Three-State Biaryl Lactone Molecular Switches with Amine Donors

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Abstract

This project is focused on the synthesis of four bridged biphenyl molecules with amine donors. These three-state biphenyl molecules, due to their chemical properties, will find applications as nanoscale fluorescent sensors and molecular mechanical devices. Biphenyl molecules have known dihedral angles, leading to differing optical and conducting properties when manipulated. By using a lactone-bridge we can force the molecule into and out of planarity; at low pH the molecule takes a planar conformation ("ON"), while at high pH it's non-planar ("OFF"). Research from previous groups has shown similar two-state molecules' effectiveness at readily switching conformations when exposed to different chemical environments. We are researching the addition of diethylamine and diphenylamine donor groups. By combining previously used cyano and nitro acceptors and differing amino donors within biphenyl molecules, we can enhance optical properties and pH sensitivity. This pH sensitivity will be more precise with the addition of a third "OFF" state of the molecule. At low pH, the amino group should become protonated, leading to the second "OFF" state and giving the molecule a narrow "ON" state. The "ON" state would result in heightened visible color differences than the "OFF" state of the molecule. These characteristics would improve the usefulness of these molecules as pH sensors. Two of the target molecules, one molecule being the cyano acceptor group with diethylamine donor group and the other molecule having a nitro acceptor group and diethylamine donor group, have been successfully synthesized.

Introduction

Molecular switches, which are molecules that have the ability to reversibly switch between two geometrically distinct states when exposed to outside stimuli, have recently become a popular area of study over the last few years. Due to this new interest, the possible uses for molecular switches has widely grown. The known applications for these molecular switches includes nanotechnology, biomedicine, and the design of computer chips.[1] As stated, molecular switches have the ability to reversibly switch between states and the applications rely on the controllable switching of the molecule when exposed to stimuli.[2] These outside stimuli can take the form of electrical current, light, magnetic fields, biological impulses, or acid-base chemistry.
Our research group is interested in the biphenyl molecule and its ability to switch between a planar and non-planar state. The choice of this structure for our research stems from the dihedral angle of the aryl-aryl bond while in the planar state, which results in intermolecular

charge transfer due to the high degree of pi-orbital overlapping. Controlling the geometry of the biphenyl molecule will also allow us control of its inherent properties[3], like electronic excitation, emissions, non-linear optics, conductance,[4] and fluorescence.[5]

It has already been experimentally determined that the biphenyl conformation occurs with a twist angle of 30-40°.[6] This angle of 30-40° reflects the steric hindrance of the hydrogens on each ring, opposing one another, and the electronic communication due to the molecule's planar system. The molecule is unable to be perfectly planar due to the hydrogens, but the electronic communication is favorable. This slight angle allows for a middle-ground, by allowing the greatest possible conjugation and relatively low steric hindrance. The dependence on angle regarding electronic communication allows the possibility of manipulation, where we control the optical properties by simply changing the angle.

The biphenyl molecule by itself cannot be controlled conformationally, meaning it would not serve as a molecular switch. By using a derivative of this biphenyl molecule, we should be able to control the angle, which would make it a candidate for a molecular switch. The different angles of the molecule, otherwise referred to as states, would result in differences of conductance and fluorescence.

Previous work conducted by the Dahl research group resulted in the molecular switch observed in Figure 1.[4] The control over the biphenyl angle stems from the lactone bridge connecting the rings, which can be cleaved and reformed by adding acid or base. The bridge, once formed, forced the molecule into a planar conformation. This planarity allows the greatest electronic communication due to pi-orbital overlapping.[7] Once the bridge is cleaved, the molecule succumbs to the steric hindrance of the hydrogens, allowing the rings to revert to its non-planar state. This structure, a biphenyl molecule connected by a lactone bridge, is a blank slate in regard to what groups we could add on. The acceptor and donor groups are of interest to enhance the optical properties of the molecule, which would make it more valuable as a molecular switch.

Figure 1

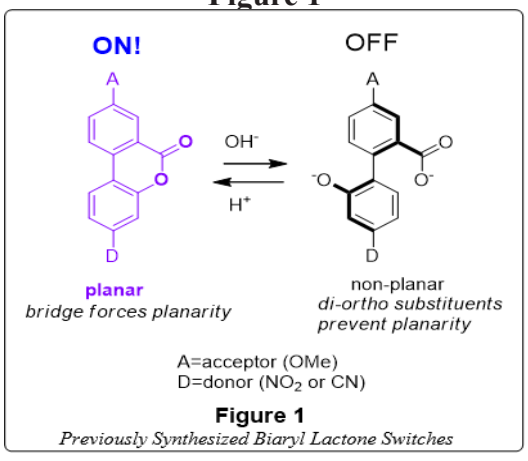
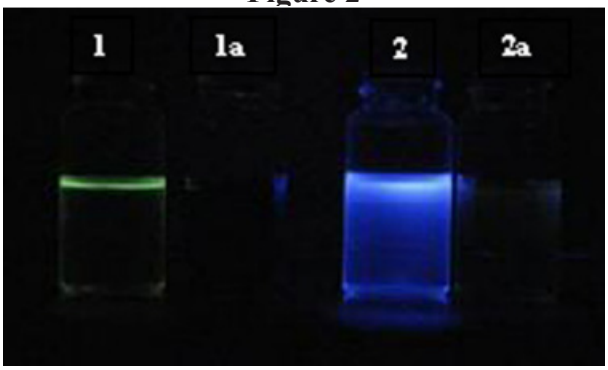


Figure 1
Previously Synthesized Biaryl Lactone Switches

The molecule in Figure 1 is considered a two-state molecular switch, where the molecule has one "ON" state and one "OFF" state. The "ON" state is where the lactone bridge is formed and the rotation, or angle, of the biphenyl molecule is restricted. This hindrance results in a loss of energy compared to the angled version of this molecule. The energy being lost is observed as

light being emitted and the wavelength of light is within the UV region of the spectrum. Figure 2 is an example of the previous switches synthesized,[4] where 1 and 2 are the "ON" state and 1a and 2a are the molecule once the lactone bridge has been cleaved.

Figure 2



The two-state switches mentioned were synthesized in multiple separate reactionary steps. The starting material chosen was 2-bromobenzoic acid, which was nitrated and esterified. A Suzuki reaction and lactonization were then performed to create the biphenyl structure and close the lactone bridge. This is a relatively easy synthesis, which can theoretically be modified to produce alternative switches.

Knowing that the biphenyl molecule combined with the lactone bridge could be synthesized and reversibly controlled when exposed to acid of base, our research project aimed to expand on the structure and optical properties. By changing the acceptor and donor groups located at the top and bottom of the biphenyl rings, it was proposed that a three-state switch would be possible. This three-state switching has been performed by other successfully synthesized, albeit larger conjugated molecules, where they observed two "ON" states and one "OFF" state.[8] This proposed change to the skeleton and properties of the molecule would make it a much more effective and useful as a molecular switch.

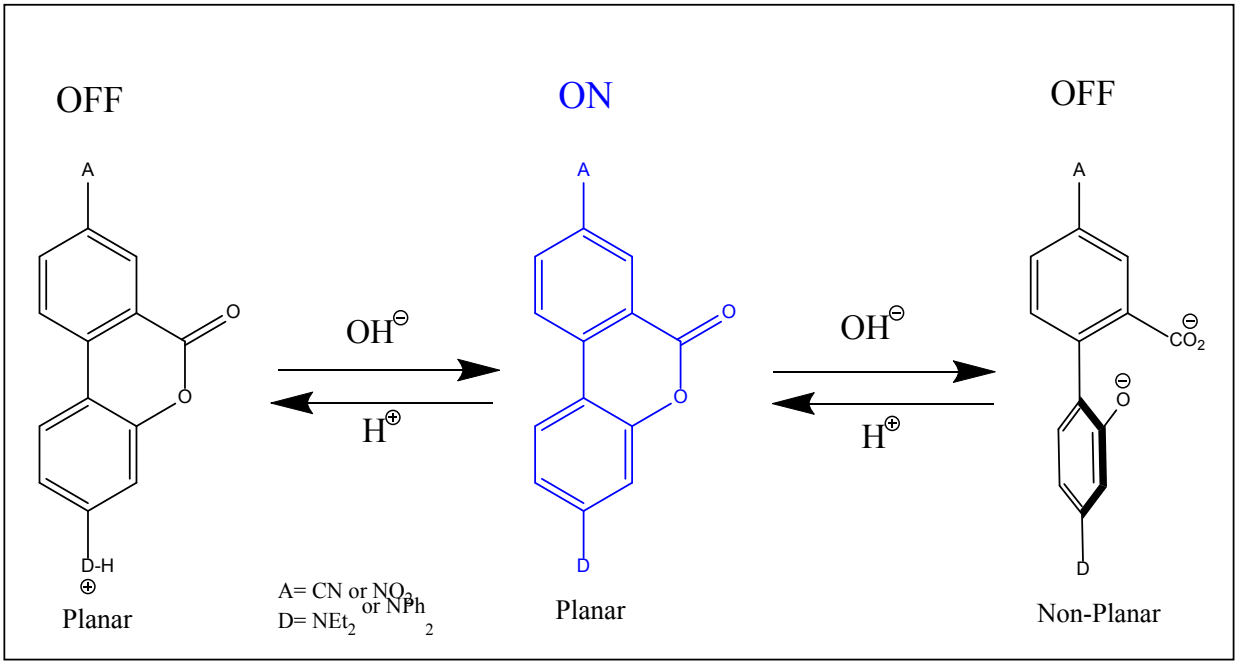
The alternative donor and acceptor groups of this molecule had to be carefully chosen in order to achieve the three-state nature of our molecules. We proposed four new three-state molecular switches with two sets of donors and acceptors combined. Initially, the donor groups of diphenylamine and dimethylamine were chosen due to their increased intermolecular charge transfer through the rings and higher basicity. Dimethylamine was later changed to diethylamine due to greater yields during synthesis, however diethylamine still serves as a very strong donor group compared to the previous two-state switch's methoxy donor. The strength of the donor group and increased intermolecular charge transfer should correlate with the optical properties observed with the final molecules. The addition of an amine group to the molecule also allows the possibility of a third state.

The acceptor groups for the molecular switches were also chosen to alter the optical properties. The groups chosen were the nitrile and nitro acceptors. Theoretically, the nitro group should afford more color within the molecule, but it does have the ability to quench the fluorescence. So, these molecules should not be as bright. The nitrile group should be very fluorescent once synthesized but they would not be as colorful as the nitro switches. Once the donor group,

acceptor group, biphenyl rings, and lactone bridge are brought together, we should have a three-state "OFF"-"ON"-"OFF" switch. This designation shows that there is only one optically interesting state, which will increase the precision of the switch.

The "OFF"-"ON"-"OFF" states of the molecule are allowed because of the addition of the amine group onto the molecule, whether it be diethylamine or diphenylamine. The "ON" state is where the lactone bridge is intact, and the amine group is unprotonated. By adding acid to this state, we were able to protonate the amine group, causing the intermolecular charge transfer of the molecule to be stopped. This, in turn, stops the fluorescence. If we add base to the "ON" state of the molecules, we cleave the lactone bridge. This allows the structure to adopt a non-planar conformation. Since the molecule is non-planar, there is no pi-bonding between the rings. This also stops the fluorescence and leads to the second "OFF" state.

Figure 3



As mentioned, the usefulness of these switches would be increased once the third state is achieved. Two-state molecular switches often find uses in more basic nanotechnology devices, whereas a reversibly switching three-state molecule could have more in-depth nanotechnology uses. These potential applications could include molecular wires, molecular conductance switches, potentiometers, molecular logic devices, and more.

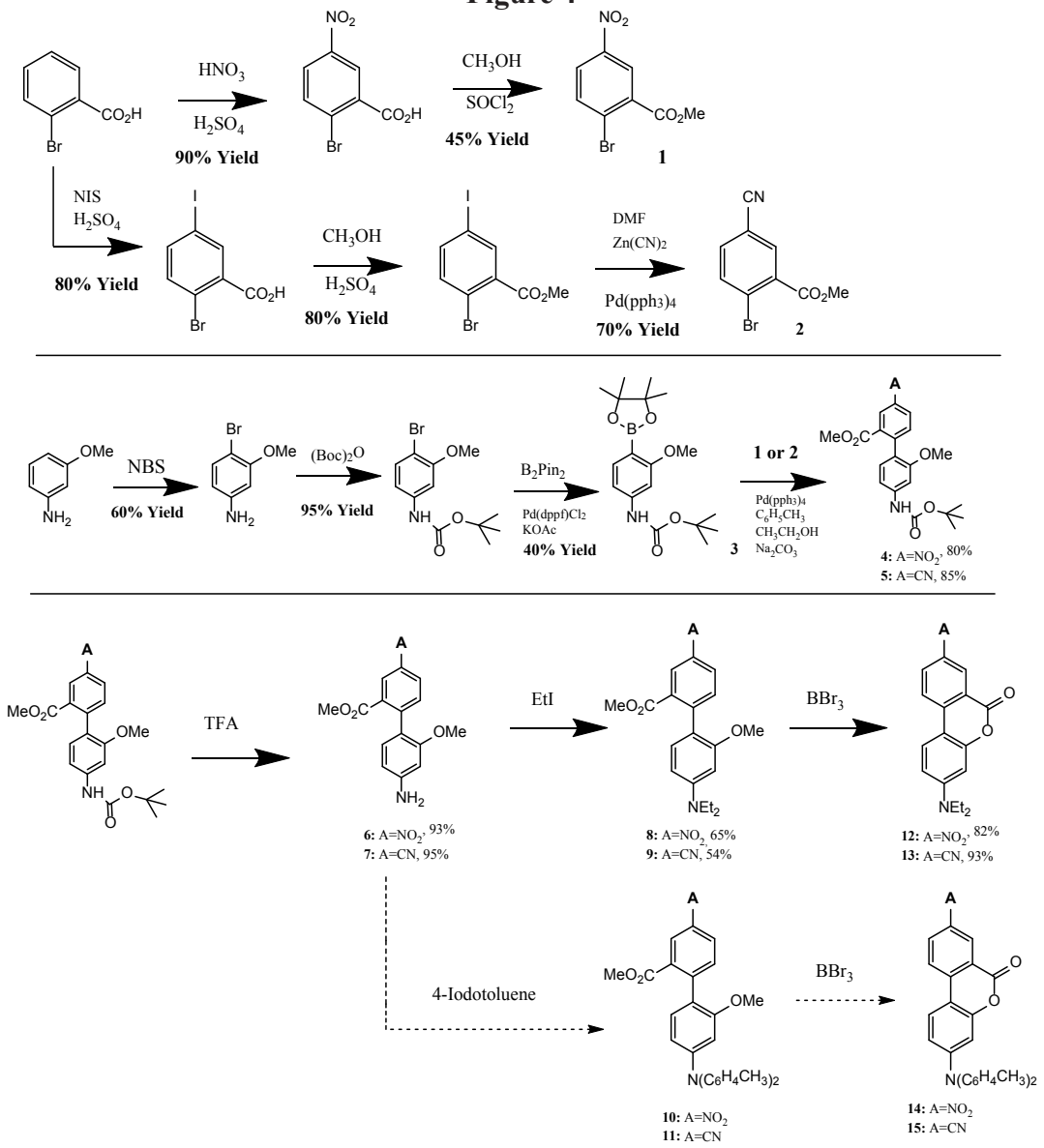
Experimental Synthesis

Overall Synthesis

The synthesis of our molecular switches involves two different reaction paths to synthesize the top and bottom phenyl rings, which later get coupled via a Suzuki reaction. The complete synthesis diagram of our research can be seen in Figure 4. Each arrow represents a separate

reaction, most of which are air sensitive and run overnight. Take note that the reactions with a complete black arrow are those that our group has successfully synthesized, while the dotted arrows are those that we are still working on. The percentage underneath each arrow shows the percent yield of the reaction, which is how much product we obtained versus how much we expected based on starting materials.

Figure 4



Reactions in synthesis work are trial and error, wherein we find a reaction with a similar end product and customize their procedure to suit our reactants. Reactions are often done multiple times with slightly different conditions or completely new procedures. Molecule 3 for example was first attempted via a borylation reaction with the simple amine molecule. This reaction route resulted in protodeboronation, where the molecule forms and then immediately decomposes. By adding a protecting group, seen at the bottom end of molecule 3, were able to find a workaround

for this difficulty and successfully couple the top and bottom phenyl rings.

Each reaction has a procedure that indicates how much of each reactant is used and how to set up the reaction. An example of the procedure for molecule 2 on Figure 4 can be found below, along with the characterization information used to identify the compound.

Methyl-2-bromo-5-cyanobenzoate: Methyl-2-bromo-5-iodobenzoate (2.77g, 8.13 mmol) was dissolved in 40 mL of DMF and sparged with Ar for 15 min. $Pd(pph_3)_4$ (0.520 g, 0.450 mmol) and $Zn(CN)_2$ (1.07 g, 9.15 mmol) were added, and the mixture was heated at 70°C and refluxed under Ar for 16 h. The reaction was cooled to room temperature and then diluted with H_2O. The reaction was extracted 3x with 100 mL of Et_2O. The combined organics were washed 3x with 25 mL of brine, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified with column chromatography (20% EtOAc in hexane) to achieve a white powder (1.52g, 78%). 1H NMR (400 MHz, $CDCl_3$) δ 8.1 (d, J = 1.7 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.6 (dd, J = 8.2 Hz, J = 1.8 Hz, 1H), 3.98 (s, 3H).

We successfully synthesized two of the four molecular switches thus far as indicated within the synthesis diagram. The nitrile-diethylamine switch and the nitro-diethylamine switch. In total, these molecules required 7-8 separate reactions for completion. The restricting factor on synthesis within our plan is the borylation reaction, resulting in molecule 3. The yield on this reaction ranges from 25% to 40%, which requires significant time to prepare the precursor molecules with high enough quantity to produce this molecule.

Flash Chromatography

After a reaction has been completed or run for an adequate amount of time, collection, and purification of the product of interest is necessary. After completion, we have a solution containing multiple solvent, starting materials, intermediate products, and presumably the intended product. To separate these components, flash column chromatography is conducted. Flash chromatography is a variant of regular column chromatography, which separates molecules based on the polarity of their structure. This alternative utilizes air pressure to separate components rapidly and is very common within organic chemistry.

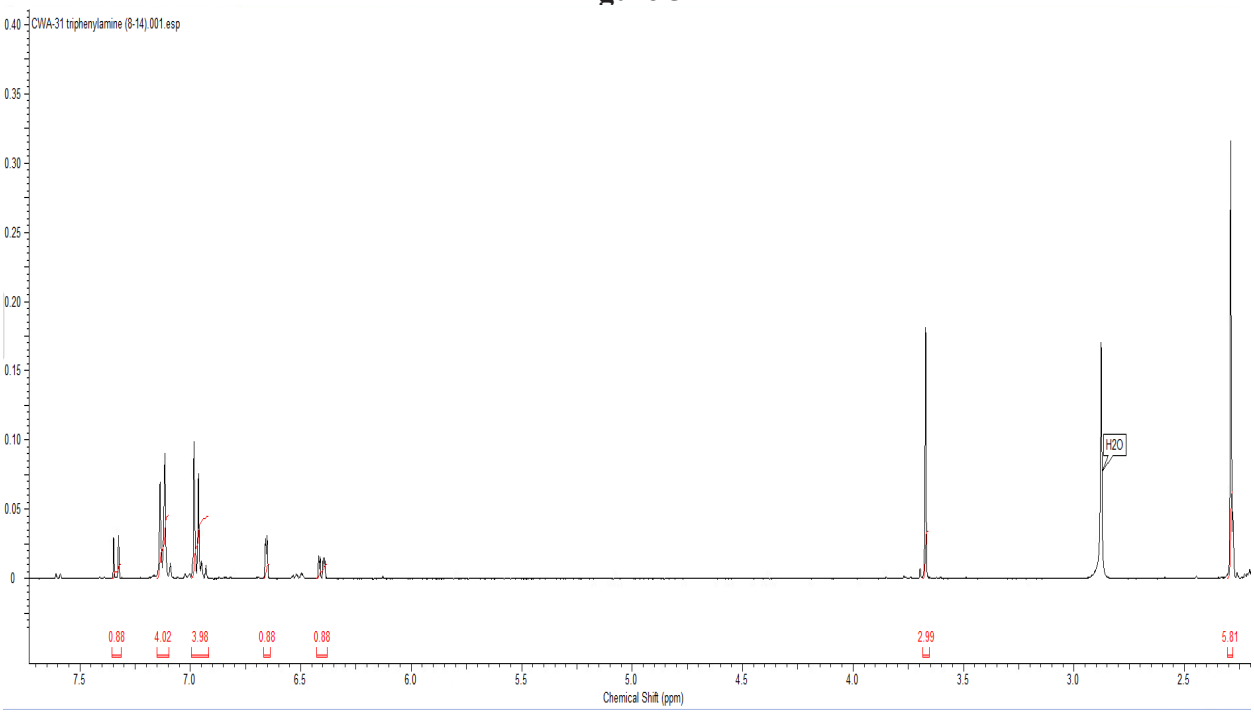
The separation of components is based on the polarity of the molecules. Polarity stems from the bonded atoms sharing electrons unequally. Due to the electronegativity of an atom, it might have a stronger pull on the electrons. This unequal sharing results in partial dipoles throughout a molecule. The overall dipole moment of the molecule will explain the polarity. A flash column contains two components, the moving phase and the stationary phase. Depending on the polarity of the molecule, it will either be more attracted to the moving phase and move quickly through the column, or it will be more attracted to the stationary phase and move slowly through the column.

By examining our theoretical products, we are often able to predict the relative polarity of the molecule and when it should come through the column, allowing for collection and ultimate purification. Excluding very few of the reactions within our synthesis diagram, the majority of the reactions require column separation after completion. This separation not only allows us to collect our intended product, but also any starting materials for repurpose. It is also possible to collect any alternate products collected in order to analyze them and determine what went wrong with the reaction or what could be improved overall.

NMR Spectroscopy

Nuclear magnetic resonance spectroscopy is a widely used tool within chemistry. Although this type of spectroscopy is mainly utilized by organic chemists and biochemists, it is applicable to any molecule that has nuclei with spinning states. NMR observes the spin states of the nuclei in relation to the magnetic field generated. The data given by a NMR is in the form of chemical shifts. To interpret the chemical shift of your subject, there are several different components to consider that would affect the shift on your spectra. Bonding to an electronegative group and hydrogen bonding are aspects of your molecule that could change the location of the signal on your spectra.

Figure 5



NMR spectroscopy is the quickest way for our group to identify a potential product, compare to ensure we have the same product, or determine purity of the product. The specific form of NMR used within this research is proton NMR where we focus on the hydrogens residing mainly on the biphenyl rings. An example of a typical NMR can be seen in Figure 5. Depending on the location of the protons, we expect to see them in certain ranges within the NMR. For example, Figure 5 shows the aromatic region of the NMR at the left of the spectra. This region is named due to the protons found in the region generally being located on an aromatic ring, like the rings found within our molecular switches. One example of a common impurity within a sample can be seen at around 2.7 ppm, which signifies the region where water is found. Samples can collect water through the air, so being able to detect this impurity via NMR is very important.

X-Ray Diffraction

The successful synthesis of the final molecular switches was determined initially via

NMR spectroscopy. Due to the importance and ultimate nature of these molecules, further characterization was done in the form of X-ray diffraction. This is a technique used to determine a sample's crystalline structure. Based on chemical concepts, this technique essentially draws your molecule for you. This allows a researcher to confirm the overall structure of their sample. The limiting factor with this analysis is that you must have crystals of the compound you wish to study. After collection and purification of our compounds, the samples are in the form of a powder. Crystallization of the final two compounds needed to be done using different methods. To obtain the crystal of the nitro-diethylamine compound, the compound was dissolved in dichloromethane and allowed to slowly evaporate into the air at room temperature. This easy process afforded large red crystals, which were given to a fellow professor at our college to identify.

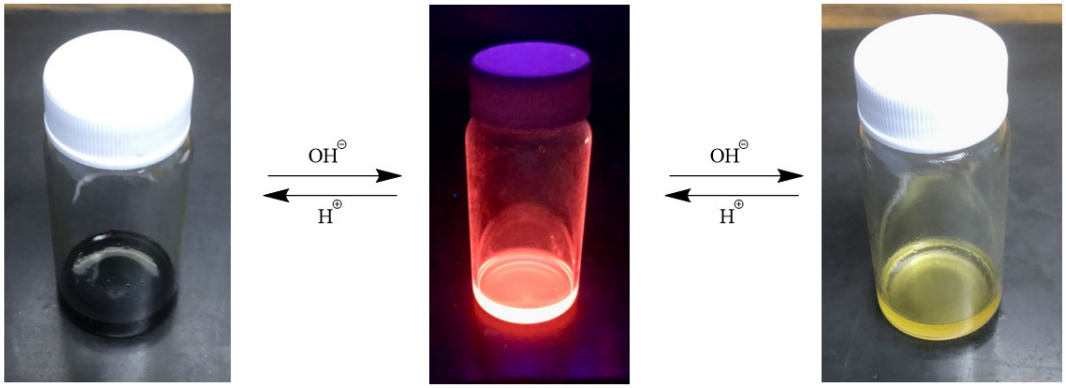
The process to obtain crystals for the nitrile-diethylamine compound was more rigorous. Slow evaporation of this compound resulted in a film rather than crystals, which does not work for X-ray diffraction. Instead, the technique of vapor diffusion was used. For this process, a small amount of compound was placed in a small vial which was combined with a solvent it could dissolve in. This smaller vial is put within a larger vial containing solvent that the product is insoluble in. The combined vials were then put in a cold environment where the outer solvent was allowed to evaporate and enter the smaller vial. Since the molecule is insoluble with the outer solvent, it is very slowly forced out of the solution. This ultimately results in crystals forming on the inside of the smaller vial. The yellow/orange crystals obtained were still difficult to analyze and had to be sent out of state for analysis.

Results and Discussion

Nitro-Diethylamine Switch

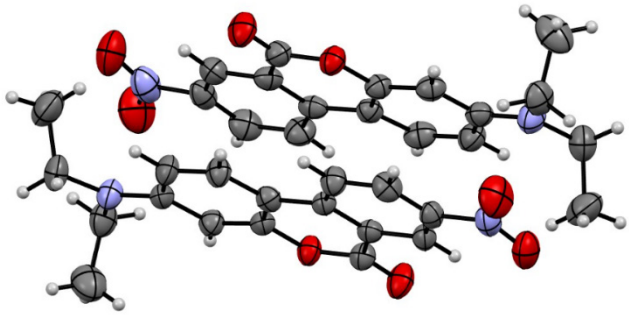
The first switch obtained during this research was the nitro-diethylamine switch, which was promptly tested for the switching capabilities. This compound can be seen in Figure 4, molecule 12. Initial tests for pH driven conformational change were done on a small scale in the laboratory. This compound is red as a powder and it orange once dissolved in a solvent such as dichloromethane. Under a UV lamp, the solution fluoresces a bright orange color. The switching of this molecule can be seen in Figure 6. This diagram has the same overall format as Figure 3 in the molecule having the amine group protonated, unprotonated, and lactone bridge cleaved. The OH^- above the arrows designates a base being added to the solution and the H^+ shows acid being added. The arrows going opposite directions in the diagram also shows the reversibility of the switching.

Figure 6



X-ray diffraction of this molecule, as mentioned above, was done with the help of another professor, Dr. Gerlach from UWEC, and can be seen in Figure 7. The first thing obtained from this image was the basic structure of the molecule, to see if we had what we thought we had based on NMR analysis. The optical properties of this compound rely on the planarity of the molecule and this X-ray image confirmed the molecule was very planar. We also learned that there are two unique molecules in the unit cell of this crystal. This relates to how the distinct molecules form with each other in the crystal.

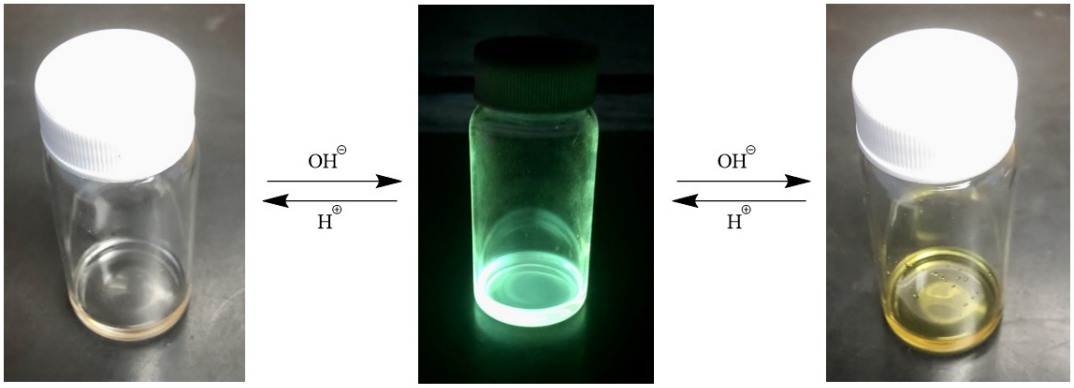
Figure 7



Nitrile-Diethylamine Switch

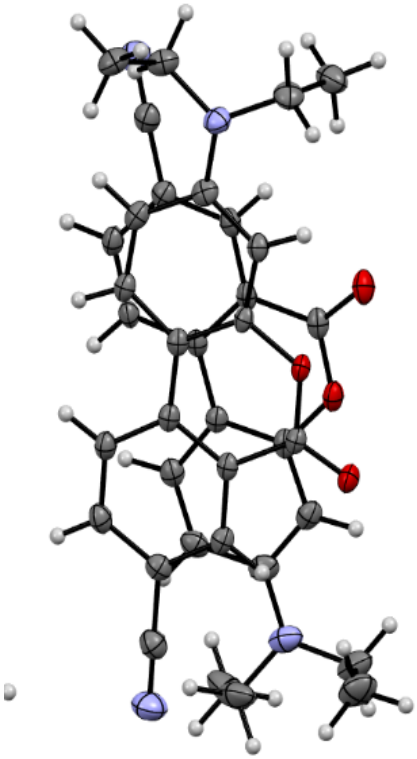
The second switch obtained in this research was the nitrile-diethylamine switch. This compound can be seen in Figure 4, molecule 12. Like the nitro switch, this compound was also tested on a small scale for its switching capabilities. This switching can be seen in Figure 8. As expected, this compound was visibly brighter than the nitro due to the quenching capabilities of the nitro group.

Figure 8



The X-ray image was also able to give some information about the difficulty behind crystallization and X-ray analysis. The crystals for this molecule are merohedrally twinned. In general, when a crystal is twinned, its diffraction pattern is altered. This complicates the structure determination, hence the reason the crystal was sent out of state for analysis. The planarity of the image was also measured to be around 178°. A perfectly planar molecule would have a dihedral angle of 180°, so this molecule is very planar like the nitro switch. This crystal differed from the nitro switch in that the unit cell contains three unique molecules.

Figure 9



Newly Synthesized Precursor Molecules

Throughout our synthesis, we utilized many known compounds. The unnumbered compounds

in Figure 4 are the known compounds used in our synthesis plan. These previously known compounds were easier to synthesize and identify due to chemical literature available. In addition to the replication or known compounds, our group also had to create completely new compounds that have never been synthesized in the past. The completely new compounds are those that are numbered within Figure 4. Including the two final switches, we were able to create a total of nine new compounds. All nine of these compounds must be purified further and characterized by proton NMR, carbon NMR, melting point tests, IR spectra, and mass spectra in order to publish our results.

Other Two Molecular Switches

The remaining switches yet to be completed, the nitro-diphenylamine and nitrile-diphenylamine, have been postponed due to time constraints and difficulties with synthesis. A recent experiment indicated that molecule 11 was successfully synthesized, in an unknown amount but lost during the flash column. Our group theorized that our compounds have a very low sensitivity on the detector. Therefore, instead of collecting the product the machine dumped them into the waste container. The Dahl research group may continue the attempts to synthesize these remaining switches in the future.

Conclusion

We have conducted experimental organic synthesis to produce several new three-state "OFF"-"ON"-"OFF" molecular switches containing an acceptor group, donor group, and lactone bridge situated on a biphenyl skeleton. Two of the ultimate switches were successfully synthesized and shown to have switching capabilities. The newly synthesized seven precursor molecules, along with the two final switches will be further categorized with UV-vis, fluorescence spectroscopy, melting points, carbon NMR analysis, melting points, and mass spectroscopy. The success of this research provides a deeper understanding of the range of molecular switches as well as the future work possible with the biphenyl structure.

References

[1] Safarpour, M. A.; Hasemianzadeh, S. M.; Kasaeian, A. *J Mol Model* **2008**, *14*, 315-323.

[2] **a**. Feringa, B. L., Ed.; Wiley-VCH, Weinheim, **2002**; **b**. Balzani, V.; Venturi M.; Credi, A. V. *Molecular Devices and Machines: A Journey into the Nanoworld; Wiley-VCH, Weinheim*, **2003**.

[3] Zoloff, M. E.; Michoff, E. C. M.; Ezequiel L. P. M. *J. Phys. Chem. C* **2015** *119* (9), 5090-5097

[4] Carlson, Erik J.; Riel, Asia Marie S.; Dahl, Bart J. "Donor-Acceptor Biaryl Lactones: pH In duced Molecular Switches with Intramolecular Charge Transfer Modulation." *Tet rahedron Lett*. **2012**, *53*, 6245-6249.

[5] **a**. Fahrni, C. J.; Cody, J. *Tetrahedron* **2004,** *60*, 11099-11107; **b**. Sherwood, D. W.; Calvin, M. *JACS* **1942**, *64*, 1350-1353; **c**. Berlman, I. *Handbook of Fluorescence Spectra of Aromat ic Molecules; Academic Press: New York*; **1971**.

[6] **a**. Eaton, V. J.; Steele, D. *JACS, Faraday Transactions* 2 **1973**, *69*, 1601-1608**; b**. Akiyama, M.; Watanabe, T.; Kakihana, M. *J. Phys. Chem*. **1986**, *90*, 1752-1755.

[7] **a**. Herrmann, C. *J. Phys. Chem. A* **2019**, *123*, 10205-10223; **b**. Sakamoto, R.; Kume, S.; Nishihara, H. *Chemistry – A European Journal* **2008**, *14*, 6978-6986

[8] Raju, M. V.; Ramakrishnam, R. P.; Lin, M.; Lin, H. *Macromolecules* **2013**, *46*, 731-6743