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Squaramide Structure and Interactions with Benzene

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Abstract: The chemical industry's continued reliance on expensive and toxic metal catalysts has driven the search for greener and more sustainable alternatives. One such option is hydrogen bonding organocatalysts, a group of inexpensive compounds made from renewable feedstocks. However, the interactions of these compounds with aryl groups is not currently understood, limiting their overall effectiveness. Dual hydrogen bond donors such as squaramide and thiourea have been a focus of study for some time, but the structure and interactions of unsubstituted squaramide have not been thoroughly reported and present an unknown in catalyst design. This study seeks to understand the structure of squaramide and how it interacts with aryl systems, specifically benzene. We used the Truhlar M06-2X functional with Dunning's aug-cc-pV[D, T]Z basis sets and MP2 with Dunning's aug-cc-pV[D,T]Z basis sets for geometry optimization and energy evaluation. Additionally, we employed the Boys and Bernardi counterpoise method to account for basis set superposition error (BSSE) to compare to the uncorrected values. From these calculations, it was apparent that squaramide possesses multiple available geometries that may be interchangeable with a considerable impact of BSSE. Additionally, there are several ways that squaramide can interact with benzene, and these interactions have been compared to the better studied benzene dimer, comparing both with their BSSE corrected structures and energies. This work provides valuable insight into how squaramide-based catalysts may interact with aryl groups, how squaramide's structure changes based on those interactions, and the potential effects of BSSE on both.

Introduction

Catalysis has become an increasingly important field as chemical industry has grown throughout history.[1] Many common catalytic processes use metal catalysts, which are often expensive due to their scarcity.[2] Palladium is estimated to have less unmined reserves than gold, and it currently costs over $200 more per gram than gold.[3-4] Palladium and other transition metals are also frequently toxic, risking drug contamination or bioaccumulation in organisms that can be fatal.[5] The principles of Green Chemistry as outlined by Anastas and Warner have driven the search for less harmful and less wasteful alternatives (Figure 1).[6]

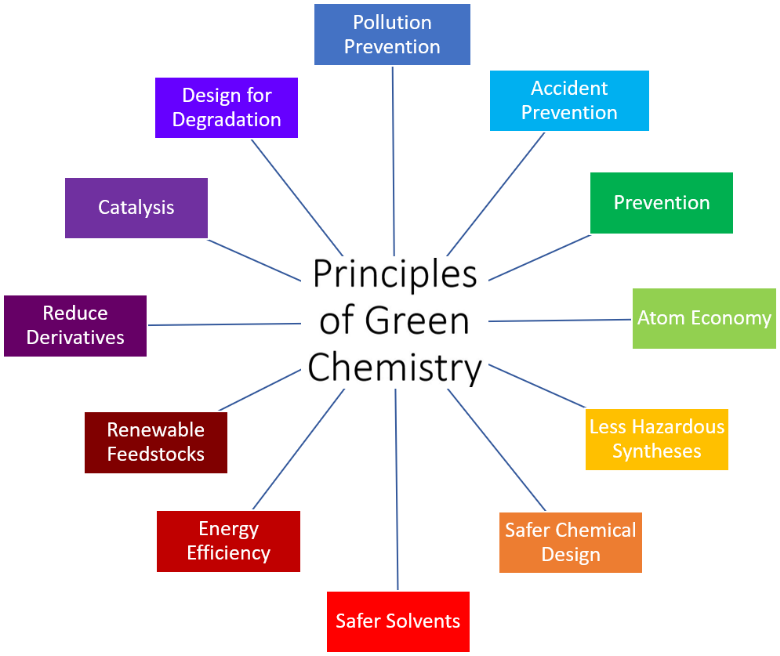
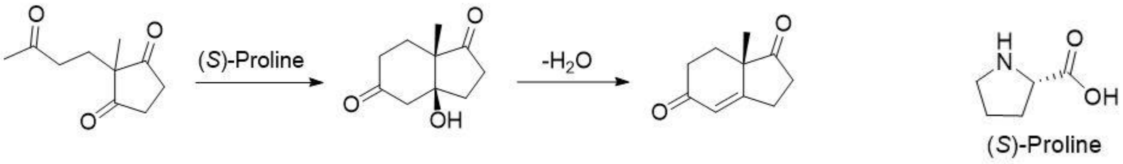


Figure 1. Twelve principles of green chemistry[6]



Scheme 1. Proline-catalyzed HPESW reaction[7-8]

One such alternative is organocatalysis, or the use of small organic molecules to catalyze reactions in place of metals. One notable reaction from the initial uses of organocatalysts was the Hajos-Parrish-Eder-Sauer-Wiechert (HPESW) reaction, which utilized amino acid proline to catalyze an aldol reaction (Scheme 1).[7-8] This reaction reported 90-100% yields and about 80-90% enantiomeric excess (*ee*), showing that these new catalysts could be an effective alternative to metals.[7-8] Along with others such as Shi, Denmark, Yang, Jacobsen, and Corey, the HPESW reaction set the stage for the development of an entire field, seeking to replace metal cores with organic ones.[8-13] Jacobsen, Corey, and their coworkers presented some of the first findings on a subfield of organocatalysis, using specifically hydrogen-bonding catalysts.[12-14] These have been a focus of study over the past several decades that continues to grow due to their versatility, particularly dual hydrogen bond donor (DHBD) catalysts such as thiourea (Figure 2a).[15-18] In particular, asymmetric thiourea derivatives have been a popular choice, one use of which has the thiourea-catalyzed alkylation of α-chloroether electrophiles with silyl ketene acetals using two equivalents of the catalyst (Scheme 2).[19] This reaction appears to involve strong interactions between DHBD molecules and aryl systems, but these non-covalent interactions (NCIs) have not been well explored, unlike hydrogen bonding and the π–π interactions that aryl systems can participate in (Figure 3).[14, 20]

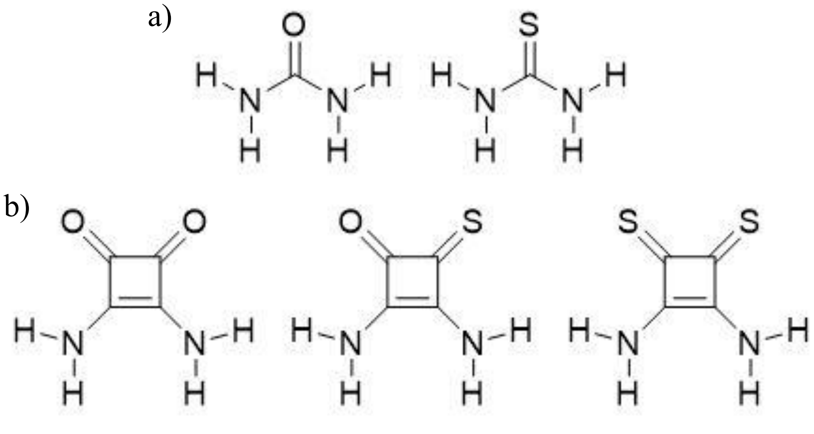
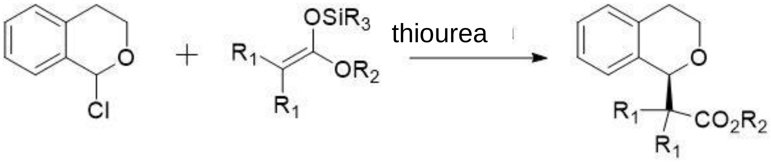


Figure 2. Dual hydrogen bond donors. a) urea, thiourea.
b) squaramide, hemithiosquaramide, thiosquaramide



Scheme 2. Thiourea-catalyzed alkylation of α-chloroether electrophiles with silyl ketene acetals

π–π interactions in benzene dimers have long been a focus of study due to the role of these NCIs in both biological and synthetic systems.[21] The computational development of the potential energy surface of benzene dimers is an ongoing but thoroughly studied process, making these an effective benchmark for other π–π interactions.[22-26] The two most energetically favorable benzene dimers were computationally determined to be the parallel displaced and T-shaped configurations (Figure 3).[27-29] These two dimers were also observed to exist experimentally using single crystal X-ray diffraction and other analytical methods.[30-34] Another commonly observed benzene dimer is the parallel stacked configuration, but this was determined to be a saddle point on the potential energy surface and is much higher in energy than the abovementioned dimers (Figure 3).[22-23, 35] Consequently, the parallel stacked dimer has never been observed experimentally.

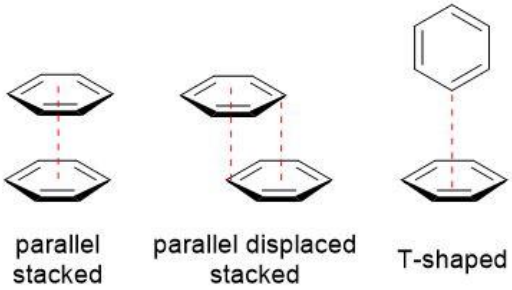


Figure 3. Major π–π interactions of the benzene dimer[21]

Squaramide is a DHBD analogous in structure to thiourea and has become increasingly popular as an organocatalyst (Figure 2b).[36-37] Its hydrogen bonding capabilities have been shown to be stronger than thiourea-based catalysts, and additionally, squaramide displays a greater potential for π interactions, offering greater diversity in how these molecules interact through NCIs. Squaramide is also generally more acidic than thiourea, so it participates in stronger hydrogen bonds than analogous thioureas do.[38] These properties may alter squaramide's behavior as a catalyst, but this has yet to be elucidated and so is prime for study. This work explores squaramide's combination of hydrogen bonding and π interactions with aryl systems as compared to the benchmark benzene dimer interactions in order to uncover heretofore unexplored reactivity. My hypothesis is that squaramide will interact more strongly with aryl substrates than benzene interacts with itself or other aryl rings, as squaramide has the potential for both hydrogen bonding and π interactions while benzene can only participate in π interactions.

As dual hydrogen bond donors grow in popularity, understanding the base interactions that drive their catalytic behavior becomes increasingly important. Unsubstituted squaramides have not been well studied, leaving a gap in the field that this work begins to fill. This problem is also one of many research projects working towards a more sustainable world. As the environmental crisis worsens every year, it becomes even more important to lower the waste and danger levels associated with chemical industry, and the first step is to understand the greener methods currently available to us, including organocatalysis.[39] The transition to greener catalysis in the chemical industry is a necessary one, making the world a cleaner and better place.

Methods

Computational chemistry methods including meta-hybrid density functional theory[40] and second-order Møller-Plesset perturbation theory (MP2)[41] were performed at the Center for Computational Sciences (CCS) at Duquesne University[42] using Gaussian 16.[43] The M06-2X functional[44] with Dunning's aug-cc-pV[D, T]Z basis sets[45] were used for geometry optimizations and to calculate electronic, enthalpic, and free energies for structures. Truhlar and coworkers' M06-2X is reported to be within 0.37 kcal/mol of accuracy for non-covalent interaction energies.[44] To verify this accuracy for our calculations, higher level MP2 calculations were performed on the same structures with the same basis sets.[46] The Boys and

Bernardi counterpoise method was used to correct for basis set superposition error (BSSE), which results from the use of limited basis sets that may over- or underestimate energies and alter geometries.[47] All calculations were performed in the gas phase.

Results and Discussion

In order to measure the strength and extent of squaramide's interactions with aryl systems, we modeled unsubstituted squaramide, hemithiosquaramide, and thiosquaramide individually with benzene (Figure 4). Because the benzene dimer is such a well-studied interaction, it acts as a good point of comparison to squaramide's π interactions. We started our calculations in seven different orientations based on the established π interactions XH-π, lone pair-π, and π stacking (Figure 4). These led to three major interactions: parallel displaced and parallel stacked, named after the benzene dimers, and a bifurcated orientation with no comparable benzene dimer (Figure 5). The energies of these complexes were compared with those of the relevant be After the issue of BSSE came up in these findings, some preliminary calculations on benzene dimers were performed, and those are presented in this work as well.

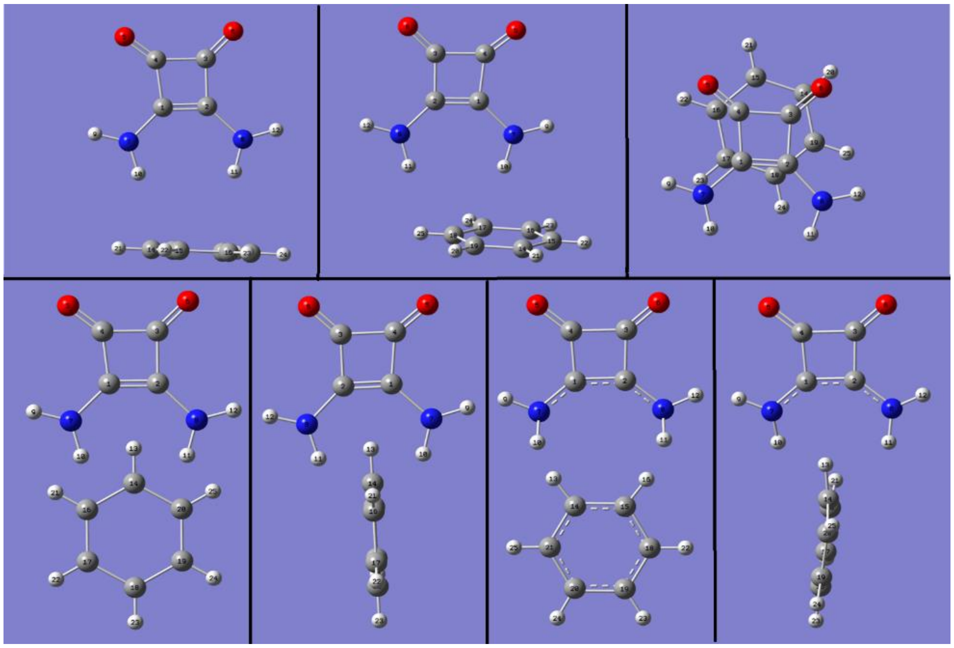


Figure 4. Starting geometries for squaramide-benzene complexes.
Identical geometries were used for hemithiosquaramide and thiosquaramide.

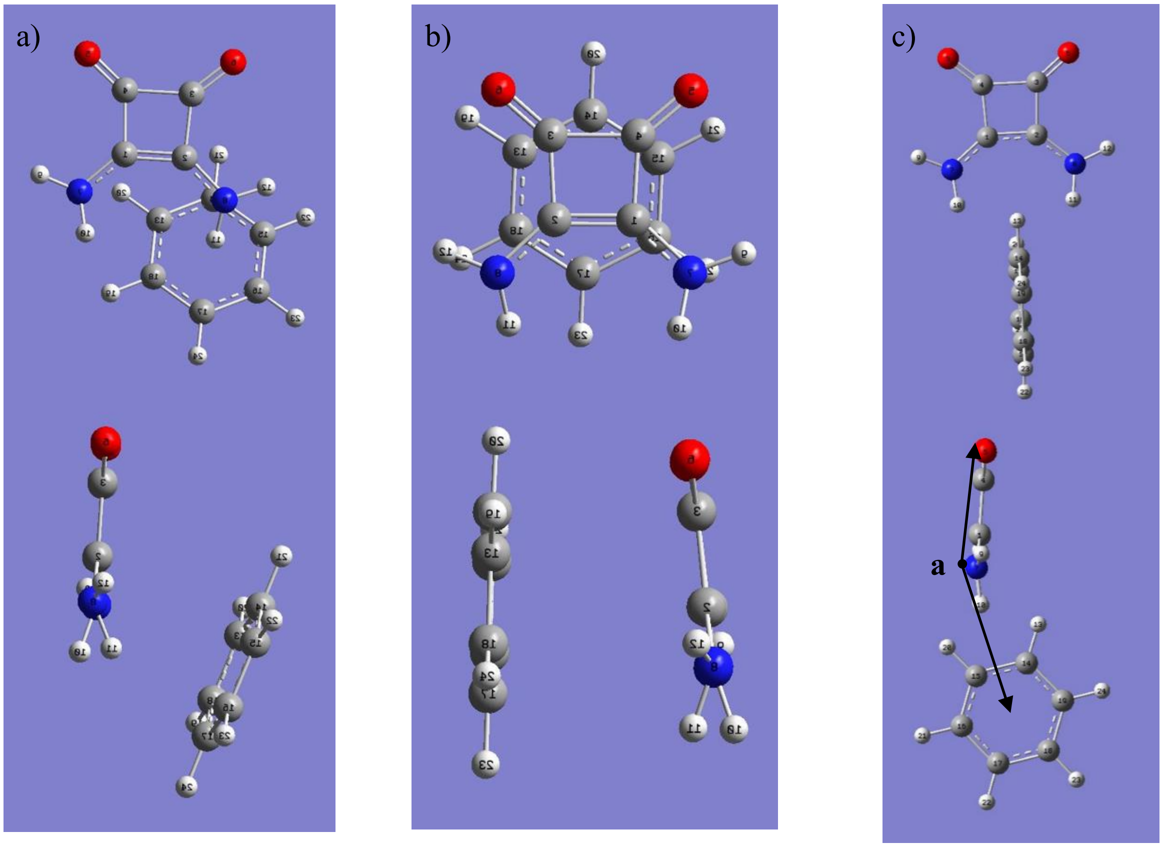


Figure 5. a) Parallel displaced squaramide-benzene interaction. b) Parallel stacked squaramide-benzene interaction. c) Bifurcated squaramide-benzene interaction. Similar interactions found for hemithiosquaramide and thiosquaramide

Parallel Displaced Interaction

The parallel displaced configuration of squaramide and benzene appears to involve multiple points of interaction on the molecules (Figure 5a). Benzene is relatively parallel with squaramide, but it shifts to center on one N-H bond. This presents the opportunity for π stacking between benzene and the π system of squaramide, similarly to the parallel displaced benzene dimer. Additionally, one N-H bond points toward the center of benzene, allowing the potential for an XH-π interaction. Both hydrogens were puckered, or twisted out of the squaramide plane towards or away from the plane of benzene, but the one directly interacting with benzene is far more puckered than the indirectly involve one. This structure is consistent across every level of theory we tested and was found from multiple of the presented starting points. Structural differences between level of theory include various levels of puckering in squaramide's hydrogens and a slight twist in the squaramide core of up to 3°. The parallel displaced structure is also consistently the most energetically favorable interaction, or lowest energy ground state, of the three ground states that we found (Table 1).

Table 1. Interaction energies of squaramide-benzene complexes (kcal/mol)

Molecule	Method	Basis set	PD	PS	B
Squaramide	M06-2X	aug-cc-pVDZ	-7.79	-7.10	-4.10
		aug-cc-pVTZ	-6.72	-5.96	-3.26
	MP2	aug-cc-pVDZ	-12.90	-13.09	n/a
		aug-cc-pVTZ	-10.44	-10.35	-5.49
Hemithiosquaramide	M06-2X	aug-cc-pVDZ	-8.32, -8.23	-7.86	-4.46
		aug-cc-pVTZ	-7.10, -7.05	-6.63	-3.53
	MP2	aug-cc-pVDZ	-14.02	n/a	n/a
		aug-cc-pVTZ	-11.41, -11.38	-11.30	n/a
Thiosquaramide	M06-2X	aug-cc-pVDZ	-8.81	-8.43	-4.73
		aug-cc-pVTZ	-7.51	-7.13	-3.74
	MP2	aug-cc-pVDZ	-15.05	-14.92	n/a
		aug-cc-pVTZ	-12.45	-12.39	-6.17

PD: parallel displaced. PS: parallel stacked. B: bifurcated. Values listed for hemithiosquaramide in the PD column are with the benzene interacting with the sulfur side of the molecule and the oxygen side of the molecule, respectively. N/a results are in progress.

There are several differences in how the three squaramides interact with benzene here. In the M06-2X calculations, while squaramide and benzene are not quite parallel to one another, thiosquaramide and benzene are essentially parallel. As expected, hemithiosquaramide appears somewhere in between the two, being closer to parallel than with squaramide. The hydrogens for these three compounds were different levels of puckered. Squaramide's hydrogens were the most puckered, thiosquaramide's the least puckered, and hemithiosquaramide again somewhere in the middle. This is a trend throughout all of these calculations. Hemithiosquaramide is always a middle ground between squaramide and thiosquaramide, sharing some of both of their properties. At the MP2 level, these differences become less apparent. The hydrogen puckering trend remains the same as with M06-2X, but each system is about the same level of parallel. An energetic trend is clear as thiosquaramide has the lowest interaction energy while squaramide has the highest (Figure 6).

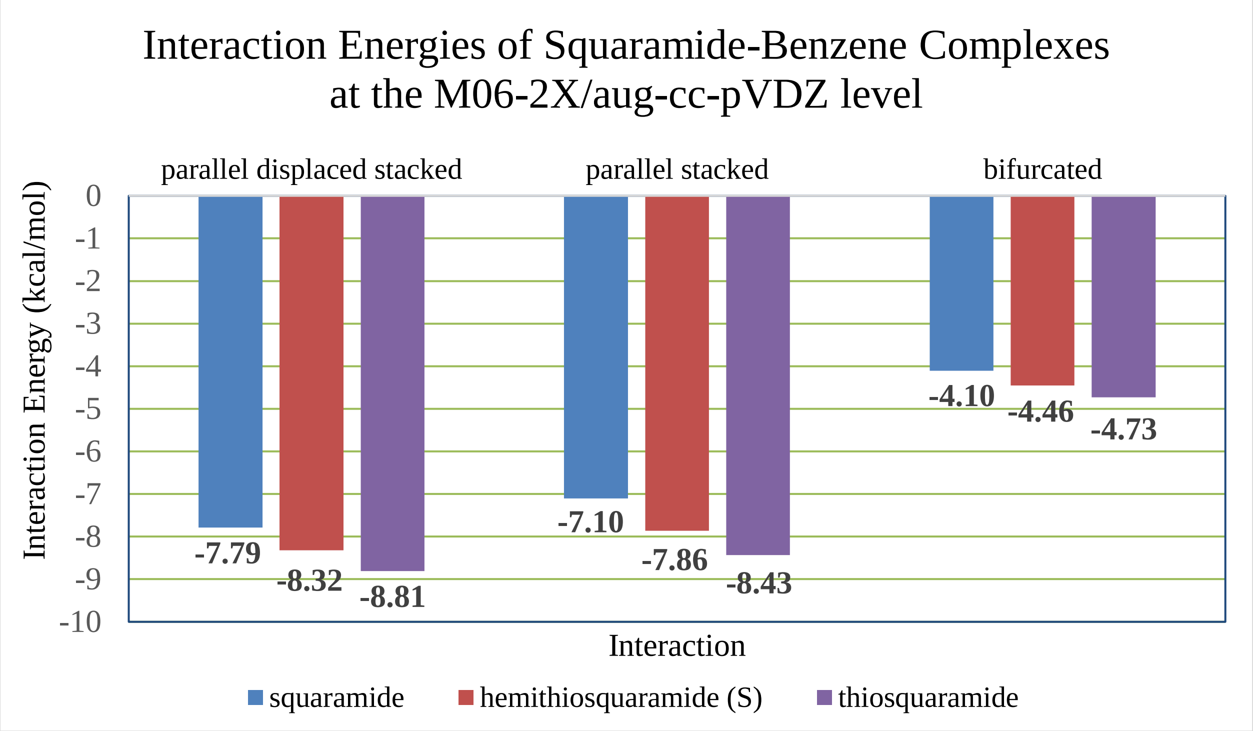


Figure 6. Interaction Energies of Squaramide-Benzene Complexes at the M06-2X/aug-cc-pVDZ level. Trends are consistent across levels of theory.

Parallel Stacked Interaction

The parallel stacked configuration of squaramide and benzene is very similar to the parallel stacked benzene dimer, with the two π systems stacking directly on top of one another (Figure 5b). Unlike the benzene dimer, which is a saddle point,[22-23, 35] the squaramide-benzene complex appears to be a true ground state minima. This is likely because the π system of squaramide does not build up electron density in the same way that benzene's does, so the direct repulsive interactions in the benzene-benzene dimer are not present here. Because of the size difference between a hexagonal benzene ring and the square ring of squaramide, benzene may be interacting with more than one part of the molecule. There are two optimized geometries for this structure, one with both hydrogens on squaramide pointing toward the benzene and one with oppositely puckered hydrogens, as in the parallel displaced configuration (Figure 7). Both are ground states, but energetically they are slightly different. The geometry is fairly consistent across levels of theory.

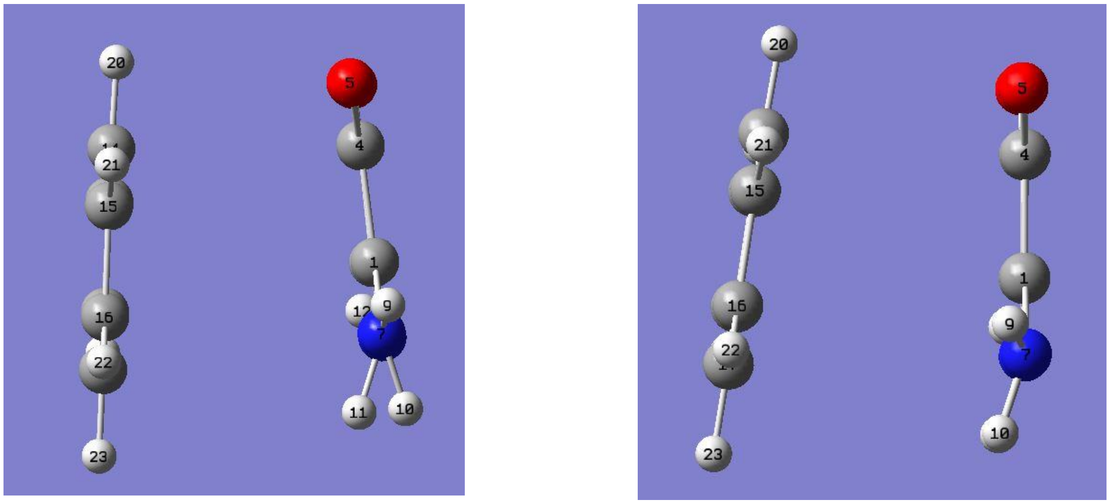


Figure 7. Two optimized geometries of the parallel stacked squaramide-benzene interaction.

The one major difference between the squaramides in parallel stacked configuration is the relative orientation of the benzene ring. Benzene is the most aligned with the square ring with squaramide while with thiosquaramide, it is most aligned with the plane of the nitrogens, much lower on the molecule. This is likely due to the more diffuse atomic orbitals of sulfur as compared to oxygen, which may force the benzene to be further away from that part of the molecule. As seen earlier, benzene is in between these two positions for hemithiosquaramide, with the molecule rotated to put its carbon atoms further away from the sulfur atom**,** supporting the previous explanation of sulfur pushing benzene away (Figure 8). The same energetic trend appears for the parallel stacked as the parallel displaced, thiosquaramide being the lowest and squaramide being the highest (Figure 6). The parallel stacked structure is also consistently higher in energy than the parallel displaced, showing that the latter is slightly more favorable. However, the interaction energies tend to be similar, which makes sense when considering the similarities of the structures.

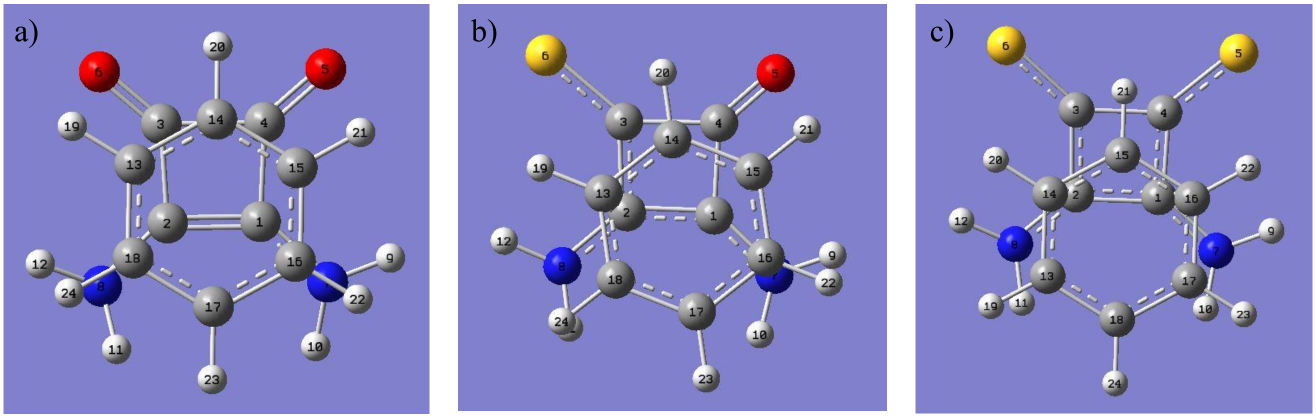


Figure 8. Parallel stacked geometries of a) squaramide, b) hemithiosquaramide, and c) thiosquaramide

Bifurcated Interaction

The bifurcated configuration of squaramide and benzene is the most different of the three orientations presented in this work. In this orientation, squaramide and benzene adopt perpendicular positions, two of benzene's protons pointing evenly spaced upward toward the square ring. The two -NH_2 groups of squaramide straddle the topmost point of the benzene. There is no comparable benzene dimer because the edges of two benzene monomers are both electron deficient and would repel each other. In this interaction, it appears that the electron deficient edge of benzene is interacting with the π system of squaramide and the hydrogens of squaramide are interacting with the electron rich π-cloud above and below the benzene plane.[48] The two molecules are not always perfectly perpendicular, but a considerable portion of the calculations yielded very close to perpendicular orientations. This interaction is approximately half as energetically favorable as the parallel displaced interaction.

Of the three squaramides, thiosquaramide produces the closest to a truly perpendicular structure across all levels of theory, with little or no puckering in its hydrogens. Squaramide typically has its puckered hydrogens in line with benzene as the rest of the molecule is tilted. The hemithiosquaramide interaction is almost perpendicular, looking more like thiosquaramide than squaramide, but its angles are slightly less exact (Table 2). This difference is likely due to sulfur's greater participation in the delocalized π system compared to oxygen and creating a stronger pull on the molecules to be upright in order to maximize overlap. The same energetic trend continues, thiosquaramide being the most favorable interaction and squaramide being the least favorable of the three (Figure 6). This trend can be explained in the context of the bifurcated orientation as sulfur appears to interact more strongly than oxygen, producing a more stabilized interaction.

Table 2. Angle a (Figure 5) for bifurcated squaramide-benzene interactions (degrees)

Method	Basis set	Squaramide	Hemisquaramide	Thiosquaramide
M06-2X	aug-cc-pVDZ	161.1	178.4	179.98
	aug-cc-pVTZ	161.6	178.9	179.6
MP2	aug-cc-pVDZ	n/a	n/a	n/a
	aug-cc-pVTZ	156.8	n/a	176.4

N/a results are in progress.

Benzene Dimer Comparison

The energies of the parallel displaced and parallel stacked squaramide-benzene complexes were compared to those of the relevant benzene dimer geometries. As a variety of factors such as level of theory and solvation can impact energy, we performed calculations of benzene dimers under identical conditions to those used for squaramide. However, significant work on benzene's NCIs has been performed.[22-23, 25, 27, 31, 49] Squaramide's interactions with benzene appear to be more favorable than benzene dimer interactions, showing that squaramide can interact strongly with substrates through NCIs (Figure 9). This supports my hypothesis that the squaramide-benzene complexes would interact more strongly than benzene dimers.

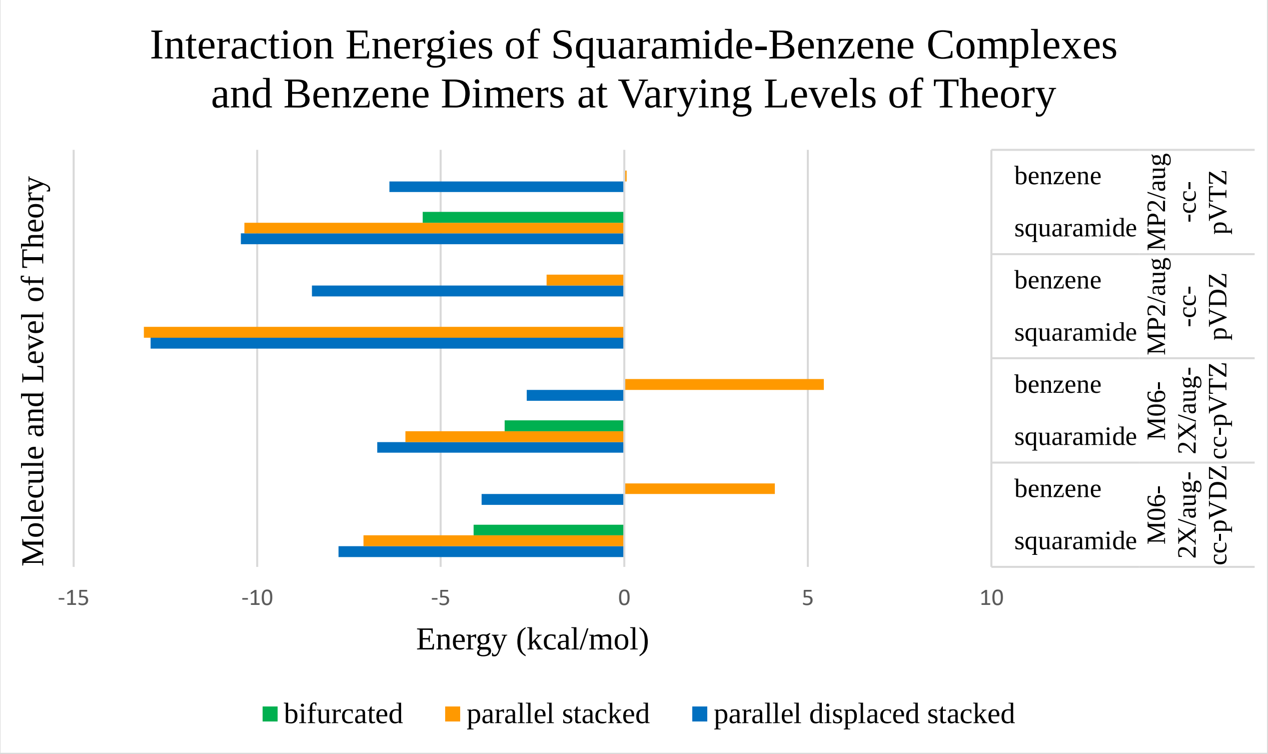


Figure 9. Interaction energies of squaramide-benzene complexes and benzene dimers at varying levels of theory.

BSSE Investigation

The exploration of BSSE became important as it became clear that it could significantly impact energies as well as geometries.[50] We performed counterpoise corrected calculations on benzene dimers at the levels of theory used previously to test how much the geometries would change with this specific method. There was some amount of geometric change, largely encountered in the rotation of the benzene monomers. The interaction energies of the dimers were artificially lowered by up to 3.75 kcal/mol (Figure 10). Based on these results and those determined previously[22, 50], it is likely that BSSE impacts the squaramide-benzene complexes as well.

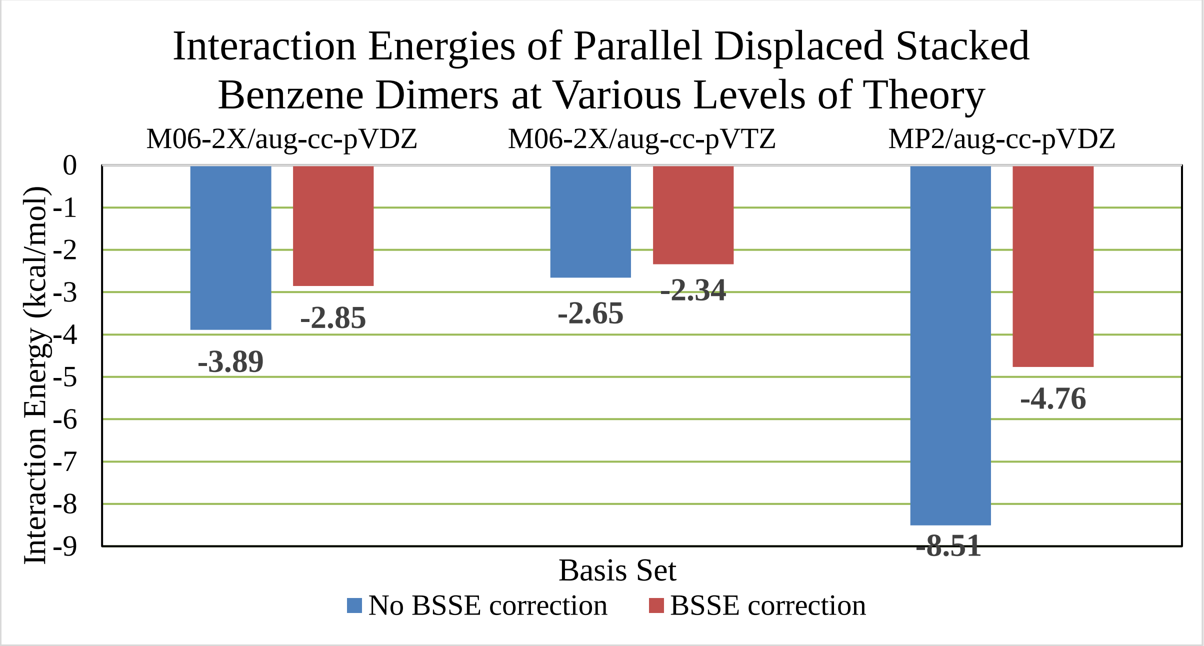


Figure 10. Interaction energies of parallel displaced stacked benzene dimers at various levels of theory

Conclusion

The interactions of unsubstituted squaramides and benzene were demonstrated by our calculations to be similar to those of benzene dimers, including parallel displaced and parallel stacked style interactions. A new interaction, the bifurcated system, also appears to be a true ground state minima, though less favorable than the others. The potential for both π stacking and XH-π interactions gave these squaramide-benzene complexes much more stabilization than the comparable benzene dimers under comparable conditions. It has been shown that the effects of BSSE are not negligible on systems of this type. Follow-up calculations should include counterpoise correction on these new interactions to determine the extent to which BSSE impacts their energies and geometries and confirm the validity of these ground states.

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