Synthesis and Inclusion of 1-(5-Cyanonaphthyl) Diazomethane with B-Cyclodextrin

Scott Tobias Forrest

College of William & Mary - Arts & Sciences

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Synthesis and Inclusion of
1-(5-Cyanonaphthyl)diazomethane
with
β-Cyclodextrin

A Thesis
Presented to
The Faculty of the Department of Chemistry
The College of William and Mary

In Partial Fulfillment
Of the Requirements for the Degree of
Masters of Arts

by
Scott Tobias Forrest
1992
APPROVAL SHEET

This thesis is submitted in partial fulfillment of
the requirements for the degree of

Masters of Arts

[Signature]
Scott T. Forrest

Approved, May 1992

[Signature]
Christopher J. Abel, Ph.D.

[Signature]
W. Gary Hollis, Jr., Ph.D.

[Signature]
David W. Thompson, Ph.D.
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ABSTRACT

A relatively stable, solid complex of β-cyclodextrin with 1-(5-cyanonaphthyl)diazomethane is made. Pyrolysis of the solid complex produces carbene intermediates which undergo insertion reactions with the hydroxyl groups of the β-cyclodextrin. Insertion is probably selective for the C3 hydroxyl and is unusual in its binding strength while in solution making separation and identification of the regioisomers difficult.
SYNTHESIS AND INCLUSION OF
1-(5-CYANONAPHTHYL)DIAZOMETHANE
WITH
β-CYCLODEXTRIN
INTRODUCTION

Cyclodextrins (CDs) represent an exciting and relatively new focus in carbohydrate research and industry. Although CDs were first isolated in 1891, the last two decades have seen cyclodextrin research grow exponentially. The main interest in cyclodextrins lies in their ability to act as host molecules which can include guest molecules or parts of molecules, both in the solid state as well as in solution. These inclusion complexes have vast implications both in the scientific and industrial worlds.

Industrial applications have reached the pharmaceutical, agricultural, food, and cosmetic industries. The recent explosion of cyclodextrin research, which has provided the realization of industrial scale production combined with a reassuring toxicity profile, has enticed many other industries to follow their lead.

The surge in cyclodextrin technology can be exemplified in the pharmaceutical and agricultural industries, where over one third of all industrial cyclodextrin patents are held. The unique inclusion properties of cyclodextrins are responsible for the swell of interest. The inclusion complex formation of a compound, in this case a drug or pesticide, results
in the modification of its physical and chemical properties which can often be advantageous for drug therapy or agricultural technology. These include, among others, transformation of liquid compounds into a more stable crystalline form, masking of an unwanted smell or taste, and mixing of incompatible compounds due to the protection of one of the components by inclusion complex formation.³

The bioavailability of poorly soluble drugs and the efficiency of sparingly soluble pesticides can also be enhanced by cyclodextrin complexation.⁴ When included, the degree of solubility as well as the rate of dissolution of these poorly soluble substances can be extraordinarily increased. Cyclodextrins can also provide physical and chemical stability to volatile drugs or pesticides. Stabilization from evaporation, oxidation, decomposition, disproportionation, and polymerization as well as protection for light, acid, or base sensitive compounds are just a few advantages that inclusion can provide.⁵

It is important to note that not all drugs or pesticides are complexable with cyclodextrins. In fact, only about 10% of orally administered drugs seem to be compatible with inclusion complex formation,⁶ but that in itself may one day represent a multi-million dollar cyclodextrin market.

Stabilization of food flavors and fragrances also comprises a large market for cyclodextrins. Both the food and cosmetic industries have discovered that inclusion complex formation represents an efficient and
increasingly inexpensive method in the elimination of hygroscopicity, undesired odors and tastes, as well as microbiological and other undesirable contaminants. This is again the result of the inclusion complex's protection of the guest molecule against oxidation, light-induced reactions, thermal decomposition, evaporation, and sublimation, which tend to plague many of the products of these industries.

It is quite clear that cyclodextrins have made a dramatic debut in the industrial world, but by no means are they confined there. Cyclodextrins have become increasingly valuable in the research world as well. For instance, cyclodextrins are currently being used in the laboratory to catalyze many types of organic reactions, to separate mixtures of aromatic hydrocarbons through complexation, to determine the stereochemistry of selective guest molecules via complexation with the chiral CD host, and for chromatographic separation. This complexation ability of cyclodextrins also gives rise to perhaps their major interest in research, that of the artificial enzyme.

Since nearly every biochemical reaction is catalyzed by an enzyme, the implications of duplicating or perhaps even improving them using man-made enzymes are certainly vast. Natural enzymes catalyze biochemical reactions by binding small substrate molecules into an active site while the catalytic groups of the enzyme are held nearby so that they all may interact effectively. Enzymatic catalysis is extremely selective and is often under
strong geometric control resulting in products with quite specific spatial arrangements.

Similarly, cyclodextrins possess the ability to bind substrate molecules into their interior cavities and are also extremely selective in doing so due to size, shape, and polarity considerations of the substrate.\textsuperscript{12} By modifying the cyclodextrins, whether it may be monosubstituted, disubstituted, capped, or joined with another to form a duplex, even greater specificity can be achieved while simultaneously increasing already large accelerations in reaction rates. As a result, a large proportion of current research involves this chemical modification of cyclodextrins.

The research in this paper focuses on the modification of $\beta$-cyclodextrin through the synthesis and inclusion of a particular reactive cyanonaphthyl guest compound into $\beta$-cyclodextrin with the prospect of designing a specific, tethered, CD host capable of acting as a photoinduced electron-transfer sensitizer to a variety of included guests.
Cyclodextrins

Discovered by Villiers in 1891, cyclodextrins are produced by the action of the amylase of *Bacillus macerans* on starch and other similar compounds. However, it was not until several years later when Schardinger first isolated them and could describe their preparation. He found that cyclodextrins are cyclic oligosaccharides composed of α-(1,4)-linked D(+)-glucopyranose units in the C1 (chair) conformation. The three most abundant homologues consist of 6, 7, and 8 glucose units and are designated as α-, β-, and γ-cyclodextrin respectively (Fig. 1). Homologues of up to 12 glucose units have also been reported, but their isolation is uncommon making their structural characterization difficult. Cyclodextrins with less than six glucose rings cannot be formed due to steric hinderances.

**Figure 1:** Structures of α-, β-, and γ-Cyclodextrins.
As a consequence of the chair conformation of the glucopyranose units, cyclodextrins have a V-shaped hydrophobic cavity, a hydrophilic face, and the shape of a truncated cone. The secondary hydroxyls (on the C2 and C3 atoms of the glucose units) are located on the wider side of the cone and the primary hydroxyls (on the C6 atoms of the glucose units) are located on the opposite side, which is narrower due to the free rotation of the primary hydroxyls that effectively reduce their diameter and allow them to partially block an opening of the cavity. The secondary hydroxyls impart rigidity to the CD structure due to hydrogen bonding with secondary hydroxyl groups of their neighboring glucose units. A relatively apolar cavity is created due to the presence of a ring of C-H groups, a ring of glycosidic oxygen bridges, and another ring of C-H groups. The non-bonding electron pairs on the oxygen bridges are also directed toward the center of the cavity producing a high electron density within the hydrophobic cavity (Fig. 2).

Figure 2: Molecular Structure of β-Cyclodextrin.
Cyclodextrins are easily dissolved in water, with their solubility being a function of the hydrogen bonding between the secondary hydroxyls. β-Cyclodextrins possess the strongest hydrogen bonding system, making them the least soluble. Their system is unique since the hydrogen bonds inside their cavities form a complete ring unlike the hydrogen bonds in α- or γ-cyclodextrins.\textsuperscript{16}

Crystallization of cyclodextrins in an aqueous solution produces "empty" species with their cavities not really empty, but filled with water molecules. However, if an excess of a guest compound is added to the cyclodextrin solution, the resulting inclusion complex can be isolated in crystalline form. Packing of these cyclodextrin complexes within the crystal lattice occurs in one of two modes described as channel or cage structures according to the overall appearance of the cavities formed.\textsuperscript{17} In the channel type complexes, the cyclodextrin molecules are aligned on top of each other forming a long row or channel. This alignment is stabilized by hydrogen bonding between the primary and secondary hydroxyls of neighboring molecules. In the cage type structures, the cavity of one cyclodextrin molecule is blocked off on both sides by another cyclodextrin molecule forming small isolated cavities. The formation of a channel structure seems to be preferred by large or ionic molecular guests while smaller compounds prefer the caged structures.\textsuperscript{18}
Inclusion Complexes

As mentioned previously, cyclodextrins are unique as well as valuable due to their ability to form inclusion complexes with various compounds. Inclusion complexes are molecular compounds in which one compound (host molecule) spatially encloses another. The enclosed compound (guest molecule) is situated in the cavity of the host without significantly affecting the host framework structure apart from a slight deformation in the size and shape of the host cavity. Cyclodextrins may act as host for a variety of guest compounds ranging from polar reagents such as acids and amines, to small ions such as halogen anions, to highly apolar aliphatic and aromatic hydrocarbons. Inclusion complexes can be formed both in solution, with water as the primary solvent, or in the crystalline state.

The host-guest relationship of inclusion complexes is quite specific. Geometric rather than chemical factors are decisive in determining which guest molecules can penetrate the host cavity. Only compounds having a size which is compatible with the dimensions of the host cavity may be included. In the case of the three primary homologues of cyclodextrins, α-, β-, and γ-cyclodextrins possess internal cavities of different diameters and thus will correspondingly accommodate molecules of different sizes. This is well demonstrated with inclusion studies of halogenated benzenes. Data have shown that chlorobenzene, the smallest guest of those studied,
could form a true, 1:1 guest:host complex with α-cyclodextrin, which possesses the smallest cavity, but proved to be too small to complex effectively with the larger β- or γ-cyclodextrins. Somewhat larger bromobenzene was able to complex with both α- and β-cyclodextrins, while the iodobenzene, the largest of the three guest molecules, formed inclusion complexes with both β- and γ-cyclodextrin molecules, but was too large to include with α-cyclodextrins.

The guest molecule is arranged in such a position to achieve maximum contact between the hydrophobic regions of the guest and the apolar cyclodextrin cavity. The hydrophilic part of the guest molecule remains as far from the cavity as possible to insure maximum contact with both the solvent as well as the hydroxyl groups of the host. In some guest molecules, this hydrophilic region may be quite large. Complexation in this manner is achieved in such a fashion that only certain hydrophobic groups or side chains may penetrate the host cavity.

Stereoelectronic requirements also play an important role in determining a proper guest-host relationship. This can be demonstrated by the inclusion preference of testosterone over cortisone acetate into β-cyclodextrin by a factor of four.23 Although these two guest compounds have very common structural features, the hydroxyl group in testosterone is relatively unobstructed whereas cortisone acetate bears a bulky side chain that sterically crowds the hydroxyl group (Fig. 3).
The extent of complex formation is also highly dependent on the polarity of the guest molecule. This is exemplified by the fact that strongly hydrophilic, hydrated, or ionized molecules are not significantly complexed.\textsuperscript{24} Similarly, the stability of the complex is also a function of the hydrophobic character of the substituents.\textsuperscript{24} This can be illustrated by the increase in stability produced by the addition of a methyl or ethyl group in an ortho position to a carbonyl group. These substitutions provide a shielding effect on the carbonyl group and increases the hydrophobic character of the whole molecule thus increasing its complexability.

The driving force behind the inclusion of a guest molecule into a cyclodextrin cavity is essentially the substitution of the included water molecule with the more apolar guest. Although this driving force is still not fully understood, it is certain that it is the result of several factors.\textsuperscript{25,26} These include Van der Waal and hydrogen bonding interactions between
guest and host, the release of cyclodextrin ring strain upon complexation, and substitution of the energetically unfavorable apolar/ polar bonding between the cyclodextrin cavity and the included water molecule with the favored apolar/ apolar interaction between the cavity and the included guest molecule. With this substitution, a further stabilizing increase in entropy of the solvent also results as the once included water molecules join those already in the solvent medium. The extent to which each of these factors will contribute is dependent upon the nature of the guest compound to be included.

Preparation of cyclodextrin inclusion complexes can range from being quite simple to extremely difficult and is dependent upon the character of the guest compound. In principle, no solvent is necessary for inclusion complex formation as complexes have been synthesized by mixing the crystalline host and guest together and storing them at ambient temperatures over a period of several months.\textsuperscript{24} Obviously this method is too slow to be practical and as a result, complexation is usually performed in the presence of a solvent, predominantly water.

Cyclodextrin inclusion complexes are typically prepared by the addition of the guest compound, or more often a solution containing the guest compound, into an aqueous solution of cyclodextrin. This mixture is often stirred or shaken for several hours to promote inclusion. Alternatively, complexation may be achieved by adding the guest compound to an
aqueous suspension of cyclodextrin or even by kneading the guest into a cyclodextrin paste.\textsuperscript{27} These methods as well as the reaction times and temperatures will vary with the nature of the guests.

Following the preparation of the inclusion complex, analysis of the complex is necessary to insure that the inclusion was true and homogeneous. It is often the case that many compounds are poorly complexed or cannot be complexed at all. Others may form complexes in solution, but not in the solid state, and in many instances, the product is a mixture of the complex, the uncomplexed guest and the "empty" cyclodextrin. The methods of analysis also vary upon the particular guest to be included and range from thermoanalytic, to spectroscopic, to chromatographic techniques.\textsuperscript{28}

Of particular interest are thin layer chromatography (TLC) and nuclear magnetic resonance (NMR). In TLC, complexation can be determined by the analysis of the $R_f$ values of the complex in comparison to the pure guest compound.\textsuperscript{29} An inclusion complex is verified when these $R_f$ values are considerably lower for the complex. NMR provides the highest degree of inclusion complex verification.\textsuperscript{30} In $^1$H NMR, chemical shifts of the shielded hydrogen atoms (C3-H and C5-H), which are located inside the cyclodextrin cavity are compared to the unshielded hydrogen atoms (C2-H, C4-H, and C6-H), which are situated on the outer face and will show no chemical shifts. The extent of these shifts determines the position of the guest
molecule within the cyclodextrin host. \(^{13}\)C NMR is also a valuable tool for inclusion complex analysis. Here again, the change in chemical shift is a function of the degree of interaction between guest and host. Spectra can determine which carbon atoms of the guest are located within the host as well as their orientation.

**Diazocompounds**

Diazocompounds are molecules containing two nitrogen atoms joined together where one of the nitrogens is attached to a single carbon atom. There has been much interest in diazo compounds for many years because of their usefulness as precursors for carbene intermediates, which are formed in the photolysis and thermolysis of diazo compounds.

Diazomethane is the simplest diazo compound and as such, has served as a prototype for the rest of the family. Its classical structure may be considered a resonance hybrid of several planar structures, and as a result, can assume the properties of a carbene source, an acid, or a base.\(^{31}\)

**Figure 4:** Bond Angles and Bond Lengths in Diazomethane.

\[
\begin{align*}
\angle HCN & = 116.5^\circ \\
\angle CHN & = 127^\circ \\
CN & = 132 \text{ pm} \\
NN & = 112 \text{ pm}
\end{align*}
\]
For many years there was controversy concerning diazomethane's structure (Fig 4) until electron diffraction and microwave spectroscopic experiments showed that the group is planar, and the C-N-N angle is 180°. Noninteger bond orders of 2.66 for N-N and 1.38 for N-C were derived from the force constants for the respective IR frequencies of CH$_2^{14}$N$^{15}$N and CH$_2^{14}$N$_2$. These results can best be explained by an examination at diazomethane's resonance structures (Fig. 5), with structures A and B being the main contributors.

**Figure 5: Resonance Structures for Diazomethane.**

![Resonance Structures for Diazomethane](https://example.com/resonance_structures.png)

Molecular orbital theory can also be used to explain the linearity of diazomethane with sp$^2$ hybridization of the diazo carbon and sp hybridization of the two nitrogen atoms. Two of the six electrons occupy the $\pi_y$ orbital and the remaining four electrons reside in the two $\pi_x$ orbitals (Fig. 6). According to this theory, the highest occupied molecular orbital (HOMO) in diazomethane is a three-center orbital with a nodal plane perpendicular to the $z$ axis containing the central N atom.
The original method used for the synthesis of aliphatic diazo compounds involves the decomposition of the corresponding amine (Fig. 7).\textsuperscript{37} However, this method sometimes fails to produce the desired diazo compound, depending on the substituents \( R_1 \) and \( R_2 \). The intermediate diazonium ion (B) is converted to the diazoalkane (C) only when deprotonation is facilitated by dipolar groups in the \( \alpha \) position, such as halomethyl, cyano, acyl, or phosphoryl groups. In cases where this condition is not met, nitrogen elimination to the carbenium ion (D) is favored over the deprotonation route.\textsuperscript{38}

When one of the substituents is an aromatic group, the diazo
compound can be obtained by the dehydrogenation of the corresponding hydrazone (Fig. 8).\textsuperscript{39} Mercuric oxide was used almost exclusively as the oxidizing agent until the 1960's when silver oxide, manganese dioxide and lead (IV) acetate were found to be efficient alternatives.\textsuperscript{40} The limiting factor of this preparitive method is, in some cases, the synthesis of the required hydrazones from a carbonyl compound and hydrazine. Usually no difficulty is encountered for aldehydes and monoketones or for di- and triketones where one carbonyl group is more reactive than the other.

**Figure 8:** Dehydrogenation of Hydrazones.

![Dehydrogenation of Hydrazones](image)

Of particular interest is the Bamford-Stevens reaction in which p-toluenesulfonylhydrazones of aldehydes and ketones undergo a base catalyzed thermal decomposition with the loss of p-toluenesulfinate to give intermediate diazo compounds (Fig 9).\textsuperscript{41}

**Figure 9:** Bamford-Stevens Reaction.

![Bamford-Stevens Reaction](image)
Diazalkanes have been frequently synthesized by the vacuum pyrolysis of dry lithium or sodium salts of the tosyl-hyrazones, but more frequently the Bamford-Stevens reaction is used as a method of in situ formation and decomposition of diazo compounds. The decomposition pathway can be categorized as either carbenic (path 1), in which nitrogen is expelled to give a divalent intermediate or as cationic (path 2), in which a diazonium or carbonium intermediate is formed by the coordination with an electron deficient reagent such as an acid. The nature of the solvent, effects from the base used to catalyze the reaction, as well as the general structure of the tosylhydrazone will combine to effect the rate of carbenic as opposed to cationic decomposition.

The thermal or photochemical decomposition of diazo compounds to form reactive carbene intermediates provides a major synthetic tool for the organic chemist. For the thermal decomposition of diazomethane (Fig. 10) there are three different pathways:

**Figure 10: Thermolysis of Diazocompounds.**

\[
\begin{align*}
\text{R}_1\text{C}=\text{N}_2 & \xrightarrow{A} \text{R}_1\text{C}: + \text{N}_2 \\
\text{R}_1\text{C}=\text{N}_2 + \text{R}_2\text{C}=\text{N}_2 & \xrightarrow{B} \text{R}_1\text{C}=\text{N} - \text{N}=\text{C} + \text{N}_2 \\
\text{R}_1\text{C}=\text{N}_2 + \text{HX} & \xrightarrow{C} \text{R}_1\text{C}-\text{X} + \text{N}_2
\end{align*}
\]
a unimolecular decomposition with the expulsion of nitrogen leading to the carbene (path A), a bimolecular decomposition with the expulsion of nitrogen to give an azine structure (path B), and reaction with the solvent or another suitable reactant before the nitrogen cleavage (path C).\textsuperscript{42} Competition between the pathways is dependent upon the nature of the diazo compound, the solvent, as well as the reaction temperature. For example, diazodiphenylmethane gives primarily unimolecular decomposition products\textsuperscript{43} while 1-diazo-1-phenylethane primarily gives azine products produced by the bimolecular decomposition.\textsuperscript{44} In contrast, and as in many instances, both the uni- and bimolecular pathways compete in the decomposition of diazophenylmethane at elevated temperatures in acetonitrile.\textsuperscript{45} The third decomposition pathway (path C) only is significant when extreme solvent conditions such as high alcohol concentrations are used.\textsuperscript{46}

Similarly, the decomposition of diazo compounds can be accomplished photochemically (Fig. 11).

\textbf{Figure 11:} Photolysis of Diazo Compounds.

\[ R\text{C}=\text{N}_2 \xrightarrow{X} R\text{C} \parallel N \]

\[ R\text{C}=\text{N}_2 \xrightarrow{Y} R\text{C}: + \text{N}_2 \]
Their irradiation with light between 200 and 500 nm will give two main reaction pathways that are dependent upon the structure and substitution of the particular diazo compound. The first involves nitrogen elimination leading to the carbene (path X) and the second is a reversible rearrangement to a diazirine structure, a cyclic valence isomer (path Y).47

**Carbenes**

A carbene is a molecule containing a divalent carbon that bears an unshared pair of electrons. Carbenes are highly reactive, have short lifetimes, and may exist in one of two different electronic states (Fig. 12). The triplet state is formed when the non-bonding orbitals are of nearly equal energy. The non-bonding electrons will fill these two unoccupied orbitals and have parallel spins. In the singlet state, the non-bonding electrons have sufficiently different energies so that the non-bonding electrons become paired and occupy the lower energy orbital.

*Figure 12:* Structures of Singlet and Triplet Carbenes.
Depending on the mode of generation, a carbene may be formed in either the triplet or the singlet state no matter which state is more stable,\textsuperscript{48} and as a result of their different electronic configurations, they will possess different geometries and chemical reactivities.

In the singlet carbene the two unshared electrons occupy an sp\textsuperscript{2} orbital and an unoccupied p orbital remains. The R-C-R angle is somewhat lower than the expected 120° due to the electronic repulsions between the unshared electron pair and the electrons in the two bonding orbitals. This was confirmed from electronic spectra of :CH\textsubscript{2} formed in the flash photolysis of diazomethane where the singlet state of :CH\textsubscript{2} was found to be significantly bent with an angle of about 103°.\textsuperscript{49} A linear structure is predicted in the corresponding triplet carbene structure formed from sp orbitals with the unpaired electrons being in two equivalent p orbitals. However, electron paramagnetic resonance measurements made on triplet :CH\textsubscript{2} trapped in matrices at very low temperatures (4K) showed that its structure is also significantly bent with an H-C-H angle of 136°.\textsuperscript{50}

Both theoretical and experimental studies are consistent with the triplet carbene structure being the ground state. Molecular orbital calculations show that the difference in energy between singlet and triplet CH\textsubscript{2} is about 9 to 11 kcal/mol.\textsuperscript{51}

Adding substituents to a carbene can favor one state over the other. Substituents that act as electron pair donors such as halides tend to
stabilize the singlet state over the triplet state by the delocalization of an electron pair into the empty p-orbital. These singlet carbenes may be classified as ambiphilic, nucleophilic or electrophilic based on their reactivity toward different nucleophilic or electrophilic compounds. It is this degree of \( \pi \) delocalization produced by electron donating substituents that will also determine the reactivity of the carbene.

There are numerous methods for the generation of carbene intermediates and of particular interest is their generation through the decomposition of diazo compounds. As discussed previously, this decomposition may be accomplished through thermolysis or photolysis, but often times is limited due to the fact that diazo compounds are often unstable and often not easily synthesized. As a result, the decomposition of the diazo is performed in situ.

The mechanisms of carbene reactions and their corresponding synthetic applications can best be understood by examining their reactions with various compounds. The addition of carbenes to the double bonds of alkenes to form cyclopropane derivatives has received the greatest amount of attention (Fig. 13). If the singlet species of the carbene adds to the alkene (path A), the geometrical relationship of the alkene substituents should be retained since the formation of the two new cyclopropane C-C bonds should occur either simultaneously or with one rapidly succeeding another. However, if the attack is by the triplet species (path B), the two
unpaired electrons cannot both form new covalent bonds since they have parallel spins. As a result, one of the unpaired electrons will form a bond with an electron from the double bond that has the opposite spin leaving two unpaired electrons with the same spin. These unpaired electrons with parallel spins must then wait until by some collision process, one of the electrons can reverse its spin. During this time, there is free rotation about the C-C bond and a mixture of geometrical isomers will result depending on the olefin substitution.\textsuperscript{53}

**Figure 13: Singlet and Triplet Car bene Addition Reactions.**

These results show that carbenes formed as singlet species, which may in time decay to the more stable triplet state, often are so reactive that they generally react before intersystem crossing can occur. However, depending on the method of generation, many carbenes can react as
triplets and still others display a mixture of both singlets and triplet reactivity.\textsuperscript{54} Thus, the reactive spin state of a carbene is not always the ground state, and, as a result, the prediction of the multiplicity of the reacting carbene is sometimes quite difficult. The determination of the subsequent reaction products is also difficult due to the differences in the stereospecificity and selectivity between the singlet and triplet states.

Of particular interest is that in carbene insertion reactions with alcohols, C-H bonds are usually more reactive with the triplet state while C-OH bonds are usually more reactive with the singlet state.\textsuperscript{55} Similarly, in carbene insertion reactions with chlorinated hydrocarbons, singlet carbenes prefer C-Cl bonds whereas the triplet species again prefers C-H bonds.\textsuperscript{56}

Reaction conditions are also a factor in the determination of the multiplicity of the reacting carbene. For instance, the reaction from the triplet state dominates at low temperatures, in the presence of an inert gas, or with certain sensitizers during photolysis.\textsuperscript{57}

\textbf{Cyclodextrins in Photochemical Reactions}

Organic chemists have long recognized the important role the reaction media plays in controlling reaction rates, product distribution, and stereochemistry. Recently, an increased effort has been directed toward the use of organized media to modify both thermal as well as photochemical
reactivity. The goal of these studies is to increases both the rate and selectivity of the chemical processes involved in much the same manner that enzymes are able to carry out selective reactions on target substrates.

Cyclodextrins are a relatively new type of organic media which have been shown to affect many photochemical and photophysical properties due to the restriction and organization of the chemical environment provided by the cyclodextrin cavity. The interior of the cavity is essentially an isolated environment that will constrain its guest by restricting its motion and by stabilizing certain conformations which may be less favored in solution. The reactive sites of the entrapped species may be encircled by the CD, and, as a result, will be protected from chemical reagents or reactive intermediates. Encapsulation mainly restricts the chemistry of the included species to intramolecular events, except in the case of multiple occupation of cavities. In addition, the hydrophobic nature of the cavity will also protect processes that are sensitive to solvent or dielectric effects. These features allow cyclodextrins to function as a microenvironment for phototransformations that combine conformational control, site selectivity, and restriction of motion.58

The microenvironment effect is quite apparent in the photochemistry of benzoin alkyl ethers complexes with β-cyclodextrin.59 Upon irradiation, benzoin alkyl ethers are known to undergo Norrish Type I reaction
pathways as their major photoprocess in isotropic organic solvents. The competing Type II reaction pathway, although feasible in these substrates, is not observed to any significant extent. Upon complexation (1:1) with β-cyclodextrin and subsequent irradiation, only Type II products are formed. Since Type II photoproducts result from γ-hydrogen abstraction, these results can best be explained by suggesting that the CD imposes a conformation in which the benzene ring is located within the cavity and the alkyl group remains outside where it is suitable for γ-hydrogen abstraction.

Similarly, complexation and irradiation of α-alkyl dibenzyl ketones with β-cyclodextrin\textsuperscript{60} gives primarily Norrish Type I photoproducts, whereas in an aqueous system, photolysis results in a mixture of products formed from both pathways. These results can be explained by suggesting a CD imposed conformation where both the benzene ring as well as the alkyl group are located within the cavity, thus restricting the γ-hydrogen abstraction.

Chemical modifications of the cyclodextrin with reactive functional groups adjacent to the binding site can provide even more powerful systems for photochemical reactions. Capping or tethering not only increases the hydrophobic binding of some guests, but also provides in some cases, some energetic interactions between the host and guest due to their unusually close proximity.

Energy transfer has been shown to occur between the benzophenone-
p,p'-dicarboxylate capped β-cyclodextrin and several naphthalene derivative guests (Fig 14, A).\textsuperscript{61} Irradiation of the benzophenone moiety yields phosphorescence from both the host benzophenone cap as well as the guest naphthalene derivatives. The triplet energy transfer was estimated to be 60\% from host to guest and is quite specific for host-guest combinations of exact structural recognition\textsuperscript{61} as no energy transfer was observed from the benzophenone cap to very hydrophilic and/or bulky energy acceptors.

**Figure 14:** Modified β-Cyclodextrins.

In an attempt to mimic the light induced electron transfer process in photosynthesis, a porphyrin tethered cyclodextrin compound has been successfully synthesized to act as an electron donor for several included quinone acceptors (Fig. 14, B).\textsuperscript{62} This study also examined the relationship
between reduction potentials of the acceptors relative to the oxidation potentials of the donor as well as the possibility of activation barriers in relation to the degree of electron transfer between host and guest.

Photochemical Electron Transfer

Since the 1970's, the study of photochemical electron transfer reactions has grown enormously due in part to the interest in new energy supplies. This intrigue stems from the ability to use light to drive a thermodynamically uphill reaction. Researchers have long understood the basic process, but the ability to model or even mimic electron transfer has proven to be more complex.

In photochemical electron transfer, a photon of appropriate energy is used to induce a transition from the ground state to an excited state. This transition may be represented by the jump of an electron from a given molecular orbital to another. The MO representation of the excited state is partially that of a radical cation with a half filled HOMO and partially that of a radical anion with a half filled LUMO. Thus, the excited molecule can potentially oxidize a donor molecule or reduce an acceptor molecule. With this excitation comes enhanced redox reactivity as acceptor-donor radical ion pairs are formed which then may undergo either a back electron transfer reaction and regenerate the original products, or diffuse apart and undergo chemical reactions leading to new products. Figure 15 illustrates
the reason for this redox enhancement.

**Figure 15: Redox Enhancement in the Excited States of A and D.**

D when excited to $D^*$ has an electron promoted to the higher lying LUMO which then can be transferred with less energy than any electron in the ground state molecular orbital. $D^*$ is therefore a far better reducing agent than D due to a decrease in the ionization potential produced by the photoexcitation. Similarly, $A^*$ is a stronger oxidizing agent than A because the vacancy created in the ground state HOMO increases the electron affinity of the excited state relative to the ground state.64

The feasibility of electron transfer between the proposed donor and acceptor molecules relies essentially on thermodynamic criteria and is related to the difference in standard electrode potentials for the reduction
of A and the oxidation of D. The standard free energy change for a photoinduced electron-transfer is given by the Rehm-Weller equation:\textsuperscript{65}

$$\Delta G^\circ_{et} = -23.06(E^\circ_{red} - E^\circ_{ox}) - \frac{e_a^2}{e_o} - \Delta E_{0,0}$$

which determines the viability of the reaction.

As stated previously, the ET step between acceptor and donor in the ground state is usually far too endergonic to occur spontaneously without the presence of a light-induced excitation. However, the addition of an ET sensitizer, which acts as a photoinduced catalyst to the reaction, will also produce the acceptor donor radical ion pair without their direct excitation.\textsuperscript{66} Defined, a sensitizer is an ET catalyst that is at least 80% regenerated after having performed its function of transforming the substrate into products.

There are many examples of ET sensitization, but the two main features of this phenomenon are that the excited state of the photosensitizer must be sufficiently long-lived to have time to interact with the substrate ($10^{-6}$ to $10^{-9}$ s for most ET steps)\textsuperscript{67} and correspondingly, the need for an appropriate fit of excited state redox properties of the sensitizer and ground state redox properties of the substrate to insure a relatively fast ET step.\textsuperscript{68} Other characteristics of a useful ET sensitizer include: 1) light absorption in a region where substrate, products, intermediates or by-products do not absorb, 2) chemical stability toward all components present in the system, and 3) photochemical stability.\textsuperscript{68}

The reaction of an ET sensitizer can take one of two forms, and most
sensitizers are said to lie somewhere between the two. The first (1) is the case where "free" excited sensitizers act as active oxidizing or reducing agents without complexation with the substrate. The alternative (2) involves the formation of an exciplex complex between the sensitizer and substrate where the charge transfer between the two does not occur instantaneously. The differences between the two reaction schemes are illustrated in Figure 16.

Figure 16: Free and Exciplex State Sensitizer Species.

The scope of reactions that are catalyzed by these sensitizers is quite vast and is quite evident by the fact that they can be found in nearly every area of synthetic chemistry ranging from simple isomerizations to
dimerizations to complex nucleophilic additions and oxidations.\textsuperscript{70} It is clear that with a better understanding of the mechanisms of these systems, this extremely powerful tool will provide an entirely different angle to organic chemistry.

**Cyano Aromatic Compounds as Electron Transfer Sensitizers**

Cyano-aromatic compounds have proven to be one of the most successful ET sensitizers and have been used in a variety of photoinduced reactions. Isomerizations,\textsuperscript{71-75} mixed cycloadditions,\textsuperscript{76-77} nucleophilic additions,\textsuperscript{78-81} as well as substitutions into C-C bonds\textsuperscript{82} have all been successfully completed using specifically 1-cyanonaphthalene (1-CN) as a sensitizer. In principle, electron transfer should occur from any species that has $E_{\text{ox}}$ which is less than the $E_{\text{red}}$ for the excited state of the photosensitizer. Thus, many donor molecules should be susceptible to electron transfer to the excited state of 1-CN, which has a $E_{\text{red}}$ of 1.82 V.\textsuperscript{80}

Norbornadiene (bicyclo[2.2.1]hepta-2,5-diene), which has a $E_{\text{ox}}$ of 1.56 V, undergoes a variety of nucleophilic additions in the presence of 1-CN.\textsuperscript{80} Irradiation of a solution of norbornadiene and 1-CN in a water and acetonitrile mixture gave 56% of A and 39% of B while irradiation of the two in methanol gave 33% of C, 33% of D, and 10% of E (Fig. 17). The mechanism proposed involves the reaction of norbornadiene with the
excited state of 1-CN to give a singlet ion pair consisting of the radical cation of norbornadiene (1) and the radical anion of the sensitizer. With the presence of water or methanol, the cation will undergo nucleophilic attack forming another radical (2) which will then equilibrate with two isomeric bicyclic radicals. Back electron transfer of these three radicals from the 1-CN anion radical will form their respective bicyclic carbanions. Quenching of the carbanions via a proton transfer from the solvents will yield the observed products.

**Figure 17:** Photoinduced Addition of Nucleophiles to Norbornadiene.
A similar mechanism is found in the photochemical trans to cis isomerization of 1,2-diphenylcyclopropanes using several electron withdrawing substituted naphthalenes, including 1-cyanonaphthalene, as photosensitizers (Fig. 18).\textsuperscript{71}

Figure 18: Photoinduced Isomerization of 1,2-Diphenyl-Cyclopropanes.

When 1-CN has been irradiated in the presence of trans-1,2-diphenylcyclopropane, formation of a singlet radical ion pair (X) involving the radical anion of the sensitizer and the radical cation of the cyclopropane is observed. Here, the cyclopropane ring remains intact since the electron has been taken from one of the adjacent phenyl groups. This radical ion pair can either deactivate by back electron transfer to reform the trans
isomer or cleave to form another radical ion pair \( \text{(Y)} \) consisting of the radical anion of the sensitizer and a ring-opened radical cation. The main decay pathway for this ion pair involves a back electron transfer to produce a 1,3-biradical \( \text{(Z)} \) of the former cyclopropane and the ground state form of the sensitizer. Rapid ring closure of the biradical accounts for the production of both the \text{cis} and \text{trans} isomers. Cycloaddition reactions have also been successfully catalyzed using 1-cyanonaphthalene as a photo-induced sensitizer. For example, furan \( \text{(A)} \) has been added to several electron rich aromatic olefins in the presence of 1-CN (Fig. 19).\(^7^6\) Irradiation of a mixture of \( \text{A, B, and 1-CN} \) in acetonitrile gives three primary cycloadducts; \( \text{C (35%)} \), \( \text{D (20%)} \), and \( \text{E (10%)} \).

\text{Figure 19: Photoinduced Addition of Furan to Electron-Rich Olefins.}

\[
\begin{align*}
\text{A} + \text{B} & \xrightarrow{h\nu, 1\text{-CN}} \text{C} \\
\text{D} & \\
\text{E}
\end{align*}
\]
The proposed mechanism involves electron transfer from B to the excited singlet of 1-CN to give a radical ion pair consisting of the radical anion of the sensitizer and the radical cation of B. This is soon followed by a nucleophilic attack by A on the cation of B which results in the formation of a radical heterodimer cation (AB⁺). Upon back electron transfer with the radical anion of 1-CN, the three corresponding crossadducts are formed.

There are many other examples of cyano-aromatic compounds that are used as photosensitizers in a variety of organic reactions. However, studies that combine these sensitizers with the unique inclusion properties that cyclodextrins can provide have not been attempted. It is the hope of this research to design a cyanonaphthyl-tethered β-cyclodextrin to act as a very unique host with the possibility of photoinduced electron-transfer sensitization for a variety of included guests.
**EXPERIMENTAL METHODS**

**General Methods:**

$^1$H and $^{13}$C NMR were obtained using a GE QE-300 Spectrometer. Thin Layer Chromatography was carried out on 0.25 mm (60F-254) precoated silica plates (Baker); spot detection was seen using an ultraviolet lamp and staining with a vanillin solution (Baker). Flash reverse-phase column chromatography was done with Baker RP-18 silica gel. Preparative High Performance Liquid Chromatography was performed on a Waters 244 system equipped with a UV detector at 254 nm and a Whatman Magnum 20 column packed with ODS-3. Analytical HPLC was performed on a Waters 600E system equipped with a variable wavelength absorption detector set at 254 or 320 nm and a Whatman ODS-3 column. Melting points were obtained on a Meltemp capillary melting point apparatus and are uncorrected. 1-Naphthoic acid was purchased from Aldrich. $\beta$-cyclodextrin was provided by Amalzo.

**5-Bromo-1-naphthoic acid:**

A 25.0 g sample (0.144 mol) of 1-naphthoic acid was dissolved in glacial acetic acid (200 mL). Bromine (10 mL, 0.194 mol) was added slowly over a period of one hour with gentle heating and stirring. A yellow solid separated during the addition, and the mixture was heated to reflux for
another two hours. After cooling, the solid was collected by Buchner filtration and then recrystallized once from acetic acid to afford 5-bromo-1-naphthoic acid (24.4 g, 0.097 mol, 67% yield, mp 255-257°C) after drying in vacuo. The product was assumed to be pure enough for further use.

5-Bromo-1-hydroxymethylnaphthalene:

A 500 mL, two-neck, round-bottom flask was equipped with a Soxhlet extractor surmounted by a Friedrichs condenser under CaCl₂ drying. A 10.0 g sample (0.0398 mol) of 5-bromo-1-naphthoic acid was placed in a paper thimble in the Soxhlet. Et₂O (100 mL) was added to the flask and 3.1 g (0.0797 mol) LiAlH₄ was added to the Et₂O cautiously. Another portion of Et₂O (100 mL) was then added to the flask and the mixture was refluxed overnight. The system was then cooled, and the reaction mixture was quenched with ethyl acetate (32 mL, 0.3187 mol), H₂O (50 mL), and finally concentrated HCl (50 mL) was added to dissolve all of the aluminum salts. The mixture was transferred to a separatory funnel, and the ether layer was separated. The aqueous layer was extracted with Et₂O (3 × 50 mL). The ether extracts were combined, dried over Na₂SO₄, and concentrated in vacuo.

This procedure was repeated on the remaining 5-bromo-1-naphthoic acid yielding altogether 22.3 g (0.0940 mol, 97% yield, mp 118-120°C) of 5-bromo-1-hydroxymethylnaphthalene.
$^1$H NMR (CDCl$_3$): $\delta$ 8.24 (dd, 1H, $J$= 2.8, 6.9 Hz), $\delta$ 8.08 (d, 1H, $J$= 8.5 Hz), $\delta$ 7.80 (d, 1H, $J$= 7.2 Hz), $\delta$ 7.53- 7.55 (m, 2H), $\delta$ 7.36 (dd, 1H, $J$= 7.8, 7.9 Hz), $\delta$ 5.11 (s, 2H).

5-Bromo-1-naphthalenecarboxaldehyde:

A 12.0 g sample (0.0506 mol) of 5-bromo-1-hydroxy-methylnaphthalene was dissolved in methylene chloride (50 mL) in a 300 ml round-bottom flask equipped with a reflux condenser under an oil bubbler. Pyridinium chlorochromate (PCC) (15.0 g, 0.0698 mol) in methylene chloride (100 mL) was added to the flask. The mixture was heated to reflux for 1.5 hours, and then allowed to cool to room temperature. A black solid collected on the bottom of the flask. Et$_2$O (50 ml) was added to the mixture, and the liquid was transferred to a separatory funnel. The PCC residue was washed with Et$_2$O (3 X 50 mL), and the washings were added to the funnel. The ether layer was washed with a 5% NaOH solution (3 X 100 mL), a 5% HCl solution (100 mL), and a saturated aqueous NaHCO$_3$ (100 mL). The ether layer was dried over MgSO$_4$ and then concentrated in vacuo. The aldehyde was recrystallized from EtOH and H$_2$O.

The procedure was repeated until all of the initial 5-bromo-1-hydroxymethylnaphthalene was oxidized to give 10.75 g (0.0457 mol, 49% yield, mp 89-92°C) of 5-bromo-1-naphthalenecarboxaldehyde. $^1$H NMR (CDCl$_3$): $\delta$ 10.39 (s, 1H), $\delta$ 9.26 (d, 1H, $J$= 8.6 Hz), $\delta$ 8.58 (d, 1H, $J$= 8.5 Hz),
δ 8.04 (d, 1H, J= 6.9 Hz), δ 7.90 (d, 1H, J= 7.6 Hz), δ 7.74 (dd, 1H, J= 7.2, 8.4 Hz), δ 7.52 (dd, 1H, J= 8.4, 8.4 Hz).

5-Cyano-1-naphthalenecarboxaldehyde:

A 6.0 g sample (0.0255 mol) of 5-bromo-1-naphthalene-carboxaldehyde was mixed with 3.43 g (0.0380 mol) of CuCN in dimethylacetamide (DMAC) (250 mL) in a 250 mL round-bottom flask and heated to reflux overnight. The DMAC was removed by distillation until approximately 25 mL remained in the flask. The remaining hot mixture was poured over a solution of 100 mL each of concentrated NH₄OH and ice. This mixture was transferred to a separatory funnel, and the aqueous layer was extracted with Et₂O (500 ml) until all solid was in solution. The ether layer was then washed with 5% HCl (100 mL), dried over MgSO₄, and concentrated in vacuo. The aldehyde was recrystallized from CH₃OH and H₂O.

This procedure was repeated until all of the 5-bromo-1-naphthalenecarboxaldehyde was cyanated to give 3.98 g (0.0220 mol, 48% yield, mp 178-180°C) of 5-cyano-1-naphthalenecarboxaldehyde. ¹H NMR (CDCl₃): δ 10.39 (s, 1H), δ 9.58 (d, 1H, J= 8.7 Hz), δ 8.54 (d, 1H, J= 8.5 Hz), δ 8.14 (d, 1H, J= 7.0 Hz), δ 8.04 (d, 1H, J= 7.0 Hz), δ 7.89 (dd, 1H, J= 7.6, 8.1 Hz), δ 7.76 (dd, 1H, J= 8.2, 7.7 Hz).
5-Cyano-1-naphthalene-carboxaldehyde p-toluenesulfonyl-hydrazone:

A 2.1 g sample (0.0113 mol) of p-toluenesulfonyl-hydrazine was mixed with punctilious EtOH (15 mL). As the slurry was stirred, 2.0 g (0.0110 mol) of 5-cyano-1-naphthalene-carboxaldehyde was added rapidly. The mixture was heated until the aldehyde dissolved, and then it was allowed to cool. Within a few minutes, the tosylhydrazone began to crystallize. After 15 minutes, the flask was placed in an ice-bath. The product was collected by Buchner filtration and washed with small amounts of cold EtOH. This procedure was repeated until all of the 5-cyano-1-naphthalene-carboxaldehyde was converted yielding 5.8 g (0.0166 mol, 75% yield, mp 183-185°C) of 5-cyano-1-naphthalene-carboxaldehyde p-toluenesulfonylhydrazone. \(^1\)H NMR (CDCl$_3$): \(\delta 8.97\) (d, 1H, \(J = 8.7\) Hz), \(\delta 8.30\) (s, 1H), \(\delta 8.26\) (d, 2H, \(J = 4.0\) Hz), \(\delta 7.95\) (dd, 3H, \(J = 6.5, 7.8\) Hz), \(\delta 7.78\) (d, 1H, \(J = 7.2\) Hz), \(\delta 7.53-7.69\) (m, 3H), \(\delta 7.34\) (d, 1H, \(J = 7.8\) Hz), \(\delta = 2.4\) (s, 3H).

1-(5-Cyanonaphthyl)diazomethane:

Sodium (0.6 g, 0.0261 mol) was reacted with ethylene glycol (25 mL) heated to 70°C. The tosylhydrazone (5.6 g, 0.0290 mol) was added, and the solution stirred vigorously for 5 minutes. The mixture was then cooled in an ice-bath and Et$_2$O (15 mL) was added, and the layers were stirred vigorously. The ether layer was then removed by pipet. The above
procedure was repeated four more times. The ether extracts were combined to give a solution of 1-(5-cyano-naphthyl)diazomethane (0.0116 mol, assuming a 70% yield).

Inclusion of 1-(5-cyanonaphthyl)diazomethane with \(\beta\)-cyclodextrin:

A solution of 1-(5-cyanonaphthyl)diazomethane in Et\(_2\)O was placed above a 0.04 M solution of \(\beta\)-cyclodextrin (19.8 g, 0.0174 mol) in an ice bath. A stream of \(\text{N}_2\) was directed over the ether layer. The solution was stirred vigorously, and small amounts of Et\(_2\)O were added periodically until all of the diazo compound was complexed (3 hours). The product was isolated by Buchner filtration and dried \textit{in vacuo} yielding 7.2 g of the complex. A sample was analyzed by \(^1\text{H} \text{NMR}\) and indicated a guest/\(\beta\)-cyclodextrin ratio of 1.6/1. \(^1\text{H} \text{NMR\ (DMSO- \(d_6\))}\): \(\delta\) 8.26 (d, 1H, \(\text{J}=8.6\) Hz), \(\delta\) 8.14 (d, 1H, \(\text{J}=7.0\) Hz), \(\delta\) 7.70-7.75 (m, 2H), \(\delta\) 7.61 (dd, 1H, \(\text{J}=7.8, 7.9\) Hz), \(\delta\) 7.22 (d, 1H, \(\text{J}=6.4\) Hz), \(\delta\) 6.66 (s, 1H).

Decomposition of the 1-(5-cyanonaphthyl)diazomethane/\(\beta\)-cyclodextrin complex:

The complex (7.2 g) was decomposed at 180\(^\circ\text{C}\) for 10 minutes, and a color change from peach to white was observed. The products were stirred in H\(_2\)O, and the solution was continuously extracted with Et\(_2\)O overnight. The aqueous layer was then dried \textit{in vacuo} to give 4.8 g of products.
Analysis of Aqueous Products:

Flash Reverse Phase Chromatography:

Small portions (ca. 1.2 g) of the water soluble products were subjected to flash reverse-phase chromatography using the following gradient elution:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>%CH₂CN:</th>
<th>Volume:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>200 mL</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
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<td>6</td>
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<td>8</td>
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<td>100</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>200</td>
</tr>
</tbody>
</table>

This process was repeated until the entire mass of water soluble derivatives had been processed. The fractions were then analyzed by thin layer chromatography and those fractions containing the desired products were concentrated in vacuo to give 0.15 g (3.1% yield).

High Performance Liquid Chromatography:

Products obtained from the flash column were further isolated and purified by preparitive HPLC using a program elution of 10% to 33% CH₃CN/H₂O over a period of 30 minutes. Four peaks of interest were observed, collected, and dried in vacuo (Peak A: 8 mg, Peak B: 70 mg, Peak C: 3 mg, Peak D: 1 mg). Separation was verified by analytical HPLC using an elution gradient of 10% to 50% CH₃CN/H₂O over 40 minutes.
Figure 20: $^1$H NMR of 5-Bromo-1-hydroxymethylnaphthalene.
Figure 21: \(^1\text{H} \) NMR of 5-Bromo-1-naphthalenecarboxaldehyde.
Figure 22: $^1$H NMR of 5-Cyano-1-naphthalenecarboxaldehyde.
Figure 23: $^1$H NMR of 5-Cyano-1-naphthalenecarboxaldehyde p-toluenesulfonylhydrazone.
Figure 24: $^1$H NMR of 1-(5-Cyanonaphthyl)diazomethane/ $\beta$-Cyclodextrin Inclusion Complex.
RESULTS AND DISCUSSION

Much of this research project focused on the synthesis of 5-cyano-1-naphthalenecarboxaldehyde. This molecule could then be tethered to β-cyclodextrin to produce an effective photoinduced electron-transfer sensitizer for various compounds included within the cyclodextrin cavity.

Since no literature was found concerning the cyano-naphthyl derivative, a general synthetic scheme was devised. It began with halogenation at the 5 position of 1-naphthoic acid, followed by substitution of the halide with cyanide, and finished with a reduction of the acid to the corresponding aldehyde. From the aldehyde, the tosylhydrazone could be synthesized, and the sodium salt could be pyrolyzed to the corresponding diazo compound. Decomposition of this diazo would form a carbene intermediate, and in the presence of β-cyclodextrin, would then form the ether tether.

Initially, 5-chloro-1-naphthoic acid was synthesized, but subsequent cyanations or reductions gave a mixture of products in poor yields.

Better results were achieved by bromination of the 1-naphthoic acid. The methyl ester derivative was made before the cyanide substitution since direct cyanation of the acid would result in reaction with the acidic proton to expel HCN. Cyanation of the bromo-ester was then attempted using the
method of Rosemund and von Braun, a nucleophilic aromatic substitution of the aryl bromide in the presence of CuCN to form the aryl nitrile. A general mechanistic description of the copper-promoted nucleophilic substitution involves an oxidative addition of the aryl halide at Cu(I) followed by the collapse of the organocopper (III) intermediate with a ligand transfer to form the nitrile (Fig. 20).\textsuperscript{83-85}

**Figure 25:** Rosemund-von Braun Reaction Mechanism.

\[
\text{Ar-X + Cu(I)Z} \rightarrow \text{Ar-Cu(III)-Z} \rightarrow \text{Ar-Z + CuX}
\]

\(X = \text{halide}\)

\(Z = \text{nucleophile}\)

Again, since CuCN easily abstracts protons to evolve HCN gas, a relatively basic and high boiling solvent was chosen. DMAC (dimethylacetamide) was fractionally distilled and stored over molecular sieves prior to use. In addition, the bromo-aldehyde was thoroughly dried in vacuo. \(^1\)H NMR showed a near complete cyanation, and yields around 50\% were reasonable as they were within the ranges found in literature.

At this point, reduction of the ester group to the corresponding aldehyde was attempted with DIBAL (diisobutyl aluminum hydride) in toluene at \(-70^\circ\text{C}\). \(^1\)H NMR confirmed the presence of the aldehyde, but a larger percentage of the corresponding alcohol and trace amounts of the
dialdehyde structure were also indicated. It was surmised that the DIBAL did not react at low temperature, but only when the reaction mixture was warmed. Under these conditions, the ester would react to form the aldehyde which would then be reduced to the alcohol. The nitrile would also react under these conditions. The presence of the dialdehyde derivative also prompted a change in the order of synthesis to better protect the cyano group. As before, 1-naphthoic acid was brominated at the 5 position followed by esterification of the acid. Two equivalents of DIBAL at room temperature reduced the bromo-ester to the corresponding alcohol, which was then oxidized using PCC (pyridinium chlorochromate) to form the aldehyde. PVPDC (polyvinylpyridinium dichromate) was first used as the oxidant since it offered a simpler work-up, but in this instance only trace amounts of the aldehyde were detected. Cyanation of the bromo-aldehyde was again successfully accomplished via the Rosemund-von Braun method.

An alternative shorter synthesis was then proposed and tested that involved reduction of the bromo-acid to the corresponding alcohol using LiAlH₄, thus eliminating the esterification and the DIBAL reduction. Using such a strong reducing agent was no longer a problem since the cyanation was now done after the reduction. Previously, when the cyanation was completed before the reduction, using LiAlH₄ would have reduced the cyano group to its corresponding amine. This new synthetic route proved to be
successful and provided an increase in the amount of cyano-aldehyde produced due to the elimination of one step.

The diazo derivative of 5-cyano-1-naphthaldehyde was generated via pyrolysis of the tosylhydrazone sodium salt in ethylene glycol. $^1$H NMR showed a negligible amount of azine formation which has been a major side product in previous pyrolysis studies by this method.

Inclusion of the cyano-naphthyl diazo compound with β-cyclodextrin was accomplished through vigorous stirring of an etherial solution of the diazo compound over an aqueous β-CD solution. The ether acts as a phase transfer agent for the system and was added in small amounts over time to promote thorough mixing. Better results were achieved when acetone was used instead of ether. The system was usually allowed to stir for several hours until complexation between the orange of the diazo and the cream of the CD produced a homogeneous peach colored mixture.

Diazot incorporation was measured by $^1$H NMR using DMSO-d$_6$ as the solvent. In solution, the complex is separated into free cyclodextrin and free diazo, and the ratio of guest to host can be determined by examining the ratio of integrated intensities of the signals for the aromatic and the anomeric protons. The spectrum indicated that the guest to host ratio was 1.6:1.

The diazo compound in the complex was decomposed through pyrolysis
at 180°C. Carbenes readily form under these conditions via the loss of N₂. A noticeable color change of the complex from peach to white after approximately 10 minutes of heating and stirring was noted, a good indication of diazo decomposition.

Ideally, the carbene will react with the β-CD, but they may also rearrange or react with other species. In order to separate these undesirable products from the water soluble β-CD derivatives, a continuous ether extraction was performed over a period of 48 hours. The derivatives bearing aromatic groups were separated from β-CD using flash reverse-phase chromatography and detected using thin layer chromatography. Further isolation and separation was done through preparative reverse-phase HPLC and the separation was confirmed by analytical reverse-phase HPLC. Detection was enhanced on the latter using a wavelength absorption setting of 325 nm, which has been found to be more suitable for cyano-naphthalene compounds. Three distinct peaks (and one smaller peak) were detected on both the preparative and analytical HPLC systems, but when the three were isolated, only the first proved to be substantial.

Carbene insertion into β-cyclodextrin can occur at one of three different hydroxyl groups (C2-OH, C3-OH, or C6-OH) making three regioisomers possible. Pyrolysis of the inclusion complexes of this particular compound seemed to indicate only production of one of these isomers. From past studies, it has been shown that products isolated from the initial eluted
peak correspond to products formed from insertion into the C3 hydroxyl. 

$^{13}$C NMR can usually identify the isomers separated by HPLC, but a significant difficulty was encountered in finding a suitable solvent and NMR results proved to be inconclusive.
5-Cyano-1-naphthalenecarboxaldehyde was synthesized and a relatively stable, solid inclusion complex of 1-(5-cyano-naphthyl)diazomethane with β-cyclodextrin was made. The complex was thermally decomposed and extracted with ether to isolate the water soluble host-guest products. The regioselectivity of the products was analyzed by HPLC and NMR. Although NMR results proved to be inconclusive, HPLC results in comparison to previous studies (particularly those from a complex formed from inclusion of 2-(6-cyanonaphthyl)-diazomethane with β-CD) indicate that C-3 insertion was favored, nearly exclusively. These results are also consistent with previous studies in which 1- and 2-naphthyl tethers to β-cyclodextrin also favor the C3 hydroxyl.

Due to the unusual binding strength of this cyanonaphthyl-tethered CD in solution, the corresponding separation and identification techniques proved difficult, but also may indicate the presence of a very powerful host. It is the hope that further studies of this compound will explore energetic considerations of this unique complex.
REFERENCES

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VITA

Scott Tobias Forrest


In August of 1990, the author re-entered The College of William and Mary as a M.A. degree candidate in chemistry with a concentration in organic chemistry.

In August of 1992, the author plans to enter The Medical College of Virginia, Virginia Commonwealth University, in Richmond, Virginia, to pursue an M.D. degree.