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Investigation into the Synthesis of Dodecahydro-3a,9a-diazaperylene

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Investigation into the Synthesis of Dodecahydro-3a,9a-diazaperylene

By
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A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of the requirements of the Sally McDonnell Barksdale Honors College

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Abstract:

Dodecahydro-3a,9a-diazaperylene (DHDAP) may serve as a potential donor for use in a donor-sigma-acceptor complex for unimolecular rectification. In order to use DHDAP as a donor, its synthesis must first be studied and altered in such manners as to add a synthetic handle. Other things of important include increasing the yield and better understanding the mechanism by which DHDAP forms. Numerous experiments were conducted in various manners such as testing various solvents among various temperatures to even adding in extra reagents to push the reaction one way or another. In the end the yield of the synthesis was found to improve with the use of a base; however, a synthetic handle is still yet to be tested in order to bind the donor to the complex. Great strides have been made on this synthesis but many more have yet to be taken.
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Andrew Palmer

Introduction:

As electronics improve further and further they also get smaller as well. In order to keep advancing technology, nanoscale electronics are being investigated. In order to do this, single molecules must be able to conduct an electrical current...not only conduct that current, but allow the electricity to pass from a donor (source of extra electrons) through a sigma bridge and into an acceptor (receiver of extra electrons), in order to allow the flow to occur one way but not in the reverse. This is the molecular equivalent of a cathode ray tube, and is known as unimolecular rectification. These donor-sigma-acceptor complexes have been shown to be viable as unimolecular rectifiers in the past thirty years and have been shown to be capable of possible electronic usage.

As part of this research, scientists in labs across the country are working on making parts of these rectifiers. Some scientists work on parts of the acceptor while others work on the donor. Through our research, the possible donor dodecahydro-3a,9a-diazaperylene (DHDAP) was studied. In order for this donor to be viable, it must be able to be produced in large quantities and adequately derivatized in order to add synthetic handles for use in building the entire complex. This donor has served the basis of the current research.
In the literature, DHDAP is synthesized in a one pot reaction. It is synthesized from p-phenylenediamine also known as 1,4-diaminobenzene. The simplicity of the procedure looked promising for the creation of the donor. This gave us hope in the creation of the donor and possible derivatives by following similar procedures. The literature reported yields of approximately 30%, which seems rather low considering none of the compounds is particularly volatile. The first step in understanding the synthesis of this donor was to recreate the literature procedure. The literature procedure involved a simple reflux and a solvent-less reaction that ran for two days under reflux. The procedure was one pot and simple, considering the complexity of adding four propyl groups that bind at two spots each. This reaction was completed, and following the work-up procedure yielded a bright red solid confirmed to be the expected donor compound by NMR. This was done by looking at several peaks. The aromatic peaks disappear as the Fridel-Crafts reaction removes the protons on the aromatic ring along with shifts in the alkyl peaks of the dihalide shifting slightly due to the change from bromine and chlorine to nitrogen and an aromatic ring system. The amount obtained was 0.66 g for a 28% yield of material.

Following this success, different ways to manipulate this synthesis were studied in various ways.

The first thing we tested was the specificity of the halides. The literature used 1-bromo-3-chloropropane, a simple dihalo propane; however, further down the line the compound will
need to have a synthetic handle added such as a carbonyl group or some other form of tag to react specifically as needed. In order to see how much flexibility we will have in introducing those more-complicated molecular portions, we explored the importance of the identity of the halogens by attempting the reaction using 1,3-dibromopropane and 1,3-dichloropropane. Since the literature reaction used the reflux temperature of 1-bromo-3-chloropropane, 140°, in the procedure, both of the new dihalides were also refluxed at their respective boiling points of 120° and 164°. Both of these reactions were allowed to run the same two days as shown in the literature; however, neither reaction turned out as was hoped. The dibromo reaction yielded what appeared to be an intractable black tar that even concentrated sulfuric acid could not dissolve, while the dichloro reaction yielded what seemed to be incomplete reactions with products that were unable to be isolated and purified and ended up decomposing before it was possible to fully identify them.

The p-phenylenediamine and the intermediates produced throughout these reactions are highly reactive due to the ease with which they are oxidized. They go from a faint red to dark blue to almost black indicative of the Wurster's blue of an oxidized diamino aromatic ring. The product DHDAP of these reactions is only stable under ambient conditions once the work up procedure has been performed where it becomes deprotonated and extracted out through ether. Through various experiments where incomplete reactions have occurred, the intermediates formed during these reactions are far more unstable than the starting materials or product. These compounds are so unstable that by hitting a vacuum during a filtration or by means of a rotovap results in nearly immediate oxidation shown by a rapid change of color on filter paper.

One of the other important goals in manipulating this synthesis was to increase the yield of product. The literature paper cites only collecting approximately a 30% yield. It was believed
that it might be possible to improve this yield through the addition of a base. The base would be able to scavenge the excess protons released during this reaction that can slow or even halt the reaction from proceeding as the buildup occurs. Scheme 1 shows Br- acting as the base but bromide is a very poor base, as reflected by the very low pKa of its conjugate acid, HBr. If the halides do not serve as strong enough bases to pull a proton off p-phenylendiamine then the reaction can be slowed or even stopped due to the positive charge found on the nitrogens as shown in scheme two. This leads to the importance of a good base in order to push the reaction forward despite the basicity of bromide and chloride.
One of the first bases tried was simply sodium carbonate. It was believed that the carbonate would be able to scavenge any extra protons and fall out of solution. However, the problem arose that the sodium carbonate would not go into solution. This led to the conclusion that the base had to fill a very tight role: not so nucleophilic as to out-compete the nitrogens of the diaminobenzene, yet strong enough to scavenge protons from it, while also remaining soluble in a solution of the dihalopropane. The solid sodium carbonate also complicated the isolation process as well as with the stirring occurring throughout the reaction. The collected product was lost once the aqueous layer was dried by magnesium sulfate; it may have complexed to the magnesium.
Another base attempted was 2,6-lutidine. The lutidine was stronger in comparison to
the diaminobenzene in competing for protons and, unlike the carbonate, was soluble in the
dihalo propane solvent. Two equivalents were used in order to scavenge the extra protons
produced during this procedure. The reaction was worked up and seemed to produce the
expected results. During isolation, a difficulty arose in the isolation of the product from the
lutidine due to similar basicity. An extraction was attempted in order to draw lutidine into water
from the organic layer. This seemed to work and the isolated product was massed at 0.12 g, or a
44% yield as compared to the 32% yield of the literature paper. Upon researching the pKₐ’s of p-
phenylenediamine, 6.31, and of lutidine, 6.65, it was found that lutidine may not be strong
enough to push the reaction as strongly as was wanted. This led to the search for a stronger
base that is hindered enough to not compete in reaction with the dihalides.

Throughout these experiments other avenues would arise that were of particular
interest. One was the change in the solubility of an intermediate or product as compared to the
starting material, so that a material would separate out of solution as the reaction proceeded in
the form of crystals. These reactions were setup on a 1:1 scale in order to decrease likelihood of
polymerization and for only one ligand to attach. If one ligand could be bound and precipitated
out it would lead to the possibility of attaching one substituent with a synthetic handle and then
allowing the solid synthetic handled included intermediate to be isolated and then reacted to
completion in order to product DHDAP with one synthetic handle in tow. Some of these
reactions were done in an NMR tube in order to attempt to measure the change in the reactants in solution during the reaction to surmise the identity of the crystals; however, this made NMRs more difficult somewhat due to the buildup of solid in the NMR tube. These crystals were collected; however, their instability prevented them from providing X-ray diffraction data, as they broke down slowly over time. These NMR reactions were tried multiple times in and outside of NMR tubes and it was found that the crystal formed in peculiar ways. The crystals from dichloropropane formed more slowly and were a little bit smaller and squarer, while the bromochloro and dibromo crystals formed faster. The crystal structures of these compounds could prove invaluable if X-rays diffraction can be achieved. The structures could have ranged from any number of intermediates produced during this reaction. It was the hope that the crystals would primarily consist of diaminobenzene with a single dihalo substituent attached, that is, compound 2 in Scheme 1, especially when no excess of dihalopropane was used.

One of the things that was peculiar in the literature procedure was the lack of a solvent. In fact, the dihalide would serve as a solvent since it was used on a scale of 50:1 excess compared to the diaminobenzene. Various solvents were attempted through numerous experiments, ranging from acetonitrile to toluene to dichloromethane, in an attempt to decrease the amount of dihalopropane needed, since this would eventually need to be a rare compound incorporating a third synthetic handle. It was found that any useful solvent needed to have a high boiling point in order to be able to allow the reaction to be heated to induce the closing of the propyl rings. The reactivity of the halides varies, which is believed to be an important factor making bromochloro the most effective dihalopropane. Since bromine is a better leaving group than chlorine, it is selectively involved during the first step of the reaction with the nucleophilic attack of the nitrogen. The chlorines then react in the second, Friedel Crafts stage, where the new rings fuse onto the aromatic ring by electrophilic aromatic
substitution reactions. Through the lower reactivity of the chlorines, it is believed that the chance of polymerization is reduced, since the chlorines remaining after the amine alkylation stage are less likely to be further alkylated.
Throughout the study, the solvents had to be degassed in order to allow the reaction to proceed with minimal oxidation side reactions. This was done by bubbling nitrogen through the solvents over the course of several minutes in order to try to remove any dissolved gases. Reactions involving undegassed acetonitrile were found to decompose in the course of a few days, which underscored the importance of degassing the solvents.

One of the last things tried with the synthesis was the use of silver salts. It is believed that the silver salts might serve as a way to encourage the second step of the reaction involving the aromatic ring attacking the second halide on the propyl groups. Complexation with silver would increase the reactivity of the chloride groups and make them more susceptible to nucleophilic attack by the pi system of the aromatic ring. Difficulties arose during this reaction concerning the color of the solid silver sulfate changing from white to black, possibly indicating oxidation or polymerization.

Reactions were also attempted in the ball-milling machine, a machine that promotes solventless reactions by rapidly mixing reagents in stainless steel cylinders. While the apparatus might prove invaluable in other experiments, the activation energy of the reaction appeared to be too high for the ball miller to break through after an hour of mixing. This is likely partially due to the liquid nature of the dihalides and the high activation energy of the reaction. A reaction was set up in the ball miller and allowed to run for an hour, only to find the starting materials in a slush-like manner in the vessels.

In the future, several other experiments are hoped to be pursued. These reactions include trying tosylate leaving groups in place of halides. This might allow an alternate way to synthesize DHDAP analogs, based on diols rather than dihalides. One possible way to introduce a synthetic handle would be to involving the use of 1,3-dihaloacetone; the ketone carbonyl in
the middle may serve as a synthetic handle for use in manipulation when creating the complete donor-sigma-acceptor complex. Because the reaction was ineffective with dichloropropane, the readily available dichloroacetone would probably not work; bromochloroacetone would be a better bet, but is not readily available. Difficulties may arise with the presence of the carbonyl group interfering with the reaction, so another reaction to attempt would also consist of a protecting the carbonyl on the dihaloacetone as a ketal.

**Experimental:**

Improved Synthesis of **Dodecahydro-3a,9a-diazaperylene**

Following a similar procedure to the literature, 0.1 g of p-phenylenediamine was combined with 5 mL of 1-bromo-3-chloropropane. This solution was heated under reflux for twenty-four hours at which time two equivalents, 0.215 mL, of 2,6-lutidine were added. The solution was then allowed to reflux for another twenty-four hours. In order to isolate the product, the product and lutidine were protonated and extracted into aqueous acid while the dihalopropane was removed in the organic, diethylether layer. Once both salts were moved into the aqueous layer, the product was then extracted into organic layer with aqueous base leaving the lutidine in the aqueous layer. The product was massed at 0.12 g or a 42% yield.

**Results and Discussion**

Beginning with the replication of the literature procedure, it was followed exactly and managed to produce a red solid. The product was massed at 0.66 g and would correlate with a 29% yield of the protonated salt. This yield was on par with that of the literature, citing a 30% yield.
Following this success, we tested the specificity of the dihalide. The experiments that followed involved both 1,3-dibromopropane and 1,3-dichloropropane under different conditions.

The literature procedure used the boiling point of 1-bromo-3-chloropropane to set the temperature for the reaction to occur. The reaction involving 1,3-dibromopropane was run at 166°C as compared to 144°C of the literature. Following a similar approach, the 1,3-dibromopropane was set up and allowed to reflux; however, this reaction diverged from the expected results. The reaction turned a darker brownish red as it reacted over the first twenty-four hours; however, at the forty-eight hour mark, it was found to consist of a black tar residue. This residue showed numerous unexpected products on TLC.

Following this result, the reaction was run again using the same small scale, but this time the temperature was only raised to 140°C to resemble that of refluxing 1-bromo-3-chloropropane. This solution was allowed to react for two days, at which time TLCs were taken. TLC or Thin Layer chromatography is a technique to separate compounds based on their solubility in a solvent and their interaction with a stationary phase. Silica plates were used that slowed down compounds with higher polarity. These showed the reaction was occurring; however, the product was incompletely formed. The reaction was heated again and allowed to react for another two days. During this reaction the nitrogen tank ran out and this may have resulted in the product becoming a black tar. This product was intractable into any solvent, and would not even dissolve in concentrated sulfuric acid.

These results were less than ideal and led to an investigation into the reaction of the bromochloro dihalide. We attempted to moderate the course of the reaction by employing a solvent. A reaction was set up consisting of p-phenylenediamine dissolved in ethanol and added
dropwise to a solution of 1-bromo-3-chloropropane dissolved in ethanol. This solution was heated, but started to turn black throughout the addition. The reaction was stopped and analyzed by TLC; the solution containing starting material, intermediates, and even some product. The reaction was heated for a week in order to allow the reaction to push the creation of the product. After this week, though, the solution had turned black and was intractable in any solvent.

In another attempt to synthesize the donor using 1,3-dibromopropane, the procedure was repeated following a heating temperature of 165°C. Following the reaction, the product was collected by vacuum filtration and the filtrate was rotovapped, a process by which solvents are removed through a combination of vacuum and heating. The solid product was massed at 0.252 g and then analyzed by NMR and found to contain no aromatic peaks, but more aliphatic peaks than what is expected in the product. Purification of the product was then attempted by column chromatography, but the fractions were TLCed to find no product remained.

Another solvent under investigation that would allow a higher reaction temperature was xylenes. A reaction was set up using bromochloropropane and heated to the boiling point of xylenes, around 145°C. It was observed that a whitish solid was rapidly produced during the first few minutes of the reaction as it heated up to reflux. Some of this solid was collected after twenty-four hours and did not dissolve in deuterated methanol but did dissolve in deuterated water. Believing the solid to be protonated intermediates, six equivalents of 2,6-lutadine were added in hopes to scavenge the extra protons. The reaction was allowed to continue for twenty-four hours at which point a black solid was found in solution. Rotary evaporation was attempted in order to remove the xylenes; however, the rotovap was not strong enough to remove it. The black solid was filtered and massed to be 0.174g; however, this product was unidentifiable but could constitute a 69.6% yield if it were product.
In another attempt, 1,3-dichloropropane was reacted with p-phenylenediamine. The reaction was heated to 120° to allow the reaction to reflux gently. The reaction was allowed to run for forty-eight hours at which point a solid was collected and washed with diethyl ether. The ether made the filter paper turn blue which is believed to be caused by the presence of peroxides causing the product to oxidize on the filter paper in order to produce the Wurster's blue. The collected solid was found to be intractable in any solvent. Sulfuric acid seemed to dissolve it somewhat, so an NMR was attempted by somewhat dissolving the solid in deuterated water with four drops of sulfuric acid; however, the sulfuric overpowered the sample and the machine was unable to successfully lock onto the sample. The filtrate from the vacuum filtration was also analyzed. A TLC was taken that gave hope and the filtrate was then analyzed by NMR, but it showed no signs of product.

Another solvent attempt was dichloromethane. A reaction was setup allowing 1-brom-3-chloropropane to react at room temperature in DCM. After a day, the solution was heated to a gentle reflux. NMR shows starting material in solution. Dichloromethane was rotovapped off and toluene was added and heated to 60°C. With no noticeable change after another day the solution was heated to 90°C. After another day, solid had formed in the flask; however, TLC showed starting materials still present, so it was allowed to heat for another two days to encourage formation of more product. Solid that had formed was vacuum filtrated and an NMR was attempted; however, the solid would not dissolve in any NMR solvents.

Dichloropropane was reattempted using the literature procedure. After two days an NMR was taken that led to the belief that the tetra alkylated compound had not closed the rings through the Friedel Crafts reaction. After rotovapping, 0.28 g of product were collected that would correlate with a 55% yield; however, this product was impure and recrystallization was attempted. The recrystallization failed using the solvents ethanol, chloroform and ethyl acetate.
A reaction was attempted using 1-bromo-3-chloropropane and the base sodium bicarbonate. Using ten equivalents of sodium bicarbonate the reaction was allowed to react for seventy two hours at which time the solid was extracted using aqueous base and diethyl ether; however, the product was lost due to an attempt to dry the aqueous layer with the product still within. The product was unable to be recovered at this point.

Lutidine was believed to be a more suitable base for use in these reactions. 2,6-Lutidine should be stronger in relation with sodium bicarbonate and should also be more soluble in solutions such as 1-bromo-3-chloropropane. The reaction was allowed to reflux at 144°C for twenty-four hours before two equivalents of 2,6-lutidine were added. After another twenty-four hours, an NMR was taken showing the presence of product and protonated 2,6-lutidine. The product was isolated by extracting the product into diethyl ether and separating the lutidine into the aqueous layer with sodium hydroxide. A mass of 0.26 g of solid was collected and purified by this extraction to 0.12 g, which correlates to a 45% yield.

One reaction was attempted using 1,3-dibromopropane at a lower temperature. In order to study the effects of heat and refluxing the reaction, a solution of dibromopropane was heated to 128°, corresponding to the reflux temperature for dichloropropane. This reaction lead to the formation of a product and NMR led to the assumption of the tetrabromo compound. The mass was found to be 0.462 g and would lead to a 54% crude yield. The compound; however, appeared to have broken down before purification could occur.

Another path that opened up with our research was the possibility of attaching one group at a time, in order to be able to attach synthetic handles later. This was believed to be possible due to the charged accumulation in the first step of the reaction. If the starting material held the charge and fell out of solution when the first group became bound, then it might be
possible; however, difficulties would arise if unreacted starting material picked up this charge and fell out of solution instead. The reaction was carried out in toluene, a solvent that would likely cause precipitation of the charged product, and an equivalent of acetic acid was added in order to further increase the charge; however, while solid did precipitate out of solution, it was found that the solid was acetic acid.

Several reactions were attempted using an NMR tube. By doing these reactions in NMR tubes it would allow the changes to be measured without having to take aliquots out of the reaction mixture. Aceonitrile was used as the solvent; however, solid crystals precipitated out on the side of the NMR tube over the course of several days. This was observed for not only 1-bromo-3-chloropropane but also dichloro and dibromo propanes. It was found that the dibromo and the bromochloro produced crystals faster than dichloro. Crystals were isolated in hopes of obtaining X-ray diffraction; however, the crystals broke down over time and became unstudyable.

Conclusion:

Much has been learned about the reaction of p-phenyldiamine and dihalo propanes in order to produce DHDAP. Through the addition of a base it is possible to encourage the reaction by scavenging protons that hinder the ability of p-phenyldiamine to react. Various bases were tried and it has been learned that the base must not only be strong enough to scavenge protons from p-phenyldiamine, but also be soluble in solvents such as the dihalopropanes, and not so nucleophilic as to out-compete the diamine. This makes an appropriate base somewhat difficult to find due to so many constraints. It is believed though
that with the appropriate base the yield of this synthesis may be pushed to higher and higher yields.

Another hope for the future is the addition of a synthetic handle to the synthesis. The handle is somewhat complicated due to the possibility of side reactions on top of the reactivity of the first step in the reaction. It is believed that the Sn2 reaction involving nucleophilic attack of the nitrogens is rather quick in comparison to the closing of the rings by the nucleophilic attack of the aromatic ring.
Supplementary Materials: