The Synthesis, Structure, and TT Stacking of 1,8 Diacridynaphthalene

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Abstract

The synthesis of 1,8 diacridynaphthalene is a five step process in which Stille and Suzuki cross coupling reactions, an inorganic catalyst, and organic substitution reactions are used to synthesize the desired product from which 4-bromo-2-chlorobenzoic acid(4) and 3, 5-dimethylphenylboronic acid(5). One of the characteristics that makes (1) unique π stacking interactions of the aromatic rings. These bonds can be identified and studied using different techniques such as $^1$H NMR spectra and x-ray crystallography. The discovery of an efficient synthesis of the (1) will allow it to be more readily available as a dual-mode enantioselective fluorosensor.

Introduction

(1) is a complex organic compound made up of primarily aromatic benzene rings connected to each other. There is a naphthalene bonded to the nitrogen rings of the main structure across from the nitrogen. The structure of the (1) has aromatic stacking which is displayed in Figure 1. The stacking is represented by the dashed lines to show that two of the aromatic rings are stacked on top of each other. So two rings are above and two rings are below. (1) has a unique ability of being an enantioselective fluorosensor of carboxylic acids. This allows for further studying amino acids, aliphatic acids, arylalkanoic acids, and...
halogenated carboxylic acids using it as for fluorosensing as well as fluorescence titrations.$^3$

The synthesis of (1) is a five step process which includes catalysts and cross coupling reactions. These schemes can be observed in the schemes shown in the results and discussion. (4) and (5) are the starting material for this synthesis.$^1$ Each of the reactants are purified using a process called crystallization. All of the other reactants and products found in this synthesis were purified using crystallization.$^1$ This allows for the purest possible products as well as the highest possible percent yields.

Crystallization is a process in which solid compounds can be purified. A solvent is found and the solid product is dissolved in this solvent. The proper solvent is important, because the solid must be soluble in the solvent when it is heated but be insoluble when the solvent is cool. Once the solid is dissolved into the solvent both the impurities and the desired product ionize and are mixed in the solvent. As the solvent cools the desired product then reforms into crystal structures that are purified. The melting and freezing points of the solvent and desired product is what allows for this interaction to take place. Once the recrystallization process is complete, the solid is filtered out so that it can be used for further reactions.$^4$

There are two main coupling reactions that are used in the synthesis of the (1). These two couplings are the Suzuki and the Stille Couplings reactions. The Suzuki reaction was discovered by Akira Suzuki and N. Miyaura in 1979. The Stille cross coupling reaction was discovered by John Kenneth Stille and David Milstein in 1977.
The Suzuki is the first cross-coupling reaction used in the synthesis. Suzuki cross-coupling is a palladium catalyzed reaction. The palladium catalyst’s first step is an oxidation-addition. During this oxidation-addition, the halide, in this case the bromide ion on the (4), is oxidized and the palladium takes the place of the bromide. The compound formed is an organopalladium species. This species is then reacted with a base which is Na$_2$CO$_3$ and forms an intermediate. Once the intermediate is formed the species goes through the process of transmetalation. Transmetalation is a process in which a ligand or ligands, either organic or inorganic, is exchanged between two metal centers. Finally, a reductive elimination reaction takes place and the palladium catalyst is kicked off and the desired product is formed. The Suzuki cross-coupling is done with the assistance of microwaves to speed up rate of the reaction. This scheme 1 is an example of simple Suzuki reaction.

The next cross coupling reaction is the Stille reaction. This reaction begins with the palladium catalyst reducing itself via ionization. Once the palladium is ionized the palladium catalyst bonds with and an organohalide in an oxidation-addition reaction. The trans intermediate formed from the oxidative-addition reactions then reacts with the organostanne through transmetalation to form the final intermediate. Once this final intermediate is formed the palladium catalyst reduces itself, leaving the desired
product. Through this process the stereochemistry of the desired product is maintained
which is what makes the Stille coupling reaction key in many of the present day
synthesis of complex compounds. An example of a Stille reaction can be seen in
scheme 2\textsuperscript{12}.

Different catalysts can be used to help improve the overall yield of a product. The
definition of a catalyst is a compound that is added to a reaction in order to increase the
rate of the reaction by changing the path of the reaction. In doing this, the activation
energy is lowered and desired product can be formed\textsuperscript{13}. Catalysts can help improve
reaction mechanisms because they lower the activation energy, thus, making the
reaction more favorable by increasing the amount of collisions between the reactants.
These more favorable conditions will allow for faster more productive reaction to take
place. With a more favorable reaction the percent yield should increase because there
will be a higher likely hood of more interaction between the reactants. Using a catalyst is
more effective than adding extra energy to the system because it is not consumed
during the reaction and some of the reactions need to be performed at specific
temperatures\textsuperscript{11}. Therefore, catalysts can help the overall yield of a desired product and
are very useful especially during multistep reactions.

There are multiple techniques that can be used to study the structure and
gometry of a compound. Two different techniques are used to study the structure,
stacking, and geometry of 1,8 diacridynaphthalene(1), 1,8 diacridynaphthalene N-
oxide(2), 1,8 diacridynaphthalene N, N dioxide(3).\textsuperscript{14} The Structures can be seen in
Figure 2. These two techniques are H\textsuperscript{1}Nuclear Magnetic Resonance Spectroscopy and
x-ray crystallography.
Nuclear Magnetic Resonance Spectroscopy is an instrument that uses magnetic fields to identify the location of different hydrogen protons. The different protons are identified by the locations of various peak displayed on the spectra. The peaks are generated by applying a large magnetic field to a sample. The first step is for the sample to be lined up to its proper magnetic configuration. Once this step is complete, the sample begins spinning and pulses are sent through the sample to disturb the magnetic equilibrium. This disturbance causes the sample to absorb and radiate the energy back out. The radiated energy is the specific resonance frequency of the sample. This information can be used to then calculate the strength of the magnetic field. After the data is collected the sample is allowed to relax. Once the relaxation has completed, the pulse begins again and this process is repeated until adequate data has been collected and the peaks generated using Fourier transform so the peaks can be identified.
X-ray Crystallography is a technique that is used to determine three dimensional shapes and structures of the crystal being examined. This process is done by mapping out the locations of the atoms that make up the structure. The location of the atoms is determined by sending x-ray waves through a crystal. When the x-ray waves strike the crystal beams, some are diffracted out in various directions which are absorbed in the film. Using the electron diffraction locations on the film, the structure and bonds can be determined using the Fourier transform formula. This technique is very helpful because it can be used to determine structures of organic, inorganic, and biochemical structures.¹⁶

π stacking is the interaction between aromatic rings. This interaction is a noncovalent interaction. Aromatic stacking is present as seen Figure 1 due to the overlapping of the aromatic rings located within the congested center of the structure. The bonds that make up the aromatic rings are noncovalent sigma and π bonds. The carbons that make up the π stacking in compounds 1, 2, and 3 must have sp² hybridization because there are only three possible bonding locations. The sp² hybridization is also needed for the rings to be aromatic. One of the easiest ways to notice the presence of π stacking is through NMR spectra. When the structure of Figure 1 as well as compound 3, another molecule that has a congested center with π stacking, is looked at it will be evident upon the location of the chemical shifts due to the shielding created by the stacking of the π bonds.¹⁵ Electron shielding occurs due to the π stacking. The overlap of the aromatic rings block the protons opposite of the magnetic field. The electrons from the aromatic ring that is closest to the magnetic field spin around the bond. In doing this the electrons oppose the magnetic field trying to reach
the proton on the opposite ring\textsuperscript{16}. This causes the peaks to shift to the right as seen in the NMR spectra presented later on in the results and discussion.

Aromatic rings are made up of alternating carbon to carbon $\pi$ bonds and sigma bonds that form a ring structure. These structures only have major resonance structures which aid the stability of the rings, because they do not have the ability to gain charge through resonance.\textsuperscript{17} The rule that aromatic compound must follow is Huckel's rule, $4n+2$. “This rule states that a ring is aromatic with extra resonance stability if and only if all ring atoms have parallel $p$ orbitals holding a total of $4n+2$ $\pi$ electrons where, $n$ is an integer\textsuperscript{17}.” These aromatic rings are the reason the shifts in the NMR spectra can be seen for compounds 1 and 3. With the help of different cross coupling reactions and catalyst, a synthesis to create (1) was discovered. This allows for the ability to compare the structures and $\pi$ stacking of different diheteroarylnaphthalenes including the created (1).

**Results and Discussion**

The conclusions that are derived in this results and discussion are based upon the results of two articles. These two articles are entitled *Highly Congested Nondiheteroarylnaphthalenes: Model Compounds for the Investigation of Intramolecular $\pi$-Stacking Interactions and Synthesis of a Sterically Crowded Atropisomeric 1,8 Diacridylnaphthalene for Dual-Mode Enantioselective Fluorosensing.*
A synthesis was proposed to create (1). The proposed synthesis contains five different reactions. The complete synthesis can be seen above in scheme 3. These reactions include two cross coupling reactions using a palladium catalysis. These cross coupling reactions are the Suzuki and Stille coupling. These methods can be used to increase the overall percent yield of the desired product from the synthesis by lowering the activation energy of the reaction. In a palladium catalyzed reaction palladium catalyst are reacted with different inorganic elements to add or alter the structures of organic compounds. Upon doing this the structures of the organic compounds become more favorable for desired reactions. The reactions become more favorable because the catalyst lowers the activation energy and increases the rate of the reaction. Increasing the rate of the reaction and lowering the activation energy make the reaction more efficient. The main catalyst that is used in these reactions is Pd(PPh₃)₄, tetrakis(triphenylphosphine)palladium(0). This catalyst will be used in cross coupling addition reactions.
The synthesis began with a microwave-assisted Suzuki cross coupling reaction in which (4) acid and (5) acid is combined in the presence of Pd(PPh$_3$)$_4$ catalyst. This synthesis can be seen in scheme 4. The reaction takes place when the palladium catalyst and the Na$_2$CO$_3$ activate the boron atom. This causes the Boronic acid to react with a halide, the bromide. This allows the formation of 4-(3’,5’dimethylphenyl)-2-chlorobenzoic acid(6) to take place as a result. The percent yield of this reaction was 96%$^1$.

The (6) was then reacted with aniline and 2-ethoxyethanol in a aromatic nucleophilic substitution reaction. This reaction can be seen in Scheme 5. This reaction takes place when the lone pair of electrons from the nucleophile, nitrogen, attacks the carbon that has the chlorine bonded to it. This causes the π bond to shift due to resonance. The neighboring carbon then takes on a negative charge. Once the nitrogen
aromatic group is added via an addition reaction, the electrons from the negatively charged carbon move back over due to resonance and kick off the chlorine atom. Through this substitution reaction adds the nitrogen group and the desired anthranilic acid(7) was formed with an 89% yield\(^1\).

The anthranilic acid(7) was then reacted with phosphorous oxybromide and the desired 9-bromoacridyl(8) was formed in 99% yield. The mechanism for this reaction can be seen in scheme 6. The mechanism begins with the treatment of POBr\(_3\) which causes the OH group to leave and a bromide to come and take its spot. Then the lone pair of electrons on the nitrogen shifts over and causes the \(\pi\) bond of the adjacent rings to break and move to form a bond between the carbon that makes up the carbonacylic
acid. Once this bond is formed the bromide is kicked off. The π bond in oxygen moves via resonance and takes on a negative charge. Then the hydrogen bonded to the adjacent ring is grabbed by the negatively charged oxygen an OH is formed as well as a double bond between the two carbons. The hydrogen bonded with the nitrogen also shifts its electrons so a double bond between the nitrogen and carbon was formed. Finally, the product was treated with POBr₂ and the alcohol group is kicked off and the bromide was added.

Once the correct isomer of the 9-bromoacridyl(8) was produced, then it was treated with butyllithium as seen in scheme 7. The butyllithium which is a nucleophile, removes the bromide which is acting the electrophile attached to the ring, but the electrons from the bromide would stay with the ring. Then an addition reaction is performed with the trialkylstannyl chloride which acts as a electrophile and bonds with the negatively charge carbon to yield 9-acridylstannanes(9). The percent yields for the two isomers were 91% and 98%¹.
These isomers were then reacted in a Stille coupling reaction with the palladium catalyst and 1, 8 dibromonaphthalene (10) and the desired product of (1) is formed. This reaction can be seen in Scheme 8. The Stille coupling works by first reducing the palladium catalyst, then the desired oxidative addition is made to the organic bromide. After this addition is made, the intermediate is formed and the transmetalation of the tin and removes the bromide from the final product of 1, 8-diacridynaphthalene. The transmetalation process then removes the tin R₃ functional group. Thus, through this reaction the desired product was formed. The beauty of this mechanism is that the stereochemical configuration of the desired product stays consistent. The final percent yield was 68\% \(^{1}\).

The structures of diacridynaphthalene(1), diacridynaphthalene N-oxide(2), diacridynaphthalene N, N dioxide(3) were examined by H\(^{1}\)NMR, x-ray crystallographic analysis, and ultraviolet-visible spectroscopy. All three structures exhibit π to π interactions. Compounds 1, 2, and 3 also exhibit different hydrogen bonding interactions with the nitrogen and oxygen atoms. Different techniques and instruments can be used to better see and understand these interactions. The structures of these three compounds can be seen in Figure 2.
The H\textsuperscript{1}NMR spectra of compounds 1 and 3 were looked at and compared to 3-(3, 5 dimethylphenyl)-9-bromoacridine (11) and 3-(3, 5 dimethylphenyl)-9-bromoacridine N-oxide (12). First, the H\textsuperscript{1}NMR spectra was taken of compounds 1 and 4. These spectra’s are shown in Figure 3 and Figure 4. The NMR spectra can reveal a lot of information about how the congested stacking and \(\pi\) to \(\pi\) interaction of the compound 1 differs from compound 4, which does not have the presence of \(\pi\) to \(\pi\) stacking.

Congested compounds are compounds that have very crowded reactions centers. The centers are congested due to the steric hindrance that is created from the bulky functional groups that are bonded around the reaction center of the central atom. Congested compounds also have overlapping aromatic rings and regular rings which can cause the shielding of the protons behind an overlapping ring. The congested compound will have its peaks shifted up field due to the \(\pi\) to \(\pi\) interaction.

These congested bonds cause shielding which can be seen in the NMR spectrum by proton shifts to the left or right. When a proton shifts to the left it will have a down field shift and if it shifts to the right it is considered an up-field shift. Electron shielding takes place when the overlap of aromatic rings shield the magnetic field produced from the NMR from the proton. This happens because the aromatic ring’s electrons produce a current called the aromatic ring current from the electrons spinning perpendicular to the plane of the compound. The spinning of the electrons will then oppose the applied force of the magnetic field being produced from the NMR. Two possible results come from this shielding that takes place. If an aromatic compound is planar deshielding takes place because the proton will be outside of the ring and feel the direct applied magnetic field. If the compound is not planar and has aromatic rings
stacked on top of each other, then shielding will take place. This is because the protons that are located behind the stacked aromatic ring will feel a smaller amount of the magnetic field. The magnetic field is being opposed by the electrons in the overlapping ring and thus causing a shift in the peak.

The following results were derived from Figure 3. The first peak seen affected by the shielding is the peak of proton c. Proton c is shifted up field. In compound (11) the peak is located at around 8.5ppm where as in compound 1 proton c is located up field at about 7.9ppm. This is due to the shielding that the latter receives from the congested stacking of the aromatic ring. Another proton that is shifted up field due to shielding is

\[ \text{Figure 3:} \text{ } \text{H}^1 \text{ NMR spectra and structure of 1,8 diaridynaphthalene is on the bottom and the H}^1 \text{ NMR spectra and structure of 9-bromo-3-(3,5-dimethylphenyl)acridine is on the top. This figure is adapted from Mei et al.}^{14} \]
proton b which in compound 1 is located at 7.0ppm, whereas, in compound 4 the peak is located downfield at 8.0ppm. The final peak that shows a significant affect from shielding is proton a. Proton a is located at 8.5ppm in compound (12). Proton a in compound 1 is located up-field at 6.8ppm. As previously stated all three of these protons are shifted up-field due to the shielding created by the aromatic ring currents that block the magnetic field from the protons that are located behind the aromatic rings.

Next compound (3) was compared to compound (12) to see if similar shifts could be observed during H¹NMR. These shifts can be seen in Figure 4. These same shifts did appear with the between compound compounds (3) and (5). Protons a, b, and c are all shifted up field due to electron shielding from the stacked aromatic rings. The reason
for this shielding as previously stated is the opposed magnetic current that is created by the electrons in the aromatic rings. Proton A for compound (12) is located at 8.4ppm, but in compound (3) proton a is shifted up-field to 6.9ppm. Proton b in compound (12) is located 8.0ppm, but in compound b it is shifted up-field to 7.1ppm. Proton c in compound (12) is located at 9.1ppm and it is located up-field in compound (3) at 8.7ppm. These shifts can be seen in the NMR spectra shown in Figure 4.

X-Ray crystallographic analysis was also done on compounds (1), (2), and (3). The results produced from the crystallographic analysis show how the acridyl ring is affected by the oxidation of one and both nitrogens forming either one or two NO groups on the diacridynaphthalene. The first observation is that when only one nitrogen is oxidized the crystal system of the single oxidized nitrogen was triclinic, while the other two were monoclinic. A triclinic structure has the least amount of symmetry. It has no mirror planes, and only a point of inversion. This is because only one of the nitrogen’s get oxidized, creating an imbalance in the geometry of compound (2). A monoclinic structure is symmetrical. Compounds (1) and (3) remain monoclinic because they maintain a consistent pattern and remained symmetrical. When the compound remains symmetrical it produces tables that can be used to calculate the number of both IR stretches and NMR signals, which help in the study of the electron structure. The symmetrical lattice allows a more desirable location for interactions to take place. The symmetrical lattice also affects the physical properties of the compound.

The results from the crystallographic analysis also showed the splaying angles of the three compounds. The splaying angle is the angle at which the overlapping rings are pitched away from each other. Figure 5 shows an example of what the splaying angle
looks like. The structure of compound (3) had the smallest angle at 5.3 degrees. The structure of compound 1 had the largest splaying angle at 11.6 degrees. Compound (2) had a splaying angle of 8.3 degrees. The reason for the difference in splaying angles is due to the

The x-ray crystallographic analysis also presented data on the lengths of the different bonds. The hydrogen bonding that takes place between the aryl heteroatom of the naphthyl ring and the hydrogens are stabilized by intermolecular forces. These intermolecular forces hold the adjacent structures to each other. The nitrogen is the h-bond acceptor or nucleophile, because it has a lone pair of electrons that can be used to interact with a hydrogen. There are different hydrogen bond lengths between compounds (1), (2), and (3).

Compound (2) had the longest hydrogen to nitrogen bond length of 2.88 angstroms. Compound (1) has a nitrogen hydrogen bond length of 2.60 angstroms. Compound 3 has the shortest hydrogen bond length of 2.55 angstroms. The reason for these different bond lengths is because of the formal charges of the nitrogens and oxygens that are found in each of the structures. Compound (3) has the shortest hydrogen bonding because of two main reasons. The two reasons are the formal charge of the oxygen and the presence of two oxygens pulling on the hydrogens instead of one. Since there are two oxygens in compound 3 both of the lone pairs on the oxygen would be interacting with the hydrogen. The oxygen has a formal negative charge because the nitrogen would a formal positive charge. When the nitrogen is double
bonded with one carbon and single bonded with the other carbon and with the oxygen, all four of its valence electron pairs are being shared leaving nitrogen with a positive charge. This means that the formal charge on the oxygen would be negative. This formal negative charge on the oxygens would hold the positively charged hydrogen very closely. The next smallest hydrogen bond is compound (1). Compound (1) has the second shortest interaction because both nitrogens have partial negative charges on them due to their lone pairs. They are also good nucleophiles because of the lone pairs. This means that they will hold the positively charged protons close. The longest interaction is compound 2 because it has both a nitrogen and an oxygen for the hydrogen to interact with. This, however, forces the hydrogen to choose between the nitrogen and oxygen during the interaction. Therefore, only one interaction takes place instead of two.

![Figure 6: The representation of the hydrogen bonding interaction that takes place between both the oxygen and the nitrogen, + represents formal charges, circled positive and negative signs represent partial charges.](https://example.com/figure6)

**Conclusion**

The synthesis that was discovered to create compound (1) was a success. The desired product was achieved in 68% percent yield which is considered an average yield. The synthesis contains five different steps that involve two cross coupling reactions, addition reactions, and substitution reactions. The cross coupling reactions are the Suzuki and the Stille reactions. All of the reactions produced very good percent
yields in the 90th percentile except for the final Stille coupling. This leads to the first area of improvement and the further research that could be made in this synthesis.

One of the areas I believe should receive further research is to try and improve the Stille coupling reaction. 68% percent yield is not extremely efficient and could be improved upon. If the desired product, compound (1) is to be used regularly and consistently the percent yield must improve. Some possible suggestion for improving the coupling is to add more energy to the reaction. For example, increasing the temperature at which the reaction takes place. Another possible way to improve upon this reaction is to do the reaction with the assistance of micro-wave technology. These are two possible ways to add more energy to the reaction, thus hopefully increasing the percent yield.

The other results that were achieved from the studied research was the ability to create a symmetrical congested compound that has floruosensor capabilities. This is important because these abilities can allow for further study in carboxylic acids, amino acids, aliphatic acids, and arylalkanoic acids. These results also show the presence of π stacking shifts in the NMR spectra and how these shifts can be seen on the spectra. With a continued way of studying and better understanding of π stacking can lead to improvements in studying other structures that have the presence of π stacking such as DNA.

Another conclusion that can be made from the research produced is how the symmetry and formal charges within a complex compound can affect the splaying angle of compound. The splaying angle is the angle at which the overlapping rings lean away
from each other. This is one of the studied structural results that would be more interesting to further study. One could investigate if it is possible to change the splaying angle, as well as, the affects this would have on the compound and its ability as a flourosensor.

Finally, I believe more research needs to be done on the flourosensor and flourosensing titration abilities of the compound (1). Hopefully (1) can be used to help better understand and identify other compounds such as animo acids and DNA. This ability is the purpose of creating compound number (1). So now that a semi-efficient way for synthesizing the desire product has been found, more research in the usefulness of this product needs to be made.
References

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