

Fall 2002

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SYNTHESIS AND CHEMISTRY OF NAPHTHALENE ANNULATED TRIENYL IRON COMPLEXES: POTENTIAL ANTICANCER DNA ALKYLATION REAGENTS

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Abstract:

Iron complex chemistry that opens a new door to the medicinal and pharmaceutical worlds is the aim of this research. Specifically, ortho-quinone methide moieties are intermediates in several antitumor drugs and have been identified as bioreductive alkylators of DNA. In our research, a class of iron compounds has been targeted to resemble these quinone methides. It is hoped that these new compounds could be modified to provide a window of opportunity toward the discovery of a selective mode of drug delivery. We have focused our efforts on generating a reactive transition metal complexed 5-membered ring analog of o-quinone methide based on our earlier reports of $\text{CpFe}(\text{CO})_2(\text{butadienyl})$ complexes. In this vein, we have elaborated this chemistry by preparing and reacting a lithionaphthalene allene with $\text{CpFe}(\text{CO})_2$, which gave the desired naphthalene annulated sigma complex. This complex thermally rearranged to the desired naphthalene annulated 5-membered ring quinone methide analog. Upon photolysis, this complex successfully mimicked its antecedent and alkylated alcohols. Thus, we here report our initial study of the preparation and chemistry of a transition metal complexed 5-membered ring quinone methide analog. Its reactions with alcohols have accomplished the first step toward the ultimate goal of selectively alkylating DNA.

Introduction:

Cancer has become a prevalent disease facing many people of the world today. Naturally, its ubiquitous and devastating character has led many attempts to synthesize a suitable drug for combat. Fortunately, scientists have determined the benevolent nature of quinone methides and their alkylation of nucleic acids as an effective mechanism for anticancer antibiotics. Ortho-quinone methide moieties are believed to be intermediates of several antitumor drugs.

Quinone methides are a class of compounds in which one of the oxygen atoms of a quinone is replaced by a methylene (or substituted methylene) group. The reactivity of quinone methides

is mainly electrophilic in nature, which can also be directly correlated to their toxicological properties. If the alkylation process is achieved under mild, ideally biological, conditions, it could be used in a number of biomolecular applications. In fact, these reactive intermediates have been used as DNA alkylating agents and crosslinkers.¹ Compounds that react through quinone methide and related intermediates moieties couple to the amino groups of guanine (N^2) and adenine (N^6) bases primarily to modify nitrogen nucleophiles; they also couple to the oxygen functional groups, most notably the phosphate and ribose oxygens as well as (O^2) of cytosine and (O^6) of guanine. The specificity of DNA alkylation depends greatly on the reaction pathway and the ability of the reactive intermediate to associate with particular nucleotide sequences or helical conformations.²

As to the nature of quinone methides, they, especially the simple ones, are unstable and are often not isolable in a pure form. Instead, they rapidly polymerize upon concentration of their dilute solutions. So far, no "simple" quinone methide has been isolated, except for cases in which the quinone methide moiety is part of a fused aromatic system with little contribution from the quinone methide form. The observed stability of such a complex could only be attributed to the formation of a strong metal-olefin bond that remains stable even at the expense of the loss of aromaticity of the quinone methide.³ Therefore, the key to synthesizing these intramolecular metal-quinone methide complexes is to retain the reactive nature of the quinone methide complexes so that it can subsequently interact and modify reagents, such as DNA.

The marriage of organometallic chemistry and drug design has only lightly been explored.⁴ Recently, the Allison group has targeted a class of organometallic compounds that resembles quinone methides and may possess potential DNA alkylation abilities. Specifically, we chose a research pathway (shown in Figure 1) that would focus on the preparation and chemistry of a selected $(\text{h}^1\text{-C}_5\text{H}_5)_2\text{Fe}(\text{CO})_2\text{-(h}^1\text{-pentatrienyl)}$ complex that should mimic new medicines.⁵

In efforts to synthesize these compounds, previous studies of the Allison group found that in general, butadienyl iron complexes converted to hydroxyferrocenones in very high yields as outlined in Scheme 1.^{6,7} The synthesis of the starting butadienyl complexes **2** was carried out with ease; yet, in the past, efforts to prepare compounds needed for our project, i.e. the analogous pentatrienyl sigma complex, had not been successful. (See Scheme 2.) The reason for this failure was thought to be due to an intermediate **4** in the mechanism that gives complex **5**. This mechanism is shown in Scheme 3, in which pentatrienyllithium attacks the carbonyl to form **4**, followed by concomitant alkyl migration and iodide displacement to give **5**.

We suspected that intermediate **4** was responsible for previous stumbling blocks in preparation of the pentatrienyl complex. Instead of the pathway shown in Scheme 3, it was thought that the intermediate underwent cyclization to give an undesired complex **6** and ultimately decomposed as shown in Scheme 4.

We carried out model theoretical calculations for an organic compound that corresponded to **4** and found that the conversion of **4** to **6** was favorable by -20kcal/mol. This estimate related the ease of the undesired cyclization to occur, followed by decomposition. In light of this problem, we sought a pentatrienyl ligand that contained a key annulated aromatic moiety.

Compounds that are classified as aromatic are characterized to be cyclic, having conjugated double bonds with delocalized electrons. Aromatic compounds exhibit unusual stability. This gain in stability is due to resonance energy and is the result of the delocalized and overlapping orbitals of the *p* electrons. With the annulated aromatic naphthalene moiety of the pentatrienyl ligand in **4cAR**, we hoped that the complex would be blocked from the undesired cyclization, i.e. **6cAR**, and facilitate migration to form the preferred iron complex **1**.⁸ (See Scheme 5.) Such would be true if the energy required to break the aromaticity of the ring was too much to allow cyclization to occur. Our synthesized pentatrienyl complex would then possess DNA alkylation potential.

Methods:

The experimental design consisted of beginning with the applicable 1-bromo-2-methylnaphthalene (**7**) and performing a series of reactions to synthesize the desired Σ^3 -naphthalene annulated pentatrienyl quinone methide complexes. The series of reactions are shown in Scheme 6.

Step 1: Preparation of 1-Bromo-2-bromomethylnaphthalene (8). A round-bottomed flask equipped with a magnetic stir bar was fitted with an air condenser. The bromo-methylnaphthalene **7** (19mL, 122mmol), NBS (24.175g, 160.75mmol), and 500mL of CCl_4 were placed inside the flask and irradiated with a 250W flood lamp for 20h while stirring. The product was recrystallized in hot hexanes to give a mass product **8** of 26.095g in 71.3% yield.

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Step 2: Preparation of 1-Bromo-2-hydroxymethylnaphthalene (9). A round-bottomed flask was equipped with a magnetic stir bar, and complex **8** (26.095g, 86.98mmol), $CaCO_3$ (44.784g, 447.84mmol), 250mL of deionized water, and 250mL of P-dioxane were added. The reaction was refluxed at 90°C for 16h while stirring. The solution was then allowed to cool. The organic product was collected by being dissolved in 600mL of CH_2Cl_2 and 800mL of 1M HCl. After separation, the organic phase was washed three times with 100mL portions of saturated $NaHCO_3$ and dried over $MgSO_4$. The product was recrystallized in hot hexanes to give a mass product **9** of 9.08g in 44% yield.

Step 3: Preparation of 1-Bromo-2-carbaldehyde naphthalene (10). Complex **9** (6.5g, 27.3mmol) was dissolved in 180mL of CH_2Cl_2 . In a round-bottomed flask, PCC (11.75g, 54.4mmol), the naphthalene solution, and a stir bar were placed. The reaction flask was fitted with an air condenser and allowed to stir for 1.5h. Ether (40mL) was added to the reaction mixture, and the black gum was washed with two 10mL portions of ether. This organic phase was passed through a column of a 1-in. layer of celite wet with ether. The product was purified over a column of silica gel in 10% ether/pentane solution. The mass product **10** was 5.907g in 92% yield.

Step 4: Preparation of Acetic acid 1-(2-bromonaphthalen-1-yl)hept-2-ynyl ester (11). In a large oven-dried Schlenk tube, a magnetic stir bar was added, and N_2 atmosphere was established. Dry ether (75mL) and 1-hexyne (1mL, 8.8mmol) were added. The reaction flask was submerged in an ice bath. $N-BuLi$ (1.6M, 5.5mL, 8.8mmol) was added dropwise over a period of 5min. The solution was allowed to stir 10min. In a small oven-dried Schlenk tube of N_2 atmosphere, complex **10** (1.872g, 8mmol) was quickly added, and the flask was degassed three times. The aldehyde was dissolved in 85mL of dry ether. The aldehyde solution was added to the reaction mixture over a period of 10min, and it was allowed to stir for 1.5h. After having warmed to room temperature, to the reaction flask was added 100mL of ether and 75mL of $DI H_2O$. After separation, the organic was washed twice with 75mL portions of $DI H_2O$ and dried over $MgSO_4$. The product was purified by passing it over silica gel in ether. The mass product **11** was 2.562g in 89% yield.

Step 5: Preparation of 2-Bromo-1-(3-methylhepta-1,2-dienyl)naphthalene (12). In a large oven-dried Schlenk tube, a magnetic stir bar was added and N_2 atmosphere was established. Quickly, $LiBr$ (2.345g, 27mmol) and CuI (5.142g, 27mmol) were added to the flask. The flask was degassed three times. The reagents were dissolved in 90mL of dry ether and allowed to stir 30min in an ice bath. $MeMgBr$ (3M, 9mL, 27mmol) was added dropwise over a period of 5min. The reaction was stirred 30min. In a small oven-dried Schlenk tube of N_2 atmosphere, complex **11** (3.2g, 8.9mmol) was added and dissolved in 25mL of dry ether. This solution was added dropwise to the reaction mixture over a period of 5min, the ice bath was removed, and the solution

was allowed to stir for 24h. To extract the compound, 40mL of DI H₂O and 50mL of ether was added to the Schlenk tube. The solution was filtered over a Buchner funnel. After the addition of 50mL of ether and 30mL of saturated NH₄Cl, the filtrate was separated. The organic phase was washed three times with 30mL portions of DI H₂O and dried over MgSO₄. The product was purified by passing it through silica gel in 2% ether/pentane solution. The mass product **12** was 1.828g in 65% yield.

Step 6: Preparation of Σ^1 -Pentatrienyl Sigma Complex (13). To a medium oven-dried Schlenk tube, a magnetic stir bar was added and N₂ atmosphere was established. Dry THF (20mL) and complex **12** (1.008g, 3.2mmol) were added to the Schlenk tube. The tube was placed in an acetone/dry ice bath at -88°C. It was allowed to stir 10min. Over a period of 5min, 1.6M n-BuLi (2.2mL, 3.52mmol) was added. The solution was allowed to stir for 1h. In a small oven-dried Schlenk tube of N₂ atmosphere, quickly FpI (0.623g, 3.52mmol) was added, and after a N₂ atmosphere had been re-established, the crystals were dissolved in 8mL of dry THF. Over a period of 10min, the FpI solution was added to the medium Schlenk tube. After stirring 10min, the ice bath was removed, and stirring was continued for an additional 20min. The reaction mixture was coated with 8.8g of 6% water/alumina gel. It was immediately transferred to the top of a N₂ saturated 6% water/alumina column, keeping in mind that this product is unstable in the presence of air. The product was eluted at a rate of one drip per second with 2.5% ether/pentane solution. The mass product **13** was 0.814g with a 62% yield.

Conversion of Σ^1 -Pentatrienyl Sigma Complex to 5-Membered Ring Quinone Methide Complexes (14). Complex **13** was thermodynamically converted to **14** by placing it in a dry flask in dark atmosphere over a period of two weeks. This quinone methide complex was purified by passing it through a N₂ saturated 6% water/alumina column with 2.5% ether/pentane solution. Two bands were present with remnants of complex **13** eluting first off the column followed by the complex **14**.

Alkylation Reactions. Four small aliquots of the 5-membered ring quinone methide complexes were dissolved in 1.5mL of CDCl₃ and placed in a NMR tube. 10mL (10 equivalents) of diethylamine, 5mL (4 equivalents) of ethanol, 20mL (20 equivalents) of methanol, and 10mL (10 equivalents) of methanol were placed in the tubes, respectively. The first three tubes were placed in an ice bath of 0°C, and the last tube was placed in a dry ice/acetone bath of -78°C. All reactions were photolyzed at 75W. These reactions were monitored through Nuclear Magnetic Resonance. See Figures 4, 5, 6, and 7 for results.

Results and Discussion:

Preparation of the desired h³-naphthalene annulated pentatrienyl quinone methide analog was successfully accomplished as shown in Scheme 6. Reaction of 1-bromo-2-carbadehyde naphthalene (**10**) with hexynyllithium followed by acylation gave **11** in an 89% yield. Reaction of **11** with CuI /

MeMgBr yielded the allene **12** in 65% yield. Reaction of the naphthalene annulated vinyl allene bromide **12** with n-BuLi followed by (C₅H₅)Fe(CO)₂I gave sigma complex **13** in 62% yield. This h¹-sigma complex is identified through ¹H-NMR by its characteristic peaks at d 6.76 and d 5.08. The absorption at d 6.76 has an integration of 1, resulting from the single proton on the allene, and the peak at d 5.08 has an integration of 5, resulting from the 5 protons on the cyclopentadienyl group. [See Figure 2.]

At room temperature, this compound was cleanly converted to the diastereometric stable quinone methide complexes **14** with a half-life of two weeks. The compound is identified through ¹H-NMR by characteristic peaks at d 4.12 and d 3.52, 3.58. The former allene peak at d 6.76 had disappeared, and two new peaks had appeared at ca. d 3.5 with an integration of 1; this represents the single proton on the h³-complex. Also, the peak at d 5.08 had shifted to d 4.12, representing the 5 protons on the cyclopentadienyl group. [See Figure 3.]

Initial alkylation reactions were performed to mimic the quinone methide analog reactions in the presence of cancerous DNA. The test reagents chosen (diethylamine, ethanol, and methanol) all represented the characteristics of amine or alcohol groups contained on DNA. In the process of alkylation, the quinone methide analog would attach itself to DNA; this reactivity is a key factor in the nature of an anticancer drug. The results of the four reactions (Figures 4, 5, 6, and 7) reveal that there were definite changes in the course of the reactions as compared to the ¹H-NMR spectrum of the quinone analog starting complex (Figure 3). In all four reactions, a set of twin novel peaks are formed at d 6.45, 6.55. However, more tests must be done on the products of the alkylation reactions to accurately determine what is exactly happening, if DNA alkylation is indeed occurring, and what is being formed.

One can note that when comparing the methanol reactions at 0 and -78°C (Figures 6 and 7) the ideal condition for photolysis is in a dry ice/propanol solution of -78°C. Here, the reaction was much cleaner and would better facilitate identification of the newly formed products. This alkylation reaction with methanol at -78°C was recently submitted for analysis via Electrospray Mass Spectroscopy. However, there has not been sufficient time to thoroughly analyze the results and begin the process of identifying the products of the alkylation reaction.

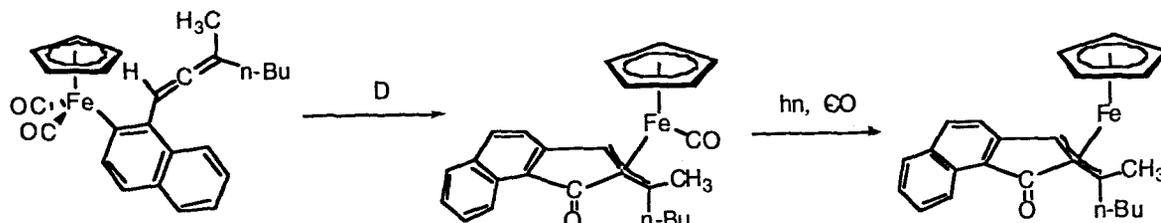
Indefinitely, this research project has provided a strong foundation in the chemistry of transition metal pentatrienyl complexed 5-membered ring quinone methide analog. It has proven successful in the synthesis of the desired complex. Thus, we have made a contributable step toward the potential of an anticancerous drug. With a promising future, we can continue in further research to study alkylation reactions with this newly synthesized product.

References:

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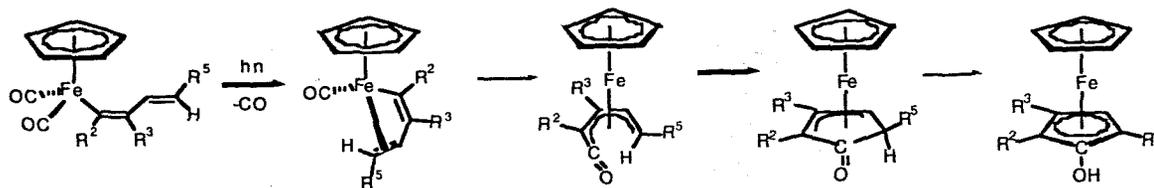
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Figure 1



1

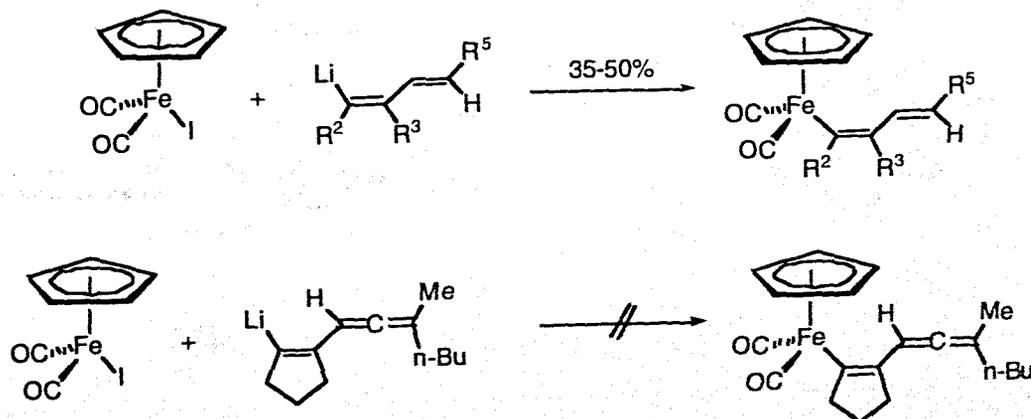
Scheme 1



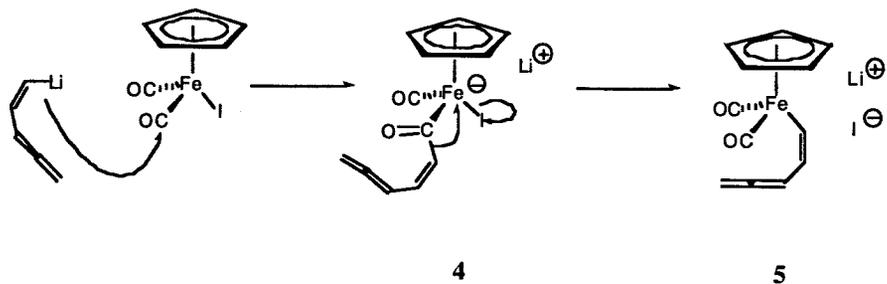
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Scheme 2

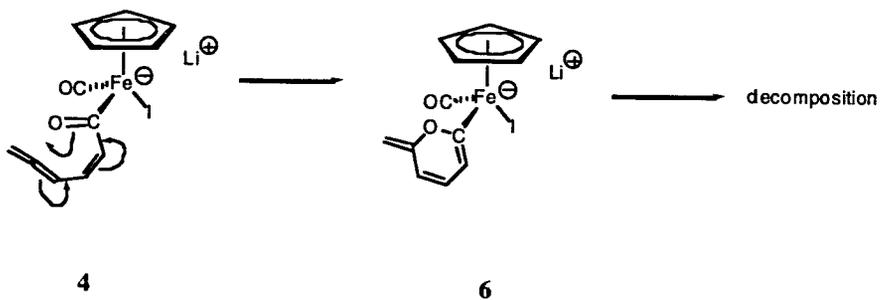
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Scheme 3



Scheme 4



Scheme 5

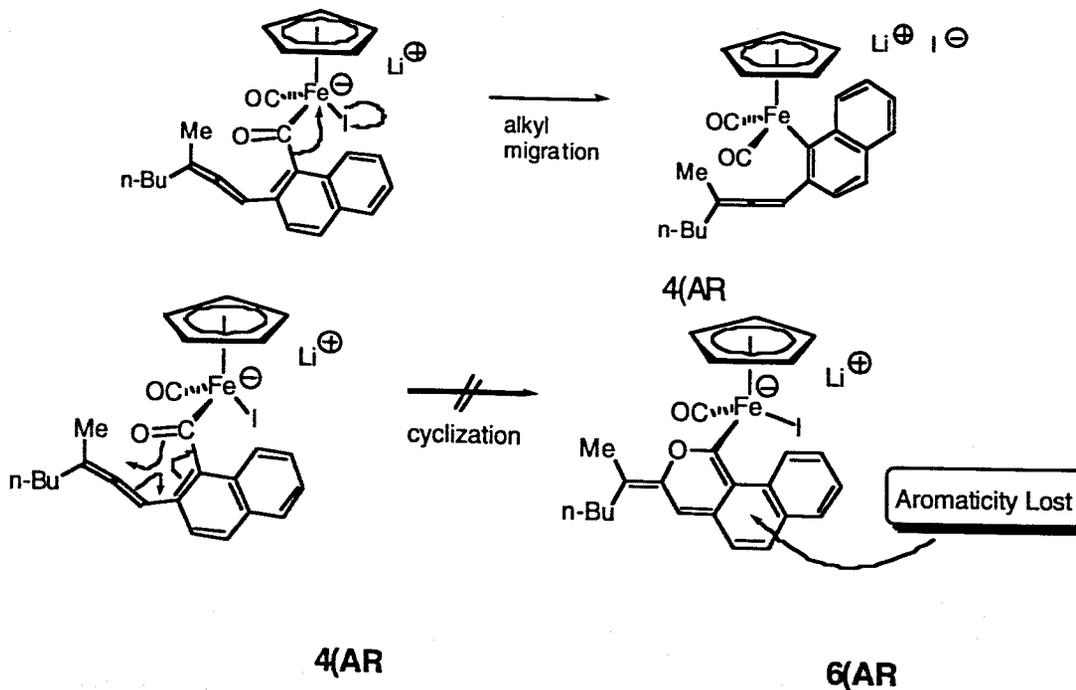


Figure 3: 5-Membered Ring Quinone Methide Complexes 14

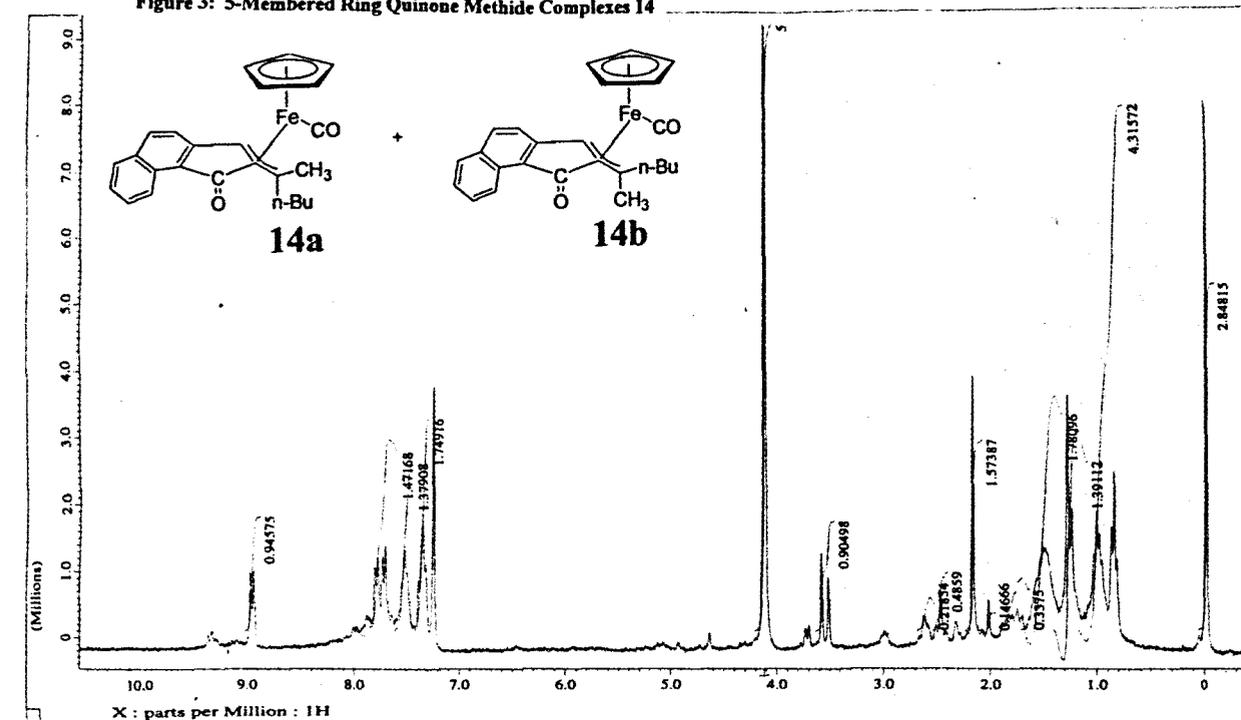


Figure 4: Diethylamine Alkylation Reaction

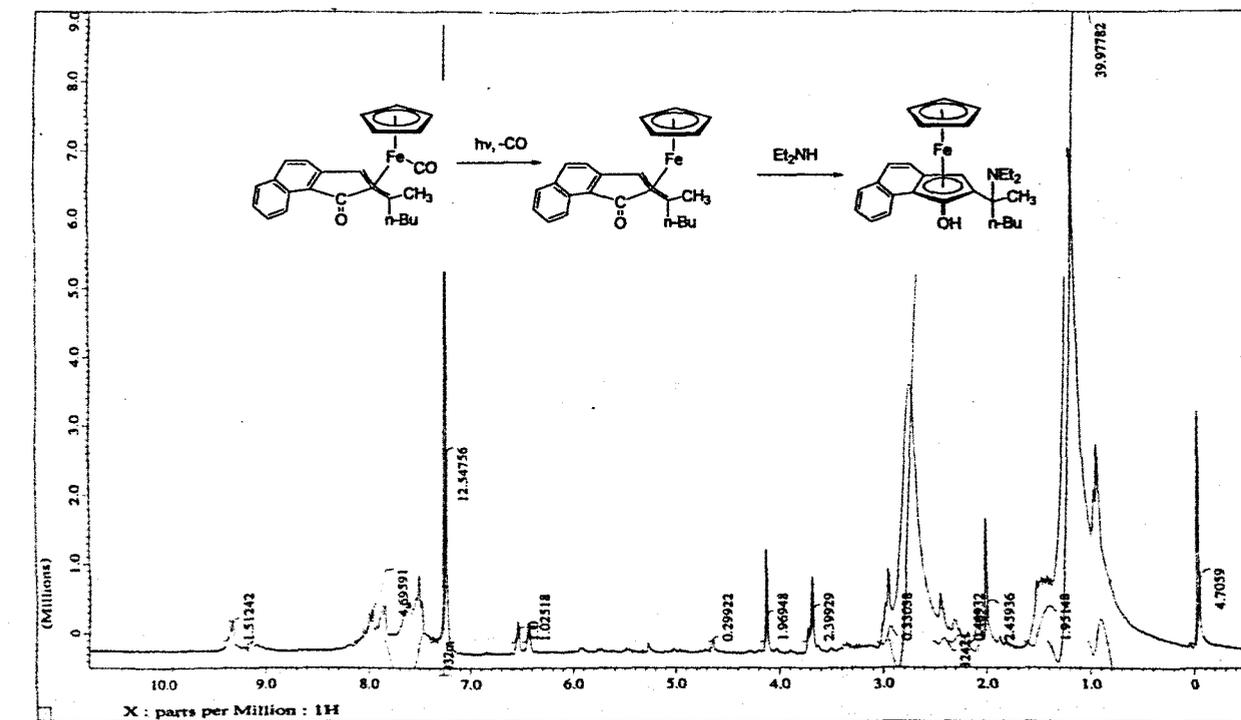


Figure 5: Ethanol Alkylation Reaction

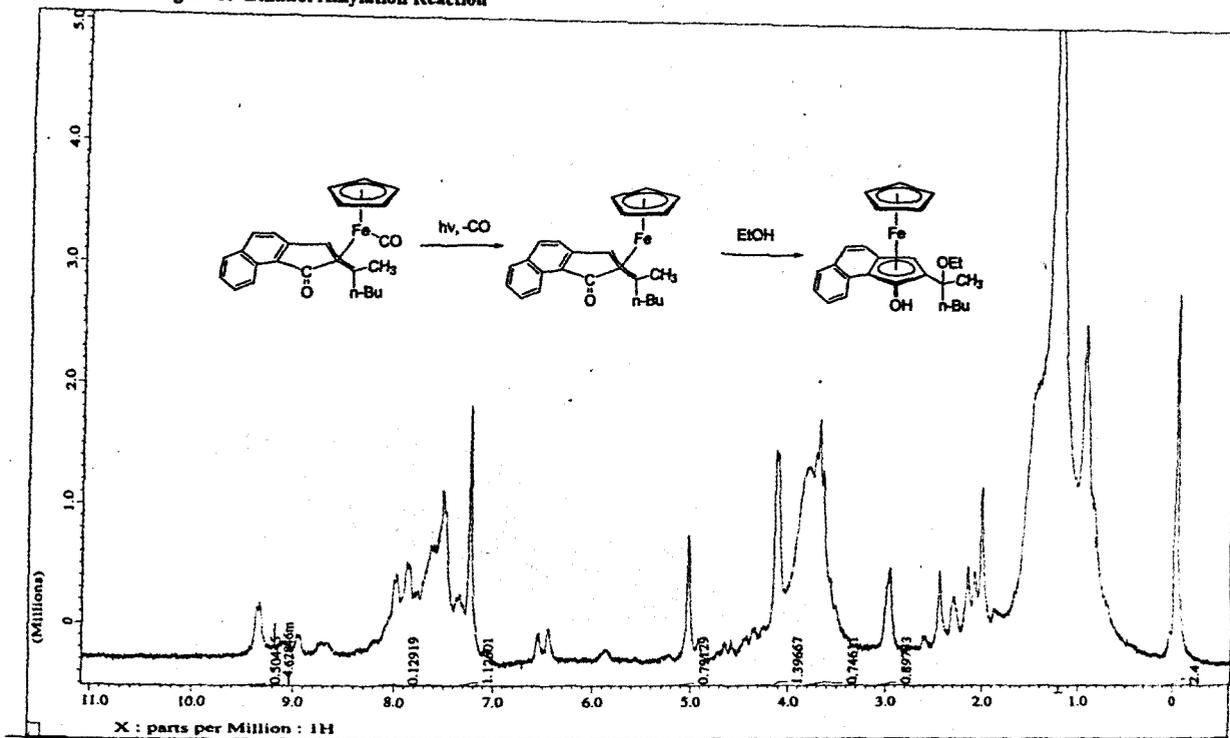


Figure 6: Methanol Alkylation Reaction at 0°C

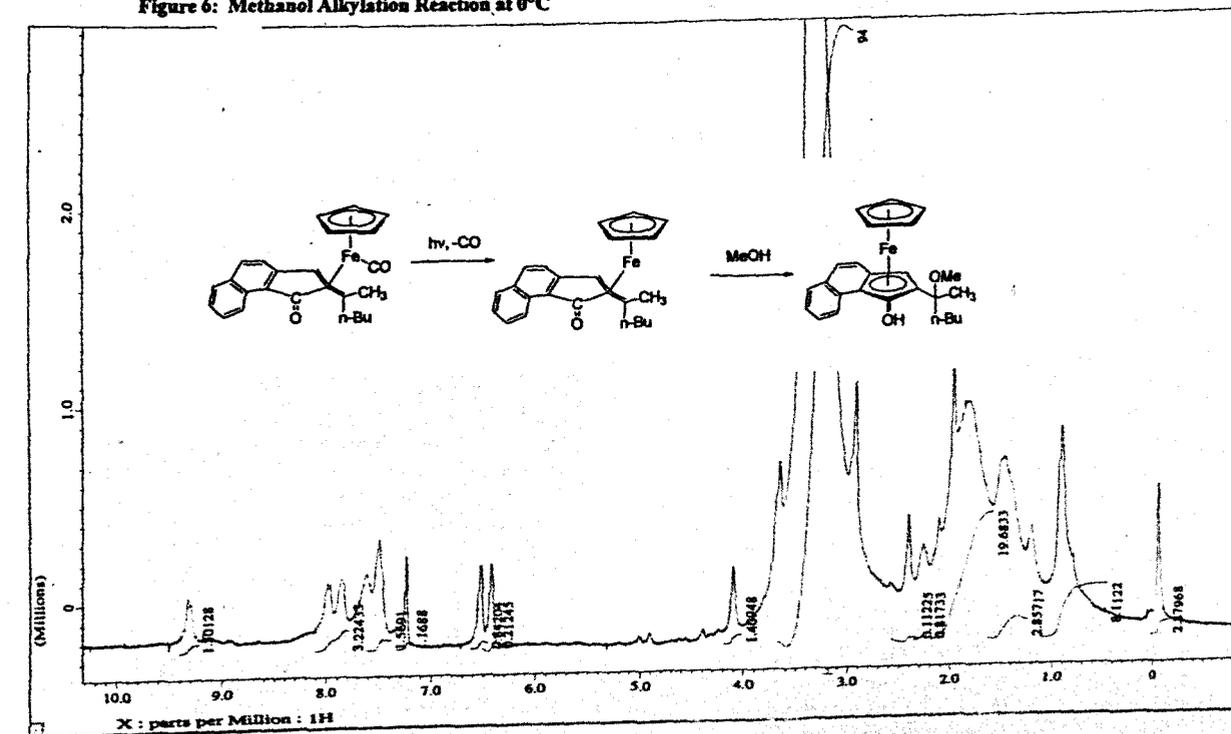
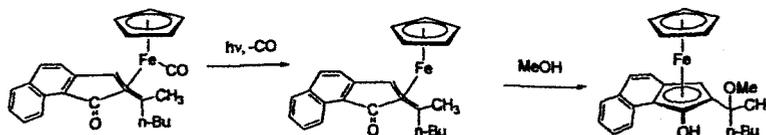
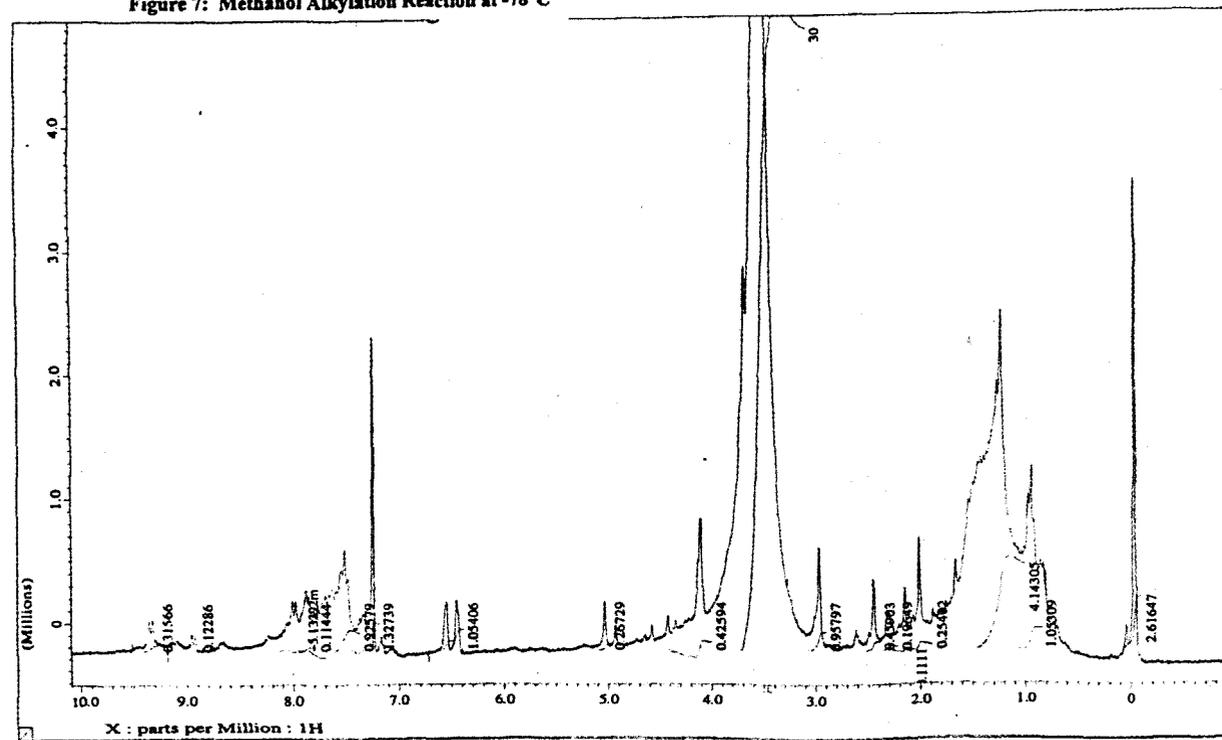


Figure 7: Methanol Alkylation Reaction at -78°C



Faculty Comments:

Neil Allison, Ms. Means' faculty mentor, is lavish in his praise of her work. He says:

My contact with Ms. Means has been extensive. First she attended my organic chemistry lab course (Organic 1, CHEM 3702) that I taught in fall 1999. In the spring 2000, she was enrolled in my organic chemistry lecture course (Organic 11, CHEM 3713). At this time she decided to carry out honors research work in my group. Ms. Means is currently working in my research lab on a chemistry problem that focuses on model studies of potential anticancer and anti-tumor drugs. She has chosen to carry out these studies as her senior honor's project in her four-year honors scholar program. This course of study is the most academically rigorous program on our campus. I would say that she is truly a multi-task person that solves all problems with gusto. Even with all of her obligations, I have found that Ms. Means is not a "bookworm" type. She is completely honest and reliable. She has an amiable personality and is well liked by our faculty and her peers. Probably most impressive on the research front is that she also is a leader in my laboratory. When she

is present, all of the students are excited about their research! This rare quality is not found in many people, and to have a person that is excited about research with an effervescent personality really tends to ignite the whole lab. The research that Ms. Means is currently accomplishing is comparable to what I would expect from a good third-year graduate student. She grasps theoretical chemical concepts instantly. In fact, after she read a grant proposal that I was writing in the area of her research, she was able to offer suggestions! I would never have expected this from an undergraduate student and only would expect a third or fourth year graduate student to be mature enough for this task. Her laboratory skills are the best I've seen from any undergraduate student (and most graduate students) in my laboratory. She has accomplished a completed project, one that I am currently writing up as a communication for publication in an American Chemical Society journal. To be published as a communication means that it must be "urgent, fast breaking research". In this paper we report that she has accomplished a new multi-step synthesis of a previously unknown compound. We anticipate that this compound will be an important

model for a new class of drugs based on an organometallic system (something previously unknown). All factors considered, of our current chemistry students I would rank Ms. Means at the top in research. Before coming to this university I studied at the University of California, Berkeley, the University of Cologne, and the University of Florida, Gainesville. I would rank Ms. Means, at her stage in her career, among the best undergraduate students that I've seen at these universities. Over the past 22 years, I've probably written 160 or so letters of recommendation for students, half of whom I would consider as outstanding students. Ms. Means is certainly in the very top handful (3 to 5) of these students.

I must also mention, although not related to research, that Ms. Means also takes on other, perhaps more mature, responsibilities. Through her compelling need to help people she is carrying out missionary work in a very impoverished area of Haiti for two months this summer and during spring break. Traci is active in helping people. I just found out that she purchases food for an elderly woman who is housebound and takes it to her apartment. In the past Ms. Means has also helped visually impaired students. This includes note taking, reading, etc.

Ms. Means' faculty advisor, Dale Johnson, is also very complimentary; his remarks follow ...

I have been Traci Means' academic advisor for the past four years so I am familiar with her great academic strengths, and I have followed her research through conversation with Ms. Means and her mentor Professor Allison. Ms. Means is a special student; she is quick to grasp concepts and can use them in new situations with ease. She has never chosen the easy academic path and is completing the four-year honors degree leading to a BS in Biophysical Chemistry, perhaps the most demanding undergraduate degree option offered by the Department of Chemistry and Biochemistry. In her own words, "I chose this rigorous major because I believe it is interesting, challenging, and will best prepare me for my next academic goal, entering medical school."

Professor Neil Allison has raved about her work ethic and the ease with which she learns laboratory skills. Despite a busy academic schedule, she is the most productive member of his research group, surpassing the output of some of our graduate students. I have read a draft of a publication that is in progress based



on her undergraduate thesis. It will be an important contribution to both organometallic and biosynthetic chemistry and will serve as the foundation for a new research direction for Allison's research group. This is the sort of contribution you hope will come from the efforts of an excellent graduate student. To see this productivity from an undergraduate is

extremely impressive.

A third chemistry professor, Wally Cordes, is equally enthusiastic about Ms. Means' research. He says ...

It is easy to say positive things about Traci Means. The expectations of the chemistry department are high; even so, the research independence developed by Ms. Means is extraordinary, and her over-all academic record is equally outstanding.

Professor Allison has had a large number of excellent undergraduate students work in his lab during his tenure here, and for him to say that Ms. Means is about the best he has ever had is a significant statement. The research she has done is not a trivial project: the extremely air-sensitive materials she has worked with require the highest level of experimental technique. And the chemical reactions she has developed and perfected are all very sophisticated organic reactions. In reading the abstract of her work I can see how Dr. Allison compares it to the work of a third-year graduate student. Organic synthesis is not an easy kind of research for an undergraduate student to pursue; it requires more patience and perseverance than many other kinds of chemical research. There are many minor details that must be handled to have decent yields of final products. In most cases of an undergraduate student doing this kind of research one expects the student to make daily visits to the research director asking for advice on how to overcome "the problem of the day". That's why it also impresses me when Dr. Allison said Ms. Means would go to the lab and attack these problems on her own, so that by the next time he saw her she would tell him how she had solved the problems and attained the desired results.

The research will be submitted for publication in one of the highest prestige research journals of the American Chemical Society, and I'm confident it will be published. In addition to the organic chemistry developed, it has important pertinence to the "hot" area of research for selective drug delivery.