ind}} + \delta(\text{HF})$. Using the RVS and DFT-SAPT energy decomposition methods, Sastry and coworkers showed the major contributors to the cation– π binding energy of benzene, phenol, and various heteroaromatics were the E_{ele} and E_{pol} terms.⁶⁹ It is worth noting that neither the energy decomposition work by Lewis and coworkers, nor the work by Sastry and coworkers, directly addresses the issue of whether cation–arene interactions are dictated by the cation interacting with the π -electron density, the substituent, or both. Cation–substituent and cation– π interactions can both be explained as owing their attraction to electrostatics and/or electron density polarization.

The medium in which cation–arene interactions are studied can have a significant effect on the strength of the interaction, and this has been widely disseminated experimentally.^{27,70} Using the SM5.42R/HF/6-31+G* level of theory, Dougherty and Gallivan computationally showed that increasing solvent polarity led to a decrease in the cation– π E_{bind} value.⁷¹ However, the decrease was found to be minimal compared to the calculated decrease in binding energy for salt bridges across solvents with different polarities. Sherrill and coworkers reported similar findings for cation– π interactions of benzene where the cation is Li^+ , Na^+ , K^+ , or NH_4^+ using the polarizable continuum model (PCM) computational approach; increasing solvent polarity decreases

the strength of the cation- π interaction.⁷² Recently, Bania and coworkers showed that the same solvent polarity trends hold for substituted aromatics partaking in cation- π interactions with Li^+ , Na^+ , or K^+ using the PCM approach to model the solvents.⁷³ The issue of specific solvation of water molecules was computationally addressed by Sastry and coworkers and they reported that solvation of the cation in cation- π complexes decreases the overall E_{bind} , while solvation of the aromatic enhances the binding strength.⁷⁴

While most studies of cation- π complexes of substituted aromatics have focused on the half-sandwich motif (Figure 1.1(b)), it is estimated that sandwich complexes (Figure 1.10), with alkali or alkaline earth metal cations, are at least as abundant in biology.¹ For instance, many of the studies that describe the importance of cation- π binding in protein folding, structure and function are in fact sandwich complexes.^{75,76} Modern computational work has aimed to address the issue of the additivity of the E_{bind} values for the cation- π sandwich complexes ($E_{\text{bind,S}}$). The issue involves whether $E_{\text{bind,S}}$ is additive, and is equal to the sum of the binding energies of the two corresponding half-sandwich complexes ($E_{\text{bind,HS}}$), or whether $E_{\text{bind,S}}$ is non-additive, and $E_{\text{bind,S}} < 2 \times E_{\text{bind,HS}}$. Initial work on this issue by Jiang and coworkers suggested $E_{\text{bind,S}}$ was additive and $E_{\text{bind,S}} = 2 \times E_{\text{bind,HS}}$.⁷⁷ More recent calculations by Orabi and Lamoureux on the topic showed the binding energy of cation- π sandwich complexes was non-additive, and $E_{\text{bind,S}} < 2 \times E_{\text{bind,HS}}$.⁷⁸ Subsequent computational efforts by the Lewis group showed that a triple- ζ basis set was required to observe the non-additivity of cation- π sandwich complexes.⁷⁹ The Lewis group also showed that non-additivity was increased when less polarizable ions were included in the sandwich complex (for instance, when Li^+ is the ion rather than Na^+ or K^+).⁷⁹

1.3.2 Predicting the Strength of Cation-Arene Interactions

Early work on predicting the binding strength of cation- π complexes of substituted aromatics focused on the electrostatic potential and Hammett substituent constants.⁵⁹ Dougherty and coworkers showed a correlation between the calculated electrostatic potential of 11 aromatics and the Na^+ binding energy.³⁴ These 11 aromatics included benzene, naphthalene, pyridine, and eight substituted benzenes. This early work by Dougherty and coworkers

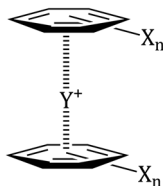


Figure 1.10 General structure of cation- π sandwich complexes for two substituted benzenes, where Y is any monovalent cation, X is any substituent, and $n = 1-6$.

also suggested a correlation between the calculated Na^+ -substituted benzene cation– π binding energies and the Hammett substituent constant σ_m .³⁴ Subsequent work by Jiang and coworkers investigated the cation– π binding of Li^+ , Na^+ , K^+ , Be^{2+} , Mg^{2+} , and Ca^{2+} with aniline, toluene, phenol, benzene, fluorobenzene, 1,4-difluorobenzene, and 1,3,5-trifluorobenzene, and an excellent correlation was reported between the binding enthalpies and σ_{Total} , which the authors define as $\sigma_{\text{Total}} = (\Sigma\sigma_m + \Sigma\sigma_p)$.⁸⁰ This is the only example of using the σ_{Total} parameter to predict the relative cation– π binding of substituted benzenes, and Jiang and coworkers suggest it means both resonance and induction are important in cation– π binding.⁸⁰ More recently, Suresh and Sayyed showed that cation– π interaction energies correlated very well with the term ΔV_{min} , which is the difference between the calculated molecular electrostatic potential on the aromatic π -region for a substituted arene and the corresponding unsubstituted analog.⁸¹ Suresh and Sayyed investigated multiple aromatic frameworks, cations, and substituents, and they found that the calculated ΔV_{min} performed very well in predicting the relative cation–arene binding energy.

Recent work by Quinonero—in response to the Houk and Wheeler work—suggesting that cation–arene interactions of substituted benzenes may be dictated by both cation– π interactions and cation–substituent interactions showed that a two-parameter equation involving a linear combination of the electrostatic energy and the polarization energy correlated very well with the cation– π binding energies of substituted aromatics.⁶⁷ As noted above, for the Quinonero and coworkers' study, the energy due to electrostatics was approximated using the calculated aromatic quadrupole moment, and the energy due to polarization was approximated *via* the calculated aromatic dipole polarizabilities. Another recent study noted above, by Lewis and coworkers investigating the energy decomposition energies of cation– π interactions of aromatics, showed a poor correlation between the binding energies/enthalpies and the $\Sigma(\sigma_m + \sigma_p)$, $\Sigma\sigma_p$, $\Sigma\sigma_m$, and Θ_{zz} values for a large number of substituted benzenes.⁶⁸ As a result, the researchers developed a cation– π binding constant, Π^+ , from the cation-binding enthalpies of the mono-substituted aromatics. Specifically, the substituent constant was derived from the equation $\Pi^+ = -\log[(\Delta H_{298}(\text{Na}^+ - \text{C}_6\text{H}_5\text{X})) / (\Delta H_{298}(\text{Na}^+ - \text{C}_6\text{H}_6))]$, and the correlation with the cation– π binding energies of the larger group of substituted aromatics, mono-substituted and multi-substituted, was excellent.

1.4 Summary

Initial computational work on arene–arene and cation–arene non-covalent interactions focused on the aromatic quadrupole moments. Over time, Hammett substituent constants and aromatic electrostatic potentials were commonly employed to understand and describe arene–arene and cation–arene interactions. Modern computational efforts have focused on the importance of substituent–substituent interactions in the binding of arene–arene complexes, and cation–substituent interactions in the binding of cation–arene

complexes. In addition, energy decomposition methods, such as SAPT, are becoming more widely employed to better understand the non-covalent interactions of aromatics. Future work will surely see energy decomposition methods applied to larger aromatic systems. Furthermore, the importance of π - π versus substituent-substituent interactions in understanding the nature of the attraction in arene-arene complexes, and the importance of cation- π versus cation-substituent interactions in understanding the nature of the attraction in cation-arene complexes, will certainly be investigated with larger, polyaromatic, systems. The concluding chapter of this book describes new directions in organic materials chemistry that are spawning this interest in larger, polyaromatic systems.

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