Computational and Synthetic Investigations of Di-ortho Substituted Arylboronate Esters

By

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Abstract

Dynamic covalent chemistry aids in the synthesis of large, complex organic materials by allowing for the exchange of many individual subunits until the most thermodynamically stable product is formed often in one high yielding step. The boronate ester condensation reaction is just one example of a reversible, thermodynamically driven reaction that has been used in the synthesis of organic materials like covalent organic frameworks and polygons. These materials have many important and diverse applications and their synthesis and optimization is a rich area of research. Small arylboronate esters are considered the building blocks for the much larger frameworks that can be more difficult to work with and study. It was found that substitution in both ortho positions of phenylboronic acid precursors has a large effect on the conformations that these molecules take. In this project several di-ortho substituted arylboronate esters were studied computationally and synthetically in an attempt to explain the varying substituent effects. Steric repulsion can account for many of the conformational preferences of di-ortho substituted arylboronate esters, however computational analysis suggests that electronic effects are also influential in some cases.
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Chapter 1: Introduction and Background
Chapter 1: Introduction and Background

1.1 Dynamic Covalent Chemistry

In the field of synthetic chemistry there is a desire to develop strategies to synthesize highly complex molecules (and supermolecules) in high yield with minimal steps. Most approaches to synthesizing large, complex structures require multiple linear synthetic steps of varying yield. These approaches, while often successful, can also be very tedious and result in low overall yields.

Dynamic covalent chemistry, by contrast, uses thermodynamic control and reversibility of reactions to synthesize a desired product. By starting with a library of various molecular substrates that can react with one another multiple, often in infinite ways, the product that will predominate will be the most thermodynamically favored, lowest free energy product. This process can often be exploited to favor a certain product by addition of a template to “lock in” one conformation or by altering reaction conditions to further favor one desired product (Figure 1). Also called dynamic combinatorial chemistry, this approach has been used to synthesize very complex organic materials that would otherwise be impossible to synthesize by traditional, kinetically controlled, stepwise synthetic techniques. By allowing for the scrambling of reagents and products until the most stable product is assembled, one can ensure an often uniform formation of the desired product.¹
Figure 1: A dynamic combinatorial library of complementary molecular subunits can combine to form several potential macrocycles. The addition of an appropriate template can amplify selection of a specific macrocycle from within such a dynamically exchanging library.

There are many types of reversible chemical reactions that can be used in dynamic covalent chemistry to assemble complex organic structures. Sanders et al. reported the synthesis of an organic trefoil knot using dynamic disulfide bond formation and alteration of reaction conditions to obtain near quantitative assembly of the complex knotted trimer (Scheme 1). Rowan et al. employed dynamic combinatorial chemistry in synthesizing, in good yield, a porphyrin macrocycle box by olefin metathesis. By first creating a library of linear and cyclic porphyrin oligomers and then adding a template to direct assembly of the desired macrocycle structure they were able to more than double the yield of the complex tetramer.
Scheme 1: Assembly of an organic trefoil knot using dynamic disulfide bond formation

The imine condensation reaction has proven to be useful for the dynamic covalent assembly of rotaxanes using alteration of the reaction conditions to push the equilibrium towards or away from imine formation. The thermodynamic reversibility of the imine formation reaction can allow for condition-dependent shuttling of a rotaxane macrocycle along a rod and can ensure error free formation of mechanically interlocked suitane assemblies (Scheme 2).

Scheme 2: Mechanically interlocked suitane assembly using dynamic imine condensation
In addition to the organic materials applications of dynamic combinatorial chemistry, this approach can also be applied to the field of drug discovery. In the simplest case, the principles of dynamic covalent chemistry can allow for the screening of multiple different drugs at once to determine which is the most efficient and selective. For example in the process of discovering an effective inhibitory drug, a dynamic library of possible inhibitors can be tested all at once with the target of interest. After initial scrambling of the library, the complex of the inhibitor with the highest affinity for the target substrate will predominate energetically giving immediate information about the efficacy of the various synthetic inhibitors. 7

It is clear that dynamic covalent chemistry is an important tool in the synthesis of complex organic materials and selective inhibitory drugs. This project will utilize dynamic covalent chemistry, specifically using the reversible boronate ester condensation reaction, to synthesize structures of interest to covalent organic materials.

1.2 Boronic Acids and the Boronate Ester Synthesis

Boronic acids are arguably most well known for their part in palladium catalyzed Suzuki-Miyaura coupling reactions, the importance of which was recognized as part of the Nobel Prize in Chemistry in 2010. 8 In addition to their use in carbon-carbon bond forming reactions, boronic acids can be condensed with alcohols in a reversible reaction forming boronate esters (Scheme 3).
One predominant structural feature that makes boronic acids and boronate esters particularly interesting is the sp\(^3\) hybridized boron which has an empty p-orbital that can act as a Lewis acid (Figure 2a). In arylboronic acids the boron is conjugated with the phenyl ring such that the carbon-boron bond may experience some amount of π character (Figure 2b).

When these boronic acids condense with a diol, specifically catechol, the electron-deficient boron can accept some donation from the electron-rich oxygen atoms. As a result of this ester condensation two water molecules are liberated. This property of the boronate ester formation reaction allows for the use of Le Chatelier’s principle to push the equilibrium in either direction by the addition or removal of water.
Dynamic boronate ester chemistry has been used in the field of biochemistry specifically by using boronic acids as chemosensors for polyhydroxylated saccharides. Additionally, this methodology has been employed in drug discovery research to identify potent protein inhibitors. The relatively simple nature of this thermodynamically driven, reversible reaction along with the ability to use water to control product formation make it a great candidate for dynamic covalent chemistry.

1.3 Organic Materials Applications of the Boronate Ester Synthesis

On a larger scale the boronate ester synthesis reaction has been used in the formation of covalent organic materials. For example, by employing diboronic acids and bis- or tri-catechol moieties of varying geometries one can assemble complex covalent organic frameworks (COFs) often in a single, high yielding step (Scheme 4). These extended porous 2D materials typically stack in layers favorably by π stacking of the extended π-conjugated system.

**Scheme 4:** Covalent organic framework assembly

![Covalent organic framework assembly diagram](image)
COFs are attractive as synthetic materials because they are lightweight, have high internal surface area, exhibit highly ordered periodic structures, and are thermally stable.\textsuperscript{14} Covalent organic frameworks have been used for gas storage,\textsuperscript{15} chiral catalysis,\textsuperscript{16} and optoelectronics.\textsuperscript{17} A limitation of COFs as organic materials is their insolubility due to the extremely tight packing interactions between the 2D sheets. Work has been done to improve solubility and obtain a more homogeneous polymerization of these materials so that they are easier to work with for their many applications.\textsuperscript{18}

Covalent organic polygons (COPs) are discrete analogues of covalent organic frameworks that do not polymerize into infinitely periodic structures the way that COFs do. By adding solubilizing groups on the periphery of the starting materials, individual polygons are assembled which can then aggregate into tube-like structures (Scheme 5).

\textbf{Scheme 5:} Covalent organic polygon assembly
The improved solubility makes these structures much easier to work with and therefore they can be used to study the optimization of COF synthesis on structurally analogous but more manageable materials. Additionally, COPs have their own potential applications as liquid crystalline materials. Many covalent organic polygons have been successfully synthesized using dynamic boronate ester formation reactions as the basis for assembly. These assemblies can continue to be fine-tuned, particularly in altering the way that the units aggregate to change their properties like solubility.

1.4 Substituted Arylboronate Esters as Building Blocks

This project looks closely at the dynamic assembly of small arylboronate ester building blocks along with conformational analysis of the resulting structures. The addition of different functional groups on boronic acid or catechol subunits has been shown to influence their dynamic assembly and spectroscopic properties. Excited state spectroscopic studies of some small boronate esters by Professor J. L. Knee (Figure 3) revealed significant deviation in $S_1$ excitation spectra for the ortho dimethyl substituted ester (OD1) compared with other substituted and unsubstituted esters. The diMe spectrum is red shifted compared with the other compounds and has a rich, low frequency vibrational structure that is unlike any of the differently substituted arylboronate esters. It was then hypothesized that this spectroscopic variation could be due to the non-planar conformation of di-ortho substituted esters. Therefore di-ortho-substituted boronate esters became of particular interest because
of suspected differences in conformational preferences around the dihedral angle about the central carbon-boron bond.

**Figure 3:** $S_1$ excitation spectra of various boronate esters revealing the variation in the diMe (OD1) spectrum. Compound identifiers are unique to this figure.
Though many aryl boronate esters adopt planar conformations their carbon-boron bond allows for 360° rotation around the dihedral angle (Figure 4) and Professor Knee’s initial research suggests substitution of the boronic acid ring may influence conformational preferences.

![Figure 4: Rotation around the carbon-boron bond](image)

When the phenyl ring is substituted, particularly in the ortho position, the conformations of the energy minima and maxima vary widely. To understand the variation in conformation for these substituted structures it is important to think about the substituent effects for each compound. For each type of substituent there are both steric and electronic effects which play key roles in how the substituent affects the ester.

In an effort to understand the ways that various substituents will influence conformational energies it is helpful to understand what one might expect based on prior knowledge and study of the substituents. Hammett parameters are values devised to describe the electronic effects of various substituents. These values have been determined from the ionization constants for the substitution in the meta and para positions on benzoic acid compared to unsubstituted benzoic acid (Figure 5).
Figure 5: Ionization of benzoic acid and Hammet equation for $\sigma$

When $\sigma$ is negative that indicates an electron-donating substituent and when $\sigma$ is positive that indicates an electron-withdrawing substituent. In the meta position the Hammett parameter gives information about the inductive effects of a substituent whereas in the para position the Hammett parameter gives information about resonance effects.$^{24}$ The Hammett parameters for the substituents of interest for this project are listed in Table 1.

Table 1: Selected substituent Hammett parameters

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$\sigma_{\text{para}}$</th>
<th>$\sigma_{i}$ (inductive)</th>
<th>$\sigma_{y}$ (size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>F</td>
<td>0.06</td>
<td>0.52</td>
<td>0.27</td>
</tr>
<tr>
<td>Cl</td>
<td>0.23</td>
<td>0.47</td>
<td>0.55</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>-0.07</td>
<td>-0.04</td>
<td>0.52</td>
</tr>
<tr>
<td>OCH$_3$</td>
<td>-0.27</td>
<td>0.27</td>
<td>0.36</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>0.54</td>
<td>0.42</td>
<td>0.91</td>
</tr>
<tr>
<td>NMe$_2$</td>
<td>-0.83</td>
<td>0.06</td>
<td>0.43</td>
</tr>
</tbody>
</table>
Relative substituent size is also an important factor in how the substituent may influence ester conformations by steric effects. Also included in Table 1 are $\sigma_v$ values which allow for the comparison of substituent steric effects based on relative size.

The boronate ester structures of interest are shown in Figure 6. These specific compounds were chosen for the variety of substituent types and synthetic or commercial availability.

![Figure 6: Di-ortho substituted arylboronate esters of interest](image)

This project aims to study these compounds both synthetically and computationally to better understand the substituent effects for each di-ortho substituted boronate ester. A better understanding of the conformations that these smaller “building blocks”
prefer, based on their substitution, can inform the synthesis of larger boronate ester assemblies like COPs and COFs and can aid in fine tuning their properties.
Chapter 2: Computational Results and Discussion
Chapter 2: Computational Results and Discussion

2.1 Conformations of Energy Minima and Maxima

To better understand the potential energy surface of di-ortho substituted arylboronate esters corresponding to rotation around the carbon-boron bond, dihedral scans were performed. The results of the dihedral scans allowed for straightforward structure optimization calculations of the global and local energy minima and transition states. The relative optimized energies for all structures of interest were then plotted together by normalizing all energy maxima to zero and connecting minima and maxima with a smooth curve (Figure 7). The diMe and FOMe compounds are believed to have another local energy maximum but attempts to optimize these transition structures were unsuccessful probably due to the low barrier to the energy minimum.
Figure 7: Structure optimization energies of global/local minima and transition states of di-ortho aryl boronate esters. Compound identifiers correspond to those given for structures in Figure 6.

A dihedral angle of 0 or 180 degrees describes the planar conformation while a 90 degree dihedral angle is the perpendicular orientation (Figure 8).

Figure 8: GaussView structures of planar and perpendicular conformations with generic, cyan colored di-ortho substituents.
The plot in Figure 7 showing the relative energies of the optimized energy minima and maxima for the eight structures of interest, allows for direct comparison between the differently substituted compounds. From a cursory glance one can see the variation in both the relative energy barriers between the lowest and highest energy conformations and the preferred dihedral angle conformations. For example the relative energy barrier to rotation for the bulky diCF₃ compound (purple) is more than 8 kcal/mol compared to the diOMe compound (red) with a barrier less than 1 kcal/mol. This variation highlights the differences in how quickly these compounds will rotate around their carbon-boron bond based on the relative stabilities of the energy minima and the relative instabilities of the energy maxima. Additionally we can see a variety of different conformations for energy minima and maxima. For example the unsubstituted ester, diH (blue), prefers the planar conformation whereas the diCl (orange) prefers the 90 degree conformation. It was this unexpected conformational variation along with Professor Knee’s experimental findings that piqued interest in attempting to understand and explain how mere changes the substituents at the ortho positions on the boronic acid could have such a drastic effect.

As a strategy to understand how electronic and steric substituent contributions influence the preferred conformations, dihedral scans and subsequent structure optimizations were calculated for the para, di-meta, mono-meta and mono-ortho analogues of the various di-ortho aryloboronate esters. By leveraging the minimal expense of computation we can study each additional structure to isolate and compare different substituent effects using their differing properties described in Table 2.
Table 2: Comparison of substituent effects for differently substituted esters

<table>
<thead>
<tr>
<th></th>
<th>Di-ortho</th>
<th>Di-meta</th>
<th>Para</th>
<th>Mono-ortho</th>
<th>Mono-meta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterics</td>
<td>Yes (x2)</td>
<td>X</td>
<td>X</td>
<td>Yes</td>
<td>X</td>
</tr>
<tr>
<td>Induction</td>
<td>Strongest</td>
<td>Less</td>
<td>X</td>
<td>Strong</td>
<td>Less</td>
</tr>
<tr>
<td>Resonance</td>
<td>Yes (x2)</td>
<td>X</td>
<td>Yes</td>
<td>Yes</td>
<td>X</td>
</tr>
</tbody>
</table>

As shown in Table 2, the di-ortho position has the largest steric, inductive, and resonance effects. The additional structures are useful for comparison because they don’t experience all of these substituent effects at once. For example the para position allows isolation of the resonance effects that exist in the ortho position without the effect of steric. The di- and mono-meta positions do not have the same resonance effect as the ortho positions and the steric effects are also eliminated so inductive effects can be isolated. Mono-ortho is useful for investigating the influence of a single ortho substituent, which decreases both steric repulsion and resonance donation, in comparison to the addition of a second substituent in the ortho position.
Figure 9: Calculated barriers to rotation for the series of para substituted arylboronate esters. Optimized energy minima (in kcal/mol) are shown in the legend.

Figure 9 shows the relative energy maxima and minima for the para substituted compounds. It is clear that there is a distinct trend in how these molecules behave, unlike the di-ortho substituted esters. All compounds prefer the planar conformation and have their energy maxima at 90 degrees. The range of energy barriers is defined more narrowly between 4 and 8 kcal/mol. Of particular interest is the para methoxy ester (p-OMe) which has the lowest energy barrier to rotation. This is the opposite of what one might expect based on the stabilizing effect of the resonance donating substituent in the planar conformation (Figure 10).
Para-methoxy and para-dimethylamino esters can resonate into the boron p-orbital in the planar conformation.

In an attempt to better understand resonance donor substituents the para dimethylamino compound was studied. As expected, p-NMe$_2$ was the most stabilized in the planar conformation and had the highest barrier to rotation. This is the first piece of data revealing that the methoxy substituent does not behave as expected.

**Figure 10:** Para-methoxy and para-dimethylamino esters can resonate into the boron p-orbital in the planar conformation.
Figure 11: Calculated barriers to rotation for the series of di-meta substituted arylboronate esters. Optimized energy minima (in kcal/mol) are shown in the legend.

Figure 11 shows the di-meta optimization data. Here the trend is even more narrowly defined, again with planar being the most stable conformation and perpendicular being the least stable. The same is true for the mono-meta data shown in Figure 12 below. It becomes more and more evident that the di-ortho substituted esters are the exception to this trend that favors planarity for other substituted arylboronate esters.
Figure 12: Calculated barriers to rotation for the series of mono-meta substituted arylboronate esters. Optimized energy minima (in kcal/mol) are shown in the legend.

Finally, the mono-ortho optimization data is shown in Figure 13. These structures reveal the same conformations for energy minima and maxima but display more variation in relative energy barriers. The ortho position is unique because of the prominent role of sterics compared to the meta and para positions. From this graph one can observe the destabilizing effects of steric hindrance in the planar conformation.
Figure 13: Calculated barriers to rotation for the series of mono-ortho substituted arylboronate esters. Optimized energy minima (in kcal/mol) are shown in the legend.

Clearly steric substituent effects are playing an influential role in the conformations that these substituted boronate esters take but steric effects alone can’t explain the significant variation in conformation and energies for the di-ortho substituted esters.

2.2 Molecular Structure Data: Bond Lengths and Angles

Once optimized, structural data can be analyzed alongside energetic data to gain insight into trends regarding conformational preferences of substituted arylboronate esters. For example in the case of the mono-ortho substituted esters it was useful to compare the carbon-carbon-boron angle on the side of the substituent to
observe how much of an effect the group had on the molecule’s conformation (Figure 14).

**Figure 14:** Carbon-carbon-boron angle (red) in mono-ortho substituted ester that can serve as a proxy for the extent of steric repulsion in the planar conformation.

Due to the sp² hybridization of the central carbon the expected angle should be 120 degrees. Table 3 shows the angle distortions for each substituent in increasing order. When compared directly with σ_v values the trend follows that as relative substituent size increases so does the carbon-carbon-boron angle.

**Table 3:** Carbon-carbon-boron angle for mono-ortho esters compared with σ_v

<table>
<thead>
<tr>
<th>Substituent</th>
<th>&lt;CCB (planar conformation)</th>
<th>σ_v</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>120.58</td>
<td>0</td>
</tr>
<tr>
<td>F</td>
<td>123.53</td>
<td>0.27</td>
</tr>
<tr>
<td>OCH₃</td>
<td>123.64</td>
<td>0.36</td>
</tr>
<tr>
<td>CH₃</td>
<td>123.67</td>
<td>0.52</td>
</tr>
<tr>
<td>NMe₂</td>
<td>124.72</td>
<td>0.43</td>
</tr>
<tr>
<td>Cl</td>
<td>126.03</td>
<td>0.55</td>
</tr>
<tr>
<td>CF₃</td>
<td>126.66</td>
<td>0.91</td>
</tr>
</tbody>
</table>
Another structural element that was explored was the carbon-boron bond length (Figure 15). This bond length can in principle tell us something about the amount of π character that the carbon-boron bond has and therefore the extent of conjugation with the aromatic ring.

![Figure 15: Boronate ester with central carbon-boron bond highlighted (blue)](image)

The bond lengths were determined for the optimized structures at both the energy minima and maxima. An expected trend emerged for the para, mono-ortho, mono-meta and di-meta substituted esters where the lowest energy, planar conformation had the shorter carbon-boron bond length while the high energy, 90 degree conformation had a longer carbon-boron bond length (Figure 16). This is consistent with the idea that when the p-orbitals are aligned in the planar conformation resonance can occur such that there is some amount of donation into the empty p-orbital of boron, giving the carbon-boron bond more π character.
Figure 16: Carbon-boron bond length measurements for para, mono-meta, di-meta and mono-ortho structures in the planar and perpendicular conformations

The di-ortho substituted esters did not reveal a consistent trend in bond lengths. The bond length data collected in Table 4 can be dissected in an attempt to explain the variation. Before extensive analysis is done it is important to point out that for many of these bond lengths the variation is on the order of a thousandth of an angstrom so the margin of error of the Gaussian calculations should be taken into account when making statements about potential trends in this case.
Table 4: Carbon-boron bond lengths at global minimum and transition states for di-ortho substituted esters

<table>
<thead>
<tr>
<th></th>
<th>Global energy minimum</th>
<th>Transition state 1</th>
<th>Transition state 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle</td>
<td>C-B length (Å)</td>
<td>Angle</td>
<td>C-B length (Å)</td>
</tr>
<tr>
<td></td>
<td>(°)</td>
<td>(°)</td>
<td>(Å)</td>
</tr>
<tr>
<td>DiH</td>
<td>0.0</td>
<td>1.540</td>
<td>90.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiF</td>
<td>0.0</td>
<td>1.549</td>
<td>90.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiMe</td>
<td>11.6</td>
<td>1.550</td>
<td>90.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOMe</td>
<td>12.6</td>
<td>1.550</td>
<td>90.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FCl</td>
<td>50.0</td>
<td>1.558</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiCF₃</td>
<td>68.2</td>
<td>1.571</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiOMe</td>
<td>90.0</td>
<td>1.556</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiCl</td>
<td>90.0</td>
<td>1.563</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Four of the eight di-ortho substituted compounds of interest (diH, diF, diMe and FOMe) appear to follow the trend described for the differently substituted esters: the lowest energy, planar conformation had the shortest bond length compared to the highest energy, 90 degree conformation. For the other di-ortho substituted esters the trend is not so clear. In the FCl and diOMe compounds it is the planar conformation that has the shortest bond length but this is the conformation of the energy maxima. In this case some amount of donation may be occurring in the planar conformation but that does not have the stabilizing effect that would be expected. The diCl ester was unique in that it’s shortest bond length occurred in the 90 degree conformation. This lead to the hypothesis that there could be potential back donation of electron density.
from the chlorine substituents into the empty p-orbital of boron that could stabilize the 90 degree conformation.

2.3 Isodesmic Calculations and Data Analysis

Another type of calculation that was employed to better understand the conformational preferences of these boronate esters is called an isodesmic calculation. These calculations consider theoretical reactions where the types of bonds broken in the reactants are the same as the types of bonds formed in the products. Scheme 6 shows the various isodesmic reactions calculated where the stability of each substituted ester was compared to that of the unsubstituted ester with the substituents on a benzene. The reaction enthalpies produced from these calculations can be compared between substituent types to understand their relative stabilities.
The isodesmic calculations ultimately produced a lot of data comparing the stabilities of many of these structures to each other. Some of this data did reveal consistent and expected trends and in many cases the ortho-dimethoxy ester deviated from the rest of the compounds, as seen previously. At the same time much of the isodesmic data did not appear to be useful or reveal identifiable trends. Here data that appears most informative about the substituted arylboronate structures is presented.

When all di-ortho substituted esters were compared with the unsubstituted ester (Scheme 6[A]) the substituents preferred to be on the benzene rather than the ester. This may be expected given the destabilizing effect of steric in the ortho
positions on the ester. Table 5 shows the reaction enthalpies for the di-ortho esters compared with their combined $\sigma_v$ values. A general trend is observed suggesting that as the size of the substituents increases, the substituted ester becomes more destabilized. DiOMe is the only ester that does not align with this trend.

**Table 5:** Reaction enthalpies for di-ortho isodesmic reaction [A]

<table>
<thead>
<tr>
<th></th>
<th>$\Delta H_{\text{forward rxn}}$ [1] (kcal/mol)</th>
<th>$\sigma_v$</th>
</tr>
</thead>
<tbody>
<tr>
<td>DiH</td>
<td>0.00</td>
<td>0</td>
</tr>
<tr>
<td>DiF</td>
<td>-1.69</td>
<td>0.54</td>
</tr>
<tr>
<td>DiOMe</td>
<td>-1.69</td>
<td>0.72</td>
</tr>
<tr>
<td>FOMe</td>
<td>-2.43</td>
<td>0.63</td>
</tr>
<tr>
<td>FCl</td>
<td>-3.40</td>
<td>0.82</td>
</tr>
<tr>
<td>DiMe</td>
<td>-3.71</td>
<td>1.04</td>
</tr>
<tr>
<td>DiCl</td>
<td>-3.90</td>
<td>1.1</td>
</tr>
<tr>
<td>DiCF$_3$</td>
<td>-3.99</td>
<td>1.82</td>
</tr>
</tbody>
</table>

Isodesmic calculations also allow for direct comparison between the di-ortho and di-meta substituted esters (Scheme 7). In every case the di-ortho esters were destabilized with respect to the di-meta esters again suggesting that steric is the dominant substituent effect at that position.
Scheme 7: Di-ortho to di-meta isodesmic reaction

To visualize the trend shown in Table 6 of enthalpies compared with $\sigma_v$ values, the variables were plotted against each other as shown in Figure 17.

Table 6: Reaction enthalpies for di-ortho to di-meta (Scheme 7)

<table>
<thead>
<tr>
<th></th>
<th>$\Delta H_{\text{ortho to meta}}$ (kcal/mol)</th>
<th>$\sigma_v$</th>
</tr>
</thead>
<tbody>
<tr>
<td>DiH</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DiF</td>
<td>-1.24</td>
<td>0.54</td>
</tr>
<tr>
<td>DiOMe</td>
<td>-2.19</td>
<td>0.72</td>
</tr>
<tr>
<td>FOMe</td>
<td>-2.26</td>
<td>0.63</td>
</tr>
<tr>
<td>DiMe</td>
<td>-2.7</td>
<td>1.04</td>
</tr>
<tr>
<td>FCl</td>
<td>-2.88</td>
<td>0.82</td>
</tr>
<tr>
<td>DiCF$_3$</td>
<td>-3.42</td>
<td>1.82</td>
</tr>
<tr>
<td>DiCl</td>
<td>-3.49</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Figure 17: Plot of reaction enthalpy and total $\sigma_v$ for di-ortho to di-meta isodesmic reaction

\[
y = -0.3907x - 0.054 \\
R^2 = 0.76123
\]
There is a definite trend revealing that as $\Delta H$ increases (such that the di-ortho compound is increasingly stable relative to its di-meta isomer), the $\sigma_v$ values for size decrease. The data reinforces the expected correlation where the majority of the destabilization of the di-ortho esters studied comes from the steric substituent effects. What makes this project and these molecules interesting to study, though, is actually the variation off the trendline. Steric effects can’t explain away all the variation that sparked interest in these compounds in the first place or else the trendline would have a closer to perfect fit. Electronic substituent effects must also impact the relative stabilities and conformational preferences of di-ortho substituted arylboronate esters.

Another way that isodesmic calculations proved useful was in the comparison between all monosubstituted esters (Figure 18). The idea here being that all three positions on the phenyl ring can be compared directly when they are each monosubstituted so that the number of substituents doesn’t have an effect. Table 7 gives the relative energies for each substituent normalized to the least stable isomer.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure18}
\caption{Mono-substituted structures for isodesmic comparative analysis}
\end{figure}
Table 7: Relative enthalpies of mono-ortho, mono-meta, and para positions for each substituent normalized to the least stable isomer

<table>
<thead>
<tr>
<th></th>
<th>H</th>
<th>Me</th>
<th>F</th>
<th>Cl</th>
<th>NMe₂</th>
<th>OMe</th>
<th>CF₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most stable</td>
<td>0.000</td>
<td>-1.470</td>
<td>-1.069</td>
<td>-2.121</td>
<td>-5.811</td>
<td>-1.990</td>
<td>-2.905</td>
</tr>
<tr>
<td></td>
<td>0.000</td>
<td>-1.051</td>
<td>-0.476</td>
<td>-1.647</td>
<td>-2.843</td>
<td>-1.425</td>
<td>-2.592</td>
</tr>
<tr>
<td>Least stable</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Four of the six substituents (Me, F, Cl and NMe₂) behaved in an expected way where the mono-ortho isomer was the least stable followed by the mono-meta and then the para being the most stable. The bulky CF₃ group deviated slightly from the trend in that it preferred the meta position over the para with, of course, the ortho being the most destabilized by almost 3 kcal/mol relative to the mono-meta. Again the methoxy substituent is observed to stand out from the group. For OMe the least stable isomer was the para position followed by ortho and meta, respectively. The fact that the para position, which would be expected to be stabilized by resonance, is actually the least stable for this resonance donor is counterintuitive. This is especially true when it is compared with NMe₂, the other resonance donor substituent. Not only is the most stable isomer for NMe₂ para but it is by far the most stabilized of all the substituents at any position by a more than 3 kcal/mol suggesting that resonance is likely a powerful stabilizing force in the planar conformation for para substituted compounds.

When comparing the two resonance donor substituents and their seemingly unique behaviors it was interesting to look back at Hammett parameters. Methoxy has a \( \sigma_{\text{para}} \) of -0.27 and a \( \sigma_i \) of 0.27 while dimethylamino has a \( \sigma_{\text{para}} \) of -0.83 and a \( \sigma_i \) of
0.06. In comparing their resonance abilities NMe$_2$ is clearly a stronger donating group which could explain some of our results where it acted much more as a resonance donor than OMe. It is also important to compare the inductive effects of each because OMe is a much stronger electron withdrawing group by induction than NMe$_2$. While it may not be relevant to compare the different types of $\sigma$ values it is curious that methoxy appears to donate by resonance the same amount that it withdraws by induction (+/-0.27). This might help us to understand at least somewhat why OMe has consistently been outside of expected trends.

2.4 Natural Bonding Orbital Analysis

One final type of calculation that was performed was natural bonding orbital analysis. For a given molecule NBO analysis determines the electron orbitals and their relative populations. This calculation proved useful in attempting to understand better the compounds that preferred the 90 degree conformation as their energy minimum. By calculating and viewing the HOMO of the chlorine molecules along with the LUMO of the boron p-orbital we could potentially see whether or not any donation was occurring. The resulting relevant orbitals for the ortho dichloro ester in the 90 degree global minimum conformation are shown in Figure 19.
Figure 19: Natural bonding orbitals for ortho dichloro boronate ester

When viewed together there is clear overlap between the HOMO of the chlorine substituents and the p-orbital LUMO of the boron. Although the Gaussian-generated orbital images depict an equal amount of constructive and destructive orbital overlap between the HOMO and the LUMO, which would indicate no significant positive orbital interaction, further investigation is required to determine if these calculations can be analyzed as such. Whether the red/green colored shading is arbitrary between orbitals is currently unclear and a better understanding of this type of calculation is necessary before further analysis.
Analysis of the wealth of computational data obtained for the structures of interest leads to some generalizing conclusions about substituted arylboronate esters. The data has shown in many cases that the di-ortho substituted esters do not behave or conform in an expected or consistent way. This is unlike the mono-ortho, mono-meta, di-meta and para substituted esters which all followed regular trends without significant deviation. Studying the di-ortho substituted esters is a worthwhile investigation as their conformational properties are not easily understood.

Specifically, the ortho dimethoxy substituted ester proved to be an interesting outlier in many cases. The diOMe ester often conformed in ways that were inconsistent with the properties with which the methoxy substituent is thought to act as a resonance donor. The unexpected properties of the diOMe ester make it of particular synthetic interest. Computational results were used as a guide for the synthetic interests and investigations for this project.
Chapter 3: Synthetic Results and Discussion
Chapter 3: Synthetic Results and Discussion

3.1 Progress Towards Synthesis of Di-ortho Substituted Esters

The synthetic goal of this project is to attempt to synthesize, with high purity, as many of the di-ortho substituted arylboronate esters as possible. The crystallization of these pure ester products was then attempted with the hope of obtaining x-ray crystallography data to compare with the computational structural data. Additionally these esters can be studied by excitation spectroscopy to continue to better understand the variation in the spectrum for di-ortho substituted esters.

Scheme 8: Successful boronate ester condensation reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1]</td>
<td><img src="image1.png" alt="Reaction 1" /></td>
</tr>
<tr>
<td>[2]</td>
<td><img src="image2.png" alt="Reaction 2" /></td>
</tr>
<tr>
<td>[3]</td>
<td><img src="image3.png" alt="Reaction 3" /></td>
</tr>
</tbody>
</table>

Scheme 8 shows the boronate ester condensation reactions that were synthetically optimized to afford pure product according to the conditions reported in the methods section: the unsubstituted (diH) [1], difluoro (diF) [2], and dimethyl (diMe) [3] boronate esters. Magnesium sulfate was used as a drying agent in each
case to drive the formation of the desired ester product by the removal of water. The success of these reactions was determined by $^1$H NMR spectroscopy (Figure 20, 21, 22).

**Figure 20:** $^1$H NMR spectrum of unsubstituted, diH boronate ester [1]
These esters were synthesized without much difficulty and had reasonable purity without the need for column chromatography. The crystallization of these three esters was then attempted first using the slow evaporation method. Both the unsubstituted and the difluoro ester crystallized well from slow evaporation in
hexanes. The successful crystallization of the dimethyl ester has yet to be optimized after many attempts of both slow evaporation and vapor diffusion in various solvent systems. Despite the relative simplicity of the synthesis of these three esters, this was not the case for the synthesis of the other esters attempted.

The synthesis of the asymmetric fluoromethoxy ester (FOMe) was attempted next. After some difficulty shifting the equilibrium towards products, a Dean-Stark apparatus using acetonitrile and toluene was utilized as an alternate water removal method to drying agents like magnesium sulfate. Unfortunately this setup was not effective in obtaining products potentially due to the small reaction scale and therefore a relatively small amount of water produced. When pure products were not obtained directly upon condensation, column chromatography was employed in an effort to separate the desired ester product from the boronic acid and catechol precursors. Several attempts were made to isolate the pure product but unfortunately this method of purification was unsuccessful. Due to the reversible nature of the boronate ester condensation reaction and the sensitivity to water most ester assemblies continually fall apart on the column and pure ester product was not obtained. The difficulty of column chromatography for these compounds posed a challenge for the goal of obtaining pure boronate ester products. Knowing this, the focus of the synthetic investigation then moved to the optimization of reaction conditions in order to avoid the necessity of purification with a column.
3.2 Synthesis of DiOMe via Condensation

Scheme 9: Condensation reaction of dimethoxy boronate ester

Attempts at the synthesis of the computationally interesting ortho dimethoxy boronate ester (Scheme 9) using the same reaction conditions as above proved unsuccessful. $^1$H NMR spectroscopy was used to determine relative conversion to product by comparing the integrations of the methoxy peaks for boronic acid starting material (Figure 23) (3.91 ppm) and the ester product (3.83 ppm).

Figure 23: $^1$H NMR spectrum of 2,6-dimethoxyphenyl boronic acid starting material

To optimize conversion to product the reaction conditions were altered in many ways including choice of solvent, concentration, temperature, reaction time and
equivalents of drying agent. To eliminate the presence of any water in the reaction the glassware was flame dried, magnesium sulfate was added to the reaction during stirring, and molecular sieves were added before filtration. These techniques were successful in almost eliminating the water peak in the $^1$H NMR spectra but did not have as strong of a driving force as expected. It is possible that the remaining water in the spectra came from the CDCl$_3$ used to prepare the NMR sample.

All initial reactions were run at room temperature but the idea to cool down the reaction was based on computational data. The energy barrier to rotation for the diOMe ester was calculated to be 0.73 kcal/mol, which is less than 2kT at room temperature (1.184 kcal/mol) so one can expect very rapid bond rotation. The calculated rate of rotation for the diOMe ester at room temperature is $1.8 \times 10^{12}$ rotations/sec. One can then postulate that it’s corresponding boronic acid precursor would also have a very low barrier to rotation, which could potentially disfavor the condensation with catechol. Cooling down the reaction should slow the rotation of the boronic acid and potentially facilitate assembly. The potential effect of cold reaction conditions should also be contrasted with the concept that due to the entropic favorability of the condensation reaction, high temperatures should favor assembly. In this case the removal of water will be the driving force for assembly in the cold conditions. Additionally to maintain this condition rotary evaporation was performed at room temperature. Decreasing the temperature also slows the reaction in general so longer reaction times were tested to determine the amount of time it would take to reach equilibrium. Ultimately, after many trials, the ratio of boronic acid starting
material to boronate ester product was improved from 3:1 to 1:1.3 with a 0.01 M solution in DCM at -78°C for more than 4 days (Figure 24).

Figure 24: $^1$H NMR spectrum of optimized diOMe synthesis

At this point it was determined that the equilibrium had likely been pushed as far towards product as reasonably possible using this method especially with the small water peak indicating that the removal of water could not be employed much more. The condensation method of synthesizing the ortho dimethoxy arylboronate ester did not prove successful enough to yield pure product for crystallization or spectroscopy and due to the limitations of column chromatography and the sensitivity of the product to water, isolation of the ester was not attempted. Instead, a different route of synthesizing the diOMe ester was attempted.
3.3 Synthesis of DiOMe via Alkylithium Reactions

Literature precedent from Yamashita et al. \(^{25}\) utilized an alkylithium reaction, shown in Scheme 10, to synthesize an arylboronate ester with some structural similarity to the desired structure of interest.

**Scheme 10:** Literature precedent for diOMe synthesis \(^{25}\)

\[
\begin{align*}
\text{Scheme 10: Literature precedent for diOMe synthesis}^{25} \\
\begin{array}{c}
\text{OMe} \quad \text{Br} \quad \text{OMe} \\
\begin{array}{c}
\text{OMe} \\
\text{Cl–B} \\
\text{OMe}
\end{array}
\end{array}
\end{align*}
\]

\[\text{i) nBuLi, -100°C, 1.5hr} \quad \text{ii) -100°C to rt, overnight} \]

This precedent was applied to the synthesis of the ortho dimethoxy ester according to the following Scheme 11.

**Scheme 11:** Desired alkylithium reaction applied to diOMe ester of interest

\[
\begin{align*}
\text{Scheme 11: Desired alkylithium reaction applied to diOMe ester of interest} \\
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{I}
\end{array}
\end{align*}
\]

\[\text{i) nBuLi, -78°C, 1.5hr} \quad \text{ii) -78°C to rt, overnight} \]

Unfortunately the \(^1\)H NMR results of this reaction were inconclusive as to whether or not product was formed. There are many possible challenges in this modified
synthesis that could have inhibited successful product formation. In the first step of the alkyllithium reaction, a carbanion is formed on the benzene between the methoxy substituents as shown in Figure 25. This is an extremely electron rich carbanion being ortho to two electron donating groups and it’s formation may be so disfavored that it could inhibit product formation. Additionally there are steric concerns with this reaction. In the literature precedent the two methoxy groups are further away from the reacting carbon. Not only does this affect the electronics of the reaction but having the methoxy groups closer may create an unfavorable steric interaction with the incoming bromocatecholborane.

Figure 25: Electronic and steric concerns for the dimethoxybenzene starting material

It is also important to note that the literature precedent calls for an aqueous workup which has the potential to hydrate any successfully synthesized ester into the boronic acid and catechol pieces. There is also the potential for error based on the quality of the alkyllithium reagent.

To distinguish which of these potential challenges to the synthesis contributed to its failure additional syntheses were performed and are shown in Scheme 12 below.
First an attempt was made to synthesize the unsubstituted ester via the alkyllithium method \([i]\). The results of the condensation formation of the unsubstituted ester showed that it was formed easily and was relatively stable to water compared to the substituted esters. Using the alkyllithium reaction did not provide sufficient evidence that the unsubstituted ester was formed. There did appear to be catechol peaks in the \(^1\)H NMR spectrum which could be due to hydration of the ester during the aqueous workup. Next to determine whether or not the electron rich carbanion formed the dimethoxyiodobenzene reagent was reacted via alkyllithium reaction with methanol \([ii]\). The \(^1\)H NMR revealed about a 1:1 ratio of the iodo starting material to the desired product. This result suggests that in fact the electron rich carbanion is not easily formed and only about 50% of the starting material actually reacts. Finally to
test steric difficulties an attempt was made to substitute a bulky TMS group onto the reacting carbon \(^{[iii]}\). There was no evidence in the \(^1\text{H} \) NMR spectrum of the characteristic TMS peak so it was determined that it is disfavored for bulky groups to add between the methoxy substituents.

Each of these reactions provided more and more insight into the shortcomings of using the alkyllithium literature precedent to synthesize the ortho dimethoxy ester. There are many possible explanations for why the reaction did not proceed as expected including electronics, sterics, and sensitivity to water. The computational interest in the diOMe ester motivated this extensive effort to synthesize pure product but unfortunately there were many barriers that ultimately inhibited its successful synthesis thus far.
Chapter 4: Conclusion and Future Work
Chapter 4: Conclusion and Future Work

Dynamic covalent chemistry is a useful tool in the synthesis of large, complex organic materials. Through the use of thermodynamic control one can shift an equilibrium to afford the most stable product of interest. The boronate ester condensation reaction is just one type of dynamic covalent reaction that can be used in these combinatorial assemblies and has proven useful in the synthesis of organic materials like covalent organic frameworks (COFs) and covalent organic polygons (COPs). These materials are often difficult to work with so the study of discrete arylboronate ester building blocks is a preferred method of investigation.

Of particular interest to this project has been arylboronate esters substituted in both ortho positions on the boronic acid phenyl ring. These compounds revealed unique excitation spectra and have widely varying lowest energy conformations around the central carbon-boron dihedral. To further investigate the substituent properties, resonance, induction and sterics, that in some combination create this variation, extensive computational analysis was performed. Ultimately this analysis revealed that steric effects, which are most intense in the diortho position, can explain much but not all of the deviation of diortho compounds compared with mono-ortho, mono-meta, para and di-meta analogous structures. Additionally, and most interestingly was the appearance of the dimethoxy ester as an outlier throughout computational analysis. The dimethoxy ester consistently did not act as expected based on resonance donor properties. Curiosity about this computationally interesting structure informed much of the synthetic work that followed.
Attempts at synthesizing pure boronate ester products for x-ray crystallography and excitation spectroscopy analysis had varying success. The unsubstituted (diH), difluoro (diF) and dimethyl (diMe) were synthesized and good crystals were obtained for the diH and diF products. After many attempts at optimization of condensation conditions for the dimethoxy (diOMe) ester and even trying a different synthetic route using alkyllithium chemistry, the most successful trial yielded a 1:1.1 ratio of boronic acid starting material to ester product. Due to the limitations of column chromatography for these water sensitive, reversible compounds, purification has not been successful.

Future work on this project should continue to focus on the synthesis and isolation of the rest of the di-ortho substituted boronate ester structures of interest so that experimental data can supplement the wealth of computational data. One potentially useful method of purification that could be helpful is a boric acid impregnated silica gel column as reported by Reid et al.\(^{26}\) which was determined to increase yields 5-10% compared to untreated silica. Any additional substituted esters that are synthesized or purified successfully should be fully characterized by \(^1\)H NMR and \(^{13}\)C NMR spectroscopy, mass spectrometry, and UV-vis spectroscopy and studied by Professor Knee’s excitation spectroscopy to compare with the initial diMe results.

By supplementing experimental data with computational analysis of these small substituted arylboronate ester building blocks a better overall understanding of how various substituents affect conformation can be achieved. This understanding can then be applied to the design and synthesis of novel organic materials like COFs.
and COPs to fine-tune their properties, especially with regard to their packing and aggregation.
Methods
Methods

Computational methods

All calculations were performed using the Gaussian 09 program. Prior to geometry optimization dihedral scans were performed first using a low level of theory (Hartree-Fock with 6-31G* basis set) to approximate global energy minima and maxima. The M06-2X level of theory was then utilized for geometry optimization. Previous research has shown that the M06-2X level of theory is a good candidate for boronate esters with the 6-311+g(d,p) basis set. Global and local minima were optimized to full convergence and thermal vibrational analysis showed the absence of any imaginary vibrational frequencies. Transition states were optimized using the Berney method and each showed a single imaginary frequency corresponding to rotation of the boronate ester C-B dihedral.

Materials

Solvents used were purchased from VWR Analytical and Fischer Chemical and were dried using 3 Å molecular sieves. The reagents used were purchased from commercial suppliers (Sigma Aldrich, Alfa Aesar, and Acros Organics). All $^1$H NMR spectra were obtained using a Varian Mercury 300 MHz spectrometer using residual solvent as the internal standard.
Experimental Methods

Scheme 13: Preparation of unsubstituted (diH) and difluoro (diF) esters

A 0.1 M suspension of boronic acid in chloroform was prepared in a clean vial with a magnetic stir bar. 1 molar equivalent of catechol was then added. Magnesium sulfate was added to the vial before stirring overnight. The reaction was then filtered, evaporated under reduced pressure and dried under high vacuum. The product was a white solid. $^1$H NMR results were consistent with reported values. $^{30}$

Scheme 14: Preparation of dimethyl (diMe) ester

Prepared according to literature Smith et al. $^{31}$ without the need for column chromatography.
Scheme 15: Preparation of dimethoxy (diOMe) ester

To a flame-dried 50 mL round bottom flask equipped with a magnetic stir bar was prepared a 0.01 M suspension of boronic acid in DCM. One molar equivalent of catechol was added to the flask followed by magnesium sulfate. N₂ was then bubbled through the solution. The reaction flask was then moved to the cold room and placed in a dry ice/acetone bath at -78°C and stirred. The bath was allowed to evaporate over time as the reaction warmed to the cold room temperature (~0°C). After 4 days the reaction was removed from the cold room and 3Å molecular sieves were added to the reaction as it was allowed to warm to room temperature. The reaction was then filtered, evaporated under reduced pressure in a room temperature water bath and dried under high vacuum. ᵃH NMR comparison of the methoxy peaks revealed a 1:1.1 ratio of boronic acid starting material to boronate ester product.
References:


