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Diene substituent effects on the retro-Diels-Alder reaction and a formal catalytic cycle for ester hydrolysis based on the Michael/retro-Michael reaction

Duerr, Brook Foster, Ph.D.
The Ohio State University, 1989

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DIENE SUBSTITUENT EFFECTS ON THE RETRO-DIELS ALDER REACTION
AND A FORMAL CATALYTIC CYCLE FOR ESTER HYDROLYSIS
BASED ON THE MICHAEL/RETRO-MICHAEL REACTION

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

Brook Foster Duerr

* * * * *

The Ohio State University

1989

Dissertation Committee:
Dr. Anthony W. Czarnik
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Approved by

Dr. Anthony W. Czarnik
Advisor
Department of Chemistry
DEDICATION

To the memory of my sister, Robin
ACKNOWLEDGMENTS

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Last, but certainly not least, I would like to thank my wife, Barbara, for proofreading this dissertation and for all the support she has provided throughout this work.
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"Diene-Substituent Effects on the Rate of the Retro-Diels-Alder
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"Synthesis of 9,10-Disubstituted Anthracenes Derived From
9,10-Dilithioanthracene." Brook F. Duerr, Y.-S. Chung, Anthony W.

"Structural Effects Controlling the Rate of the Retro-Diels-Alder
Reaction in Anthracene Cycloadducts." Yongseog Chung, Brook F.
Duerr, Timothy A. McKelvey, P. Nanjappan, Anthony W. Czarnik
PRESENTATIONS

"Synthesis and Retro-Diels Alder Kinetics of Cycloadducts from 9,10-Disubstituted Anthracenes." Y. Chung, B. F. Duerr, and Anthony W. Czarnik, Presented as a poster at the 19th Central Regional Meeting of the American Chemical Society, June 24-26, 1987, Columbus Ohio.


FIELDS OF STUDY

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LIST OF ABBREVIATIONS

Å
Ac
AMPSO
Anal
proxy
AQS
Ar
~
avg
BHT
Bu
°C
13C
Galcd
cm
cmpd
CPK
D
DA
DABCO
δ
dd
DDQ
EDTA
EI
en
Et
eu
ΔH‡
FT
g
Glu
gly
h
HEPES
His
1H
Hz
IPA
in vacuo
J

angstroms
acetyl (-COCH₃)
3-[1,1-Dimethyl-2-hydroxyethyl)amino]-2-hydroxy-1-propanesulfonic acid
analysis
approximately
8-acetoxy-5-quinoline-sulfonate
aromatic
approximately
average
2,6-di-tert-butyl-4-methylphenol
butyl
degrees celsius
carbon thirteen
calculated
centimeters
compound
Corey-Pauling-Koltun
dextrorotatory
Diels-Alder
1,4-Diazobicyclo[2.2.2]octane
donfeld shift of NMR signal from (CH₃)₄Si
dooublet of doublets
2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Ethlenediaminetetracetic acid
electron ionization
NH₂CH₂CH₂NH₂
ethyl
entropy units
enthalpy of activation
fourier transform
gram or grams
glutamic acid
glycine
hour or hours
[4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid
histadine
proton
Hertz (cycles per second)
isopropyl alcohol
under vacuum
coupling constant
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CHAPTER I

Introduction

Organization of this dissertation

The body of work covered in this dissertation can be divided into two parts: (a) diene substituent effects on the retro-Diels-Alder reaction, and (b) a formal catalytic cycle based on the Michael/retro-Michael reaction. These research projects are part of the current work in the Czarnik group involving the design of catalytic groups that function by reversible covalent bond formation. Chapter I deals with metal ion-promoted and metal ion-catalyzed hydrolysis of esters and amides, and the alcoholysis of amides. Chapter II covers the retro-Diels-Alder reaction and its use as part of a catalytic cycle based on the Diels-Alder/retro-Diels-Alder reaction. Chapters III-V cover work done on the retro-Diels-Alder diene substituent effects. Chapter VI gives an overview of the Michael/retro-Michael reaction and its use as a catalyst delivery system. Chapters VII and VIII include work completed on a catalytic cycle based on the Michael/retro-Michael reaction.

Background

The conversion of carboxamides to carboxylic esters or acids under non-forcing (i.e., not strongly acidic or basic) conditions is
a very slow process,\textsuperscript{1,2} and for this reason the use of amides
as synthetic precursors to esters and acids is seldom considered.
Certain enzymes such as carboxypeptidase A have evolved highly
efficient means of carrying out these types of transformations under
conditions of physiological temperature and pH.\textsuperscript{3} Carboxypeptidase
A is a proteolytic enzyme which hydrolyzes only the peptide bond at the
carboxyl-terminal end of proteins.\textsuperscript{4} The crystal structure of
carboxypeptidase A has been solved at 2.0 Å resolution.\textsuperscript{5} It
has also been found that there is a catalytically important zinc ion
ligated to the basic side chains of Glu-72, His-196, and His-69 in the
active site of carboxypeptidase A.\textsuperscript{6} One of the proposed mechanisms
for carboxypeptidase A utilizes the zinc ion to polarize the amide
carbonyl group via oxygen ligation; the rate of productive attack
by oxygen nucleophiles at carbon is thus increased. Similar results
should be possible to obtain in enzyme mimic systems. By providing a
binding site for a metal ion close to the carbonyl group undergoing
transacylation, it should be possible to observe metal ion promoted or
catalyzed transacylation.\textsuperscript{7}

Metal Ion Catalysis of Ester Hydrolysis

In 1952, Kroll reported that several α-amino acid esters were
hydrolyzed much more rapidly in the presence of heavy metal divalent
ions.\textsuperscript{8} For example, Kroll reported that glycine methyl ester was
hydrolyzed in the presence of 1 equivalent of Cu\textsuperscript{2+}, Co\textsuperscript{2+} or Mg\textsuperscript{2+}
at pH 7.3-7.9 and 25.4°C. Under similar conditions in the absence
of metals, the esters were quite stable. The mechanism proposed by Kroll for the hydrolysis is shown in Figure 1. He believed that the attainment of equilibrium between metal-ion and amino acid ester to form 2 (Figure 1) was a rapid process. The rate determining step would thus involve formation of the complex 4. At constant pH, the rate of hydrolysis was found to follow a first order course with respect to the ester (3). This showed that the rate determining step took place either during or after the formation of metal-ion ester complex (2).

Kroll also looked at the ratio needed between colbaltous ion and ester to obtain a maximum rate of hydrolysis. As can be seen in Figure 2, the observed first-order rate approached a maximum as the metal ion to ester ratio approached one. The attainment of a maximal hydrolytic rate, unaffected by further addition of metal ion, was further support for the existence of the postulated metal-ion ester complex (2).

Kroll also found that the reaction was sensitive to changes in pH as shown in Figure 3. An increase of one pH unit produced a four-fold increase in the rate of hydrolysis; this was attributed to a second order reaction between metal ion complex and hydroxyl ion superimposed on the relatively slow hydrolysis of the amino acid ester in the absence of added metal ion. Furthermore, the reaction was not a general base catalyzed process, since doubling the buffer concentration had no effect on the rate.

In the presence of divalent metal ions, a metal-ester complex forms (2 and 3, Figure 1) which has a greater affinity for hydroxyl ions
Figure 1: Metal ion-promoted hydrolysis of an amino-acid ester.
Figure 2: Effect of cobaltous ion concentration on the rate of hydrolysis of 0.016 molar glycine ethyl ester at pH 7.8 and 25°C.\textsuperscript{8}
Figure 3: Effect of pH on the rate of hydrolysis of 0.016 molar glycine ethyl ester in the presence of 0.016 molar cobaltous ion at 25°C.
than the free amino acid ester. The metals thus serve as Lewis acids. The product of this acid-base neutralization (4) is unstable and undergoes a rapid decomposition to the final products.

Bender and Turnquist restudied the metal catalyzed glycine methyl ester hydrolysis as well as D,L-phenylalanine ethyl ester hydrolysis. They observed a decreasing first order rate constant for the cupric ion catalyzed hydrolysis of glycine methyl ester at pH 7.3 and 25°C. This was explained by the fact that the amino acid product of the hydrolysis bound the cupric ion stronger than the ester did, and the cupric ion was thus not released to the buffer solution. The cupric ion was therefore not catalytic in the strict sense of the word since it remained complexed to the acid, and so a decreasing first order rate constant was observed for this metal-ion promoted reaction.

Bender and Turnquist also found a difference of approximately $10^6$ between the cupric ion-catalyzed and alkaline hydrolysis of D,L-phenylalanine ethyl ester (alkaline hydrolysis $k_1 = 5.8 \times 10^{-9} \text{ s}^{-1}$, Cu$^{++}$ catalyzed hydrolysis $k_1 = 2.67 \times 10^{-3} \text{ s}^{-1}$). This could not be explained solely by the presence of an increase in charge, nor could it be due to attack by a water molecule on a positively charged $\alpha$-amino ester, since Bender and Turnquist had shown previously that the rate of acidic hydrolysis of phenylalanine ethyl ester is small. Westheimer and Shookhoff have shown that the introduction of a positive charge two atoms away from the carbonyl group of an ester increases the rate of hydrolysis by a factor of $10^3$. It was thus proposed by Bender and
Turnquist that the rapid cupric ion-catalyzed hydrolysis of $\alpha$-amino esters was due to an interaction of the metal ion with the ester group. This was further supported by the fact that Bender and Turnquist had previously shown that cupric ion was completely ineffective in accelerating the hydrolysis of ethyl acetate.\textsuperscript{12}

Finally, Bender and Turnquist used $^{18}O$ exchange experiments to gain some insight into the intermediate formed during the hydrolysis.\textsuperscript{9} The results of these experiments showed that an addition intermediate was formed that was symmetrical with respect to the isotopic oxygen atom. Such an intermediate would be consistent with 9 in Figure 4. Based on the evidence they found, Bender and Turnquist proposed the mechanism shown in Figure 4 for the copper ion-promoted ester hydrolysis.

Breslow and Overman in 1970 attempted to extend the catalytic effect to the nonligand substrates by attaching a metal-binding group to a molecule with a hydrophobic cavity (Figure 5).\textsuperscript{13} For the hydrophobic cavity molecule they chose cyclohexaamylose, a toroidal polysaccharide which was well known to bind $p$-nitrophenyl acetate ($p$NPA) molecules in its central cavity. By treating cyclohexaamylose with 1 equivalent of the 5-$m$-nitrophenyl ester of pyridine-2,5-dicarboxylic acid, they were able to isolate 10 in 55-65% yield after purification. The addition of 1 equiv. of NiCl$_2$ to solutions of 10 afforded the chelate 10-Ni$^{2+}$. Compound 10 was converted to 11 by addition of 1 equiv. of pyridine-carboxaldoxime (PCA).
Figure 4: Proposed mechanism for glycine methyl ester hydrolysis.
Figure 5: Schematic structural drawing of catalytic group attached to hydrophobic binding cavity.\textsuperscript{13}
They found that 11 is about 4 times more reactive toward pNPA at pH 5.17 than is an equivalent concentration of the nickel-pyridine-carboxaldoxime (PCA-Ni\(^{++}\)) complex. This corresponds to a rate acceleration greater than \(10^3\) over the uncatalyzed rate. Control experiments further showed that the rate increase of 11 relative to PCA-Ni\(^{++}\) does not arise from the presence of cycloamylose or pyridine-2,5-dicarboxylate. They therefore suggested that the increased reactivity of pNPA toward 11 is a result of binding and reaction within the 11-pNPA complex.

Further evidence for the proposal that there was binding inside the cavity and then hydrolysis was shown by the fact that the hydrolysis of pNPA in the presence of 11 was competitively inhibited (\(k_1 = 0.05-0.07\ M\)) by cyclohexanol. The rate of the PCA-Ni\(^{++}\) catalyzed reaction was unaffected by addition of cyclohexanol. They also found that 8-acetoxy-5-quinoline-sulfonate (AQS), which is too large to fit into the cyclohexamylose cavity, was only 57% reactive toward 11. Breslow and Overman thus demonstrated that binding near the site of metal chelation can result in significant rate accelerations, and that competitive inhibition can be observed with the substrate.

In 1985, Fife and Przystas studied the hydrolysis of phenolic and aliphatic esters of picolinic acid and found significant metal ion catalysis by Ni\(^{++}\) and Cu\(^{++}\) on both the hydroxide and water catalyzed hydrolysis.\(^{14}\) They found that 0.01 M Ni\(^{++}\) produced rate enhancements of \(10^2\) to \(10^6\). Copper ion (0.001 M) on the other hand produced rate enhancements of \(10^4\) to \(10^6\) fold. The systems they studied showed Michaelis-Menten type kinetics as evident
from Figure 6. As shown in Figure 6, saturation could be observed for Ni$^{+2}$. A similar effect was found for Cu$^{+2}$, and at saturating concentrations of Ni$^{+2}$ and Cu$^{+2}$, rate enhancements of $2.7 \times 10^4$- and $1.3 \times 10^5$-fold respectively were observed.

The authors proposed that in these reactions, the metal-ion promoted, hydroxide catalyzed reactions could involve nucleophilic attack of a metal ion coordinated-hydroxide ion at the carbonyl of the ester (12, Figure 7), or attack by external hydroxide on the metal ion complex (13). Similarly, the metal ion promoted water reactions they observed might have involved nucleophilic attack of a metal ion coordinated water molecule (14) or attack of external water (15). The authors further proposed that the rate-determining step involved nucleophilic attack rather than loss of the leaving group. This was supported by the fact that upon varying the leaving group pKa from 12.4 to 4.4, no significant decreases in rate were observed.

Menger et al. recently found that metallomicelles hydrolyze phosphate triesters, diesters and other phosphorous (V) compounds.\textsuperscript{15} Metallomicelles of 16 (Figure 8) were found to catalyze the hydrolysis of p-nitrophenyl diphenyl phosphate, (PNPDPP, 17, Figure 8) very effectively. At pH 6.0 and 25°C, 16 hydrolyzed PNPDPP with a $k_{\text{obs}} = 4.1 \times 10^{-2}$ s$^{-1}$. This hydrolysis was 8000 times faster in the presence of 16 than in the absence of 16 at pH 8.0, or stated differently, 16 causes the PNPDPP hydrolysis half-life to decrease from about 20 days to 17 s. In the absence of copper ion, N,N,N',N'-trimethyl N'-tetradecylethylenediamine did not hydrolyze PNPDPP, therefore the hydrolysis was due solely to the cupric ion complex.
Figure 6: Plot of $k_{obs}$ vs. Ni$^{2+}$ concentration for hydrolysis of ethyl 6-carboxypicolinate in water at 50°C and pH 8.18.14
Figure 7: Nucleophilic attack of metal ion-coordinated hydroxide at the carbonyl of the ester (12) or attack by external hydroxide on the metal ion complex (13) and nucleophilic attack of the metal ion-coordinated water molecule (14) or attack of external water (15).
Figure 8: Top: CuCl$_2$ complex of N$_2$N$_2$N'-trimethyl-N'-tetradecylethlenediamine (16) used to form metallomicelles. Bottom: p-nitrophenyl diphenyl phosphate, PNPDPD (17).
Menger et al. also demonstrated that metallomicelles of 17 showed turnover activity, and that they were truly catalytic with respect to 17.

**Metal Ion Catalysis of Amide Hydrolysis Reactions**

Metal ions can catalyze the hydrolysis of amides in much the same way as they do esters. As has been stated, 1,2 hydrolysis of amides in the absence of metals is an extremely slow reaction. Meriwether and Westheimer showed that the hydrolysis of glycinamide was copper ion-promoted by a factor of about 30.16 They further suggested that this difference in the rate of hydrolysis compared to the corresponding ester hydrolysis was due to differences in leaving group abilities. They reasoned that if the effect of the metal ions is to facilitate nucleophilic attack at the carbonyl group, then the observed rate enhancement could be less in amide hydrolysis where the poor leaving group makes breakdown of a tetrahedral intermediate (19) rate-determining (Figure 9).

Larger rate accelerations of amide hydrolysis have been observed and reported by Breslow et al.17 Breslow found that Ni^{++} produces a 400-fold enhancement in the hydroxide ion-catalyzed hydrolysis of 1,10-phenanthroline-2-carboxamide. Much larger accelerations were seen in the hydration of 1,10-phenanthroline-2-carbonitrile (22), Ni^{++} giving 10^7-, Cu^{++} 10^9-, and Zn^{++} 10^4-fold enhancements.17 Breslow proposed that the large rate increase was due entirely to the more favorable
Figure 9: Metal ion-promoted amide hydrolysis reaction.\textsuperscript{16}
Figure 10: Two possible mechanisms, A and B of hydroxide attack on phenanthroline carbonitrile.\textsuperscript{17}
The value of $\Delta S^\dagger$ for the sodium hydroxide catalyzed hydration was $-20 \pm 4$ eu and for the Ni$^{++}$ catalyzed hydration $\Delta S^\dagger = +14 \pm 1$ eu. Such a large value for $\Delta S^\dagger$ in the Ni$^{++}$ catalyzed hydrolysis was unexpected, but it suggested two possible mechanisms for this kind of hydrolysis reaction. The two mechanisms proposed by Breslow are shown in Figure 10. There are two possible modes (A and B, Figure 10) of attack by hydroxide: (A) attack of external hydroxide on the complexed substrate, or (B) attack of a coordinated hydroxide on the complexed substrate. As has been stated, the $\Delta S^\dagger$ was positive and 14 eu, therefore mechanism B is most consistent with this observation. The transition state of B involves bonding of the developing imino anion to the metal ion, perhaps displacing a coordinated water molecule at the adjacent site, resulting in less solvation and thus a positive $\Delta S^\dagger$.

In 1966, Alexander and Busch developed a different type of substrate (26) where the metal ion was bound in a complex (Figure 11). In the studies described above, the free metal ion was in equilibrium with complex species and ligand exchange could occur. It was the goal of Alexander and Busch to develop and utilize a relatively inert cobalt (III) complex in order to permit preparation and characterization of intermediates, and isolation of the steps in the complicated overall rate process. They prepared glycine ester complexes of the type $\text{cis-}[\text{Co(en)}_2(\text{NH}_2\text{CH}_2\text{CO}_2\text{R})\text{X}]\text{X}_2$, where $\text{R} = \text{CH}_3, \text{Et, ipr}$ and $\text{X} = \text{Br or Cl}$; (Figure 12). In these ester complexes, the ester is bonded to the
Figure 11: Cobalt(III) complex used to hydrolyze glycine esters.\textsuperscript{18}
Figure 12: Proposed mechanism for cobalt(III)-promoted hydrolysis of glycine esters.\textsuperscript{18}
cobalt (III) solely through the amino group, and the ester group remains free. These complexes were fairly stable in aqueous solution and this supported a claim by Bender and Turnquist that two sites in the coordination sphere of the metal ion must be available to the ester in order to accelerate the hydrolysis.  

Alexander and Busch reacted mercury (II) ion with their halide complexes, which effected removal of the halides and formed a five-coordinate, highly reactive complex. They further found that the vacated position in the coordination sphere of the cobalt (III) was taken up by the carbonyl oxygen of the ester to yield a chelated ester complex, \( \text{Co(en)}_2(\text{NH}_2\text{CH}_2\text{CO}_2\text{R})^{+3} \) (29). In the absence of other nucleophiles, water attacked the carbonyl carbon resulting in the hydrolysis of the ester and formation of \( \text{Co(en)}_2(\text{NH}_2\text{CH}_2\text{CO}_2)^{+3} \). Infrared studies showed that the same intermediate was formed regardless of which halogen complex was used as starting material. Finally, they showed that the hydrolysis of the chelated ester was subject to nucleophilic or general base catalysis. All of these findings were in support of the mechanism proposed by Bender and Turnquist for the \( \text{Cu}^{++} \)-promoted hydrolysis of \( \alpha \)-amino esters.  

Buckingham et al. reported that glycinamide chelated through its carbonyl oxygen and terminal nitrogen atoms and peptide complexes of the type \( [\text{CoN}_4(\text{glyNR}_1\text{R}_2)]^{+3} \) show 10^4 to 10^6-fold rate increases for hydroxide ion-catalyzed hydrolysis compared to uncoordinated amides.  

They followed the base catalyzed hydrolysis of the chelated glycinamide and dipeptides
spectrophotometrically in the region 280-340 nm. The amides studied in this system hydrolyzed $10^6$-to-$10^8$ times slower than the corresponding $[\text{Co(en)}_2(\text{glyOC}_3\text{H}_7)]^{+3}$ ester. They also found a comparable difference in hydrolysis for uncoordinated molecules. Overall, however, the direct activation of the carbonyl group by the metal results in a $\sim 10^6$-fold enhancement in the rate compared to the uncoordinated molecule. To date, these results for the hydrolysis remain some of the fastest rates observed. However, Buckingham et al. concluded that it is very unlikely that $\text{Zn}^{++}$ or $\text{Mn}^{++}$ would be more effective at polarizing the carbonyl group of a peptide bond than $\text{Co}^{++}$, and so carboxypeptidase A must be exerting some type of additional activation in order to obtain the rapid rates of hydrolysis observed.$^{20,4a}$

In 1984, Groves and Chambers demonstrated that there must be a precise geometric orientation of the metal ion relative to the carbonyl group in metal-promoted amide hydrolysis.$^{21}$ They wanted to prepare metal-amide complexes in which the modes of interaction between the metal and the amide carbonyl were strictly defined. Groves and Chambers looked at the 3 families of carboxypeptidase A mechanisms shown in Figure 13, and they realized that of the 3 mechanisms shown, that summarized in 32 (mechanism C) looked to be the most reasonable given the evidence known up to that time. The role of the metal in 32 is likely two-fold: (1) to assist deprotonation of a coordinated water molecule, and (2) to position the resulting metal hydroxide for addition to the amide carbonyl.
Figure 13: Three possible modes of attack by hydroxide at an amide carbonyl.\textsuperscript{21}
Simultaneously, interactions of the amide oxygen at the metal center are also possible with this geometry. To accomplish their studies, they synthesized compounds 33 and 34 (Figure 14).

![Chemical structure](image)

\[
\begin{align*}
33 \quad X &= -\text{CH}_2\text{NMe}_2 \\
34 \quad X &= -\text{CH}_2\text{N(\text{CH}_2\text{COO}^-)}_2
\end{align*}
\]

Figure 14: Rigid metal-amide complex studied by Groves and Chambers.\textsuperscript{21}

Using the compounds described above, Groves and Chambers found large rate enhancements (10\textsuperscript{3}-10\textsuperscript{6}) of zinc and copper complexes; in these complexes, at neutral pH the metal is forced to lie above the plane of the amide. They further showed that activation parameters for the metal-promoted hydrolysis indicated that catalysis resulted from a substantial increase in ΔS\textsuperscript{‡}. Based on their observations they proposed the mechanism shown in Figure 15. They further proposed that in carboxypeptidase A, Glu-270 acts as a general base to assist the formation of a metal-bound hydroxide and that nucleophilic addition of the metal-bound hydroxide is involved in catalysis.
Figure 15: Possible mechanism for metal ion-promoted amide (35) hydrolysis.\textsuperscript{21}
In summary, the carboxypeptidase A and other metalloprotease model studies discussed above have shown many important ways to model the acyl transfer reactions of metalloenzymes. However, as has been pointed out above, rate accelerations that have been observed to date still do not approach the rates that are observed by metalloenzymes such as carboxypeptidase A. Chapter II will discuss methods that have been used to date by the Czarnik group to model metalloenzymes.
As has been shown in Chapter I, model systems have demonstrated that rate enhancements can be afforded by a metal center in the absence of enzyme. However, the thermodynamic affinity of a single amide carbonyl oxygen for metal ions in coordinating solvent is so small that successful studies to date have either: (1) required some sort of additional ligand covalently bound to the substrate amide so that an intramolecular chelate can be formed, or (2) relied on the kinetic stability of preformed metal amide complexes under the reaction conditions used. Either of these prerequisites severely limits the utility of metal ions as true catalysts.

Enzymes circumvent these problems by binding the metal and the amide separately in close proximity at the active site. This allows the substrate to interact transiently with the catalyst by the way of a preequilibrium noncovalent association. Unfortunately, however, not all reactions can be run in aqueous environments. In nonaqueous solvents, the hydrophobic binding forces utilized by proteins vanish, and hydrogen-bonding and ion pair forces may become so strong.
as to make reversible binding unlikely. It therefore occurred to us that another type of interaction should allow for the temporary complexation of catalyst and substrate group: reversible covalent bond formation. Furthermore, by carefully choosing the type of reversible reactions, organic as well as aqueous environments should be able to be used.

Figure 16 shows a generic catalytic cycle based on reversible covalent bond formation via the Michael reaction. In the cycle, a catalytic group (41) is brought into close proximity to a substrate 42 by covalent bond formation to give 43. A catalytic step \( k_{\text{cat}} \) is then carried out on 43 to give 44. The product of the \( k_{\text{cat}} \) step (44) then undergoes reverse covalent bond formation to give the transformed substrate (45) and the original catalytic group (41) ready to undergo another turn through the cycle. There are two reversible reactions that have been studied thus far by the Czarnik group that can be used to fit this type of generic catalytic cycle: (1) the Diels-Alder/retro-Diels-Alder reaction, and (2) the Michael/retro-Michael reaction. The remainder of this chapter will discuss the background on the Diels-Alder/retro-Diels-Alder reaction and its relationship to Chapters III and IV. A formal catalytic cycle based on the Michael/retro-Michael reaction will be discussed in Chapters V-VIII.

The Diels-Alder reaction is a reversible reaction that can be used to fit the generic catalytic cycle suggested by Czarnik. As shown in
Figure 16: Generic catalytic cycle based on reversible covalent bond formation.
Figure 17, the Diels-Alder reaction can be used for the first step of the reaction (step 1), and the retro-Diels-Alder reaction can be used in the final step (step 3) of the cycle. The catalytic group could be thought of as being attached to a diene (46) and then brought into close proximity to a functional group to be converted by attaching it to a dieneophile (42) as shown in step 1: the forward Diels-Alder reaction. Step 2 of the cycle would then allow the catalytic group to convert the functional group in some manner, preferably a transacylation reaction to give 48. Finally, step 3 would then utilize the retro-Diels-Alder reaction to give the converted functional group attached to the dieneophile (45), and the original diene (46) ready to re-enter the cycle.

In 1984, Czarnik introduced a novel, formal catalytic cycle for metal ion-promoted transacylation reactions. This cycle is shown schematically in Figure 18. The first step of the cycle is a Diels-Alder reaction between 9-(2-pyridyl)anthracene (49) and acrylamide (50) to yield the ortho adduct (51) and meta adduct (52) in 18 and 29% yield respectively. The ortho compound (51) undergoes ethanolysis to 53 in the presence of Ni^{2+} ion, whereas 52 does not. Cycloreversion of 53 yields 49 and ethyl acrylate (54), but cycloreversion of 52 yields only starting materials.

The catalytic cycle shown in Figure 18 had 3 limitations that needed to be overcome in order for this cycle to be useful. First, not all of the 9-(2-pyridyl)anthracene is converted cleanly to adducts in the cycloaddition step. Second, 29% of the products of the
Figure 17: Catalytic cycle based on the Diels-Alder/retro-Diels-Alder reaction.
Figure 18: Ni\textsuperscript{2+}-Promoted conversion of acrylamide to ethyl acrylate using the Diels-Alder reaction.\textsuperscript{22}
cycloaddition step were not able to enter the second step of the cycle due to their stereochemistry, leading to an unproductive branch of the cycle. Third, the cycloreversion step of the cycle requires heating to 230°C in order to be effected.

In 1987, Nanjappan and Czarnik published an expanded version of this work, which is depicted in Figure 19. In this case, acrylonitrile (55) was the dieneophile added to 9-(2-pyridyl)-anthracene (49) to give ortho adduct 56 and meta adduct 57. Only the ortho adduct 56 underwent hydration to a carboxamide adduct (51). These observations shown in Figure 18 and 19 respectively can be explained by either a 7-membered metal chelate, or more likely by the formation of metal bound hydroxides that are capable of attack on the carbonyl group of the amide 51 or the nitrile group of 56 as shown in Figure 20. The fact that only the ortho adducts can bind metal ions in proximity of the amide group in 51 or nitrile group of 56 would explain the lack or reactivity of the meta adducts.

An improvement on the cycles shown in Figures 18 and 19 would be to use a chelating ligand on the diene so that the cycloadduct does not need to "find" a metal ion prior to the \( k_{\text{cat}} \) step. This could be achieved by designing a symmetrical diene that would always have a chelating group on the same side of the adduct containing the functional group. The compound chosen for this by Czarnik is shown in Figure 21: 9,10-Bis(((2-diethylamino)ethyl)methylamino)methyl)-anthracene (60). By reacting 60 with acrylonitrile (55) or
acrylamide (50, Figure 22), adducts would be formed (61 and 62 respectively) that would be able to form metal chelates regardless of orientation of the cycloaddition step. It was also shown that 60 was able to form zinc chelates, and that these chelates could enter into Diels-Alder reactions with acrylonitrile (Figure 23).

Figure 19: Metal ion catalyzed conversion of acrylonitrile to acrylamide using the Diels-Alder reaction. 23
Figure 20: Formation of metal hydroxides on Diels-Alder adducts 51 and 56.23
Figure 21: 9,10-Bis-(((2-diethylamino)ethyl)methylamino)methyl)anthracene
Figure 22: Cycloadduct formation between 9,10-Bis-(((2-diethylamino)ethyl)methylamino)methyl)anthracene and acrylamide (62) and acrylonitrile (61).\textsuperscript{23}
Figure 23: Formation of zinc chloride chelated Diels-Alder cycloadduct.\textsuperscript{23}
Kinetic studies of the conversions shown in Figure 24 were initiated using aqueous solutions buffered to pH's between 5.0 and 9.5 (reactions A, C, and D) or absolute ethanol (reaction B) as solvent. Unexpectedly, none of these attempted reactions were observed to occur even under conditions more strenuous than those utilized in the 9-(2-pyridyl)anthracene study (Figure 18). It was proposed that binuclear complexes formed in methanolic solution are kinetic products, and that in aqueous solutions equilibrium occurs to give complexes of one metal atom per two TMEDA units; such a species would be oligomeric and probably catalytically inactive owing to the lack of available metal ligand sites for either functional group or solvent.\textsuperscript{23} It was also suggested that the TMEDA chelates formed were sufficiently large so as to prohibit metal interaction with the functional group within the adduct.

Since it had already been shown by Czarnik (Figure 17) in the 9-(2-pyridyl)anthracene study that acyltransformations were possible,\textsuperscript{22} it was decided that it would be best to redesign the catalytic cycle so that a different starting material for the cycloaddition step could be used. Furthermore, because the cycloreversion step was such a slow step, it was decided that it would be best to choose chelating groups for the anthracene diene that would allow easy cycloreversion.

The Diels-Alder reaction is a very well known and well used reaction.\textsuperscript{25,26} The factors that influence the rate of the Diels-Alder reaction are well established, and the literature provided
Reaction A 62 $(R = \text{CN})$
Reaction B 61 $(R = \text{CONH}_2)$
Reaction C 61 $(R = \text{CONH}_2)$
Reaction D 65 $(R = \text{CO}_2\text{Et})$

Figure 24: Attempted transacylation and hydration reactions using metal chelates.
us with useful information as to which functional groups would allow the first step of our cycle to proceed at reasonable temperatures. The retro-Diels-Alder (rDA) reaction is the reverse of the familiar Diels-Alder reaction. As is often the case, the factors that influence a forward reaction are not always the same factors that influence the reverse reaction. Both synthetic, and mechanistic, aspects of the rDA reaction have been reviewed. The rDA reaction has been used as a key step in some recent syntheses. Despite all of the work that has been done on the rDA reaction, a survey of the substituent effects on the rDA reaction has not been reported. In order to fill this void, our research group undertook a fairly broad study of the effects of both diene and dienophile substituents on the rDA reaction.

In order to complete the work in an organized manner, the project was divided into two parts based on the molecular components involved in the rDA reaction. Based on the structures shown in Figure 25, it can be seen that a logical division can be made between diene (68) and dienophile (45). It became apparent that it would be best to divide the study of substituent effects into two parts: one based on the diene portion of the molecule and the other half based on the dieneophile portion of the molecule. In 1986, Nanjappan and Czarnik published their results on the effects of the dienophile substituents on the rDA reaction.

Nanjappan and Czarnik studied the substituent effects of 22 widely varying substituents as shown in Figure 26. The structures of the substituents studied and the first order rate constants are shown in
Figure 25: Schematic diagram of the retro-Diels-Alder reaction.
Figure 26: Reaction used by Nanjappan and Czarnik to study dienophile substituent effects on the retro-Diels-Alder reaction.$^{30}$
Table 1. Careful inspection of Table 1 shows several general trends. First, rDA reaction of 71-type adducts shows no steric effect. This is evidenced by the fact that derivatives 71b-e cyclorevert at essentially the same rate. Molecular mechanics calculations showed that compound 71e (R = tert-butyl) would be relieved of 2.3 kcal/mol more strain energy than the H-substituted adduct (71a) upon cycloreversion. The discovery of no increase in rate upon changing the substituents from R = H to R = tert-butyl was in stark contrast to the known steric effect in the cycloaddition reaction. Vaughan and Andersen had shown that increasingly bulky substituents made the forward Diels-Alder reaction progressively slower.\textsuperscript{31} Nanjappan and Czarnik proposed that since the rDA reaction has a transition structure whose structure resembles the adduct, and the strain energy stored in the adduct is felt equally by the transition structure, and so its eventual release comes too late to provide a rate acceleration.

Nanjappan and Czarnik also found that electron withdrawing groups on the dienophile fragment made the rDA reaction faster, which was completely analogous to the forward reaction. This can be seen when entries 71a-71e and 71t-71v are compared to entries 71h-71n. The first entries (71a-71e and 71t-71v) are considered classical electron donating substituents, and their rates of cycloreversion were slower than the classical electron withdrawing substituents (entries 71h-71n). Furthermore, comparison of the kinetic activation parameters (Table 2) showed that the cycloreversion reaction was enthalpically, rather than entropically controlled.
Table 1. First-order rate constants of retro-Diels-Alder reactions at 250°C in diphenyl ether.²³

<table>
<thead>
<tr>
<th>R'</th>
<th>compd</th>
<th>$10^6 k_1$, s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>71a</td>
<td>1.21</td>
</tr>
<tr>
<td>Me</td>
<td>71b</td>
<td>1.14</td>
</tr>
<tr>
<td>Et</td>
<td>71c</td>
<td>1.09</td>
</tr>
<tr>
<td>i-Pr</td>
<td>71d</td>
<td>0.97</td>
</tr>
<tr>
<td>t-Bu</td>
<td>71e</td>
<td>0.88</td>
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<tr>
<td>Ph</td>
<td>71f</td>
<td>146</td>
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<tr>
<td>SiMe₃</td>
<td>71g</td>
<td>19.6</td>
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<tr>
<td>CO₂H</td>
<td>71h</td>
<td>168</td>
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<tr>
<td>CO₉NH₂</td>
<td>71i</td>
<td>39.8</td>
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<tr>
<td>CO₂CH₃</td>
<td>71j</td>
<td>69.0</td>
</tr>
<tr>
<td>CN⁻</td>
<td>71k</td>
<td>81.9</td>
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<tr>
<td>COCH₃</td>
<td>71l</td>
<td>217</td>
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<tr>
<td>CHO</td>
<td>71m</td>
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<td>NO₂</td>
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<td>NH₂</td>
<td>71o</td>
<td>100</td>
</tr>
<tr>
<td>NHAc</td>
<td>71p</td>
<td>16.7</td>
</tr>
<tr>
<td>NMe₂</td>
<td>71q</td>
<td>3006 (a)</td>
</tr>
<tr>
<td>NMe₃⁺TsO⁻</td>
<td>71r</td>
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</tr>
<tr>
<td>OAc</td>
<td>71s</td>
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</tr>
<tr>
<td>OH</td>
<td>71t</td>
<td>1.62</td>
</tr>
<tr>
<td>OCH₃</td>
<td>71u</td>
<td>2.70</td>
</tr>
<tr>
<td>OSiMe₃</td>
<td>71v</td>
<td>2.73</td>
</tr>
</tbody>
</table>

(a) Due to the fast reaction rate at 250°C, $k_1$ was extrapolated from the temperature dependence.
Table 2. Kinetic activation parameters for some representative substituents in the retro-Diels-Alder reactions of anthracene adducts in diphenyl ether

<table>
<thead>
<tr>
<th>compd</th>
<th>( \Delta H^\ddagger ) (kcal/mol)</th>
<th>( \Delta S^\ddagger ) (eu)</th>
<th>T(avg), °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>71b</td>
<td>44 ± 1.7</td>
<td>2.9 ± 3.2</td>
<td>245</td>
</tr>
<tr>
<td>71e</td>
<td>50 ± 2.0</td>
<td>14 ± 4.0</td>
<td>245</td>
</tr>
<tr>
<td>71j</td>
<td>38 ± 0.38</td>
<td>-1.8 ± 0.74</td>
<td>245</td>
</tr>
<tr>
<td>71q</td>
<td>29 ± 0.11</td>
<td>-11 ± 0.22</td>
<td>220</td>
</tr>
<tr>
<td>71u</td>
<td>43 ± 3.4</td>
<td>2.0 ± 6.5</td>
<td>245</td>
</tr>
</tbody>
</table>

Finally, Nanjappan and Czarnik found that if the Hammett \( \sigma_p \) constant was used to characterize electron-donating \( (\sigma_p < 0) \) or -withdrawing \( (\sigma_p > 0) \) substituents, then compounds 71f, 71g, 71m, 71o, 71q, 71s, 71t and 71u are all significantly (>25 times) faster than can be explained based solely on this parameter. In the most extreme and pronounced case, the "strongest" electron-donating group, dimethylamino (71q), makes the reaction even faster than does the "strongest" electron-withdrawing group, trimethylammonium (71r). The dimethyamino group (71q) accelerates the reaction by a factor of 3 \( \times 10^6 \) over that predicted, based on its \( \sigma_p \) value of -0.83.

With the dienophile substituent effects of the retro-Diels-Alder reaction well studied, attention in the Czarnik group was then turned toward the study of diene substituent effects on the rDA reaction. Chapter III will cover the synthesis of 9,10-disubstituted
anthracenes used to complete this study, and Chapter IV will deal with the synthesis of the Diels-Alder adducts needed to complete this study. Finally, Chapter V will cover the results and discussion of diene substituent effects on the retro-Diels-Alder reaction.
CHAPTER III

Synthesis Of 9,10-Disubstituted Anthracenes

As shown in Chapter II, Czarnik has used an asymmetrical anthracene as the diene in his catalytic cycle, and this led to two Diels-Alder adducts (Figure 18). To avoid the formation of ortho and meta adducts and the problems with separation and identification that would naturally go along with them, it was decided that symmetrically substituted anthracenes should be used. By choosing only symmetrical 9,10-disubstituted anthracenes, product isolation and characterization would involve simply isolating and identifying the desired products from the starting materials.

In order to initiate this study, multiple gram quantities of the 9,10-disubstituted anthracenes were needed. The anthracenes that were studied or attempted to be studied by us are shown in Table 3. Compounds 72, 73, 80, and 81 were available from Aldrich Chemical Company; however, for reasons that will be stated later, 73 and 81 were synthesized using literature methods or modifications of existing literature methods. Three other compounds, 83, 84, and 85 were generously provided in multiple-gram quantities by students of the OSU Honors Undergraduate Lab classes of
Table 3. 9,10-Disubstituted anthracenes studied.

![Anthracene Structure]

<table>
<thead>
<tr>
<th>R</th>
<th>compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>-H</td>
<td>72</td>
</tr>
<tr>
<td>-CH₃</td>
<td>73</td>
</tr>
<tr>
<td>-CH₂CH₃</td>
<td>74</td>
</tr>
<tr>
<td>-CH₂CH₂CH₃</td>
<td>75</td>
</tr>
<tr>
<td>-CH₂CH₂CH₂CH₃</td>
<td>76</td>
</tr>
<tr>
<td>-ipr</td>
<td>77</td>
</tr>
<tr>
<td>-tBu</td>
<td>78</td>
</tr>
<tr>
<td>-F</td>
<td>79</td>
</tr>
<tr>
<td>-Cl</td>
<td>80</td>
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<td>-Br</td>
<td>81</td>
</tr>
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<td>-I</td>
<td>82</td>
</tr>
<tr>
<td>-SCH₃</td>
<td>83</td>
</tr>
<tr>
<td>-COOH</td>
<td>84</td>
</tr>
<tr>
<td>-CN</td>
<td>85</td>
</tr>
<tr>
<td>-CO₂CH₃</td>
<td>86</td>
</tr>
<tr>
<td>-COCH₃</td>
<td>87</td>
</tr>
<tr>
<td>-C(OH)(CH₃)₂</td>
<td>88</td>
</tr>
</tbody>
</table>
1985, 1986 and 1987. The remaining compounds were synthesized or attempted to be synthesized by methods that will be discussed below.

Synthesis Of 9,10-Disubstituted Anthracenes Using 9,10-Dilithioanthracene

In order to obtain multiple-gram quantities of a starting material for a particular study, it is desirable to choose compounds that have at least one of the following characteristics: (1) they are purchasable and not expensive, (2) they are simple to make from known starting materials, or (3) they are described and fully characterized in the literature. As will be discussed, some of the compounds we studied did not fit these characteristics.

As shown in Figure 27, 9,10-dilithioanthracene (89) can be made by the halogen-metal exchange of 9,10-dibromoanthracene (81). This

![Figure 27: Halogen-Metal exchange of 9,10-dibromoanthracene to form 9,10-dilithioanthracene.](image)
reaction was first reported in 1948,32 and has been reported elsewhere.33 The starting material for this reaction, 81 can be purchased from several chemical companies or it can be synthesized in large quantities by bromination of anthracene.34 Personal experience has shown that quantities of up to 300 grams can be made with no special glassware. The halogen metal exchange reaction itself can also be performed on a fairly large scale; however, despite its possible synthetic utility, the range of electrophiles with which 89 could react has not been examined.

As shown in Figure 28, 9,10-dilithioanthracene (89) reacts with various electrophiles to afford 9,10-disubstituted anthracenes. The reaction of 89 with iodomethane has been reported to afford 73 in 16% yield.32 By optimizing the conditions of the reaction (see Experimental Section) we were able to increase the yield of the reaction to 59% based on isolated product. This allowed us easy access to gram quantities of 73 in a one pot reaction, and so we decided to explore the range of electrophiles that were useful in this reaction.

Reaction of 89 with ethyl iodide afforded 9,10-diethylanthracene (74) in 33% yield, and alkylations with n-propyl and n-butyl iodides provided 9,10-di-n-propylanthracene (75) and 9,10-di-n-butylanthracene (76) in 51 and 38% yields, respectively. Not surprisingly, attempted reactions with secondary and tertiary alkyl halides failed to give the desired products.

Reaction of 89 with such electrophiles as 2-bromopropane,
Figure 28: Synthesis of 9,10-disubstituted anthracenes using 9,10-dilithioanthracene.
2-iodopropane, 2-bromo-2-methylpropane and 2-iodo-2-methylpropane all gave only anthracene after aqueous workup. Secondary and tertiary alkyl halides appear to be too bulky to get close enough to the reaction center of 89 to react properly, and thus the reaction favors extraction of a proton by the E2 pathway.

Surprisingly, 9,10-diiodoanthracene (82) was an unknown compound when this study began. 9,10-Diiodoanthracene was the only compound we lacked in the halogen series, therefore we attempted to synthesize this compound in order to complete the series. We found that by reacting 89 with molecular iodine, 82 was formed in 47% yield. The only other halogen containing disubstituted anthracene we wished to synthesize and that could not be purchased was 9,10-difluoroanthracene (79). Two syntheses of 79 were ultimately realized by us but for continuity, only the method using 89 will be discussed here. A second, simpler method will be discussed under its own section later in this Chapter (see synthesis of 9,10-difluoroanthracene).

The fluorination of organic compounds has received widespread attention and has been the subject of two recent reviews. The concept of electrophilic fluorination has been the subject of considerable study and debate. The reason for this debate is the idea that the process of forming an electrophilic fluorine atom ("F\(^+\)) would require removal of 2 electrons from the most electronegative element. There are currently four commercial reagents that may be considered as sources of electrophilic fluorine:
perchloryl fluoride (FCI0\textsubscript{3}), xenon difluoride (XeF\textsubscript{2}), fluorooxytrifluoromethane (or trifluoromethylhypofluorite) (CF\textsubscript{3}OF), and F\textsubscript{2} itself. A few other fluorooxycompounds are known, e.g. SF\textsubscript{5}OF, CF\textsubscript{2}(OF)\textsubscript{2} and F(CF\textsubscript{2})\textsubscript{n}OF. All of these compounds have limitations such as corrosiveness, expense or toxicity that made them unsuitable as a source of electrophilic fluorine for our system.

In 1984, Barnette at Du Pont published an article showing that N-fluoro-N-alkylsulfonamides were stable sources of electrophilic fluorine capable of fluorinating carbanions under mild conditions.\textsuperscript{36} In 1986, Lee and Schwartz expanded the work of Barnette and used N-tert-butyl-N-fluoro-benzenesulfonamide to fluorinate alkenyllithium reagents.\textsuperscript{37} Based on this research, it was decided to attempt the fluorination of 89 with N-tert-butyl-N-fluoro-benzenesulfonamide. As shown in Figure 29, N-tert-butyl-N-fluoro-benzenesulfonamide (93) can be made from simple starting materials in two steps. The N-alkyl-sulfonamide (92) used in our study was previously reported in the literature by Lombardino.\textsuperscript{38} Fluorination of 92 to give 93 did provide some

![Figure 29: Preparation of N-tert-butyl-N-fluorobenzenesulfonamide](image-url)
difficulties for us in the beginning, but after a personal communication with Dr. S. H. Lee the fluorination proceeded easily. It should be noted that the concentrations given in the Experimental Section are the maximum concentrations that work effectively. At the present time Aldrich Chemical Co. sells two N-fluoro-N-alkyl-toluenesulfonamides.\(^3^9\)

With several grams of 93 on hand, the fluorination of 89 to give 9,10-difluoroanthracene (79) was attempted (Figure 30). After chromatographic purification, a 60% yield of 79 was realized. Using multiple runs of the electrophilic fluorination, we were able to obtain several hundred milligrams of 79. Although the quantities of 79 obtained were small, this method provided all the material we needed. A second method of synthesis offering different advantages will be discussed later.

Figure 30: Synthesis of 9,10-difluoroanthracene from 9,10-dilithioanthracene using N-tert-butyl-N-fluoro-benzenesulfonamide.
9,10-Dilithioanthracene (89) was previously reported to react with CO₂ to give 9,10-anthracenecarboxylic acid (84, Figure 31). Students of the OSU Honors Laboratory course found that by reacting 84 with freshly distilled thionyl chloride, and then removing the thionyl chloride \textit{in vacuo} and working the resulting solid up with methanol, they obtained 9,10-dicarbomethoxyanthracene (86). Thus, in two steps from 9,10-dilithioanthracene, 86 was obtained in 88% yield. The previously reported method of synthesis involved reduction of anthracene to the dianion, reaction with CO₂ to provide the dihydro dicarboxylic acid, esterification and dehydrogenation to give the desired product (86). \textsuperscript{40,41,42,43}

![Figure 31: Synthesis of 9,10-dicarbomethoxyanthracene.](image)

Attempts were also made at synthesizing 9,10-di-(2-propyl-2-ol)-anthracene (88) using 9,10-dilithioanthracene (89) as shown in Figure 32. The reaction failed in all attempts, possibly due to the fact that in order for the carbonyl of the acetone molecule to be attacked by the anion, the acetone molecule would have to be situated
perpendicular to the 9,10-dilithioanthracene molecule. Any other position would cause steric interference between the methyls on acetone and the peri hydrogens on 89 (Figure 33). With this failed attempt, another approach was sought. It was thought that by reacting 9,10-dicarbomethoxyanthracene (86) with excess methylmagnesium iodide or methyllithium (Figure 34), it might be possible to obtain alcohol 88. Both of these attempted reactions failed, however, a very useful outcome resulted from the reaction of 86 with excess methyllithium.

At the same time that these reactions were being carried out, Yongseog Chung of our group was attempting to synthesize the Diels-Alder adduct between 9,10-diacetylanthracene and ethyl acrylate. The 9,10-diacetylanthracene that Chung was using was synthesized according to a literature procedure. It was after several attempts at purification of the adduct that Chung noticed a
Figure 33: Steric interactions of an acetone molecule with 9,10-dilithioanthracene.

Figure 34: Attempted reaction of 9,10-dicarbomethoxyanthracene with excess methylmagnesium iodide or methyllithium.
singlet in the benzylic region of the $^1$H NMR, characteristic of an unsubstituted anthracene adduct. Careful checking of the $^1$H NMR of the starting material indicated a singlet in the aromatic region of the 9,10-diacetylanthracene starting material. This singlet indicated that the 9- and 10-positions of the anthracene ring were unsubstituted, and thus the two acetyl groups were located elsewhere on the molecule. Re-examination of the literature showed that the compound prepared by Chung was identical to the spectral data reported in the literature; however, the reported spectral data, and the spectral data found by Chung were inconsistent with a pattern expected for a compound with $D_{2h}$ symmetry. Based on its $^1$H NMR spectrum, Chung assigned structure 95 to the product of direct acylation under Friedel-Crafts conditions (Figure 35). It should be noted that $CH_2Cl_2$ was used as solvent in place of $CS_2$; however the literature reported that the desired compound had 8 $^{13}C$ peaks, and this is the same number of $^{13}C$ NMR peaks found by Chung for his compound. In fact, the $^{13}C$ NMR spectra found by Chung was identical to that reported in the literature.

![Figure 35: Reported method of synthesizing 9,10-diacetylanthracene.](image-url)
After reacting 9,10-dicarbomethoxyanthracene (86) with excess methyllithium (Figure 36), the crude reaction product was analyzed by mass spectroscopy. Although the reaction product was very crude, the major peak shown by mass spectroscopy corresponded to a molecular weight of 262, consistent with the molecular formula $C_{18}H_{14}O_{2}$. Purification of the crude mixture by recrystallization gave a compound whose $^1H$ and $^{13}C$ NMR spectra were in agreement with acetyl groups being substituted in the 9 and 10 positions of the anthracene ring. Most noteworthy was the fact that in the $^{13}C$ NMR spectrum only 6 peaks were found indicating a compound with $D_{2h}$ symmetry. The $^{13}C$ NMR of the desired 9,10-diacetylanthracene (87) is shown in Figure 37. Another surprising fact about this compound is that it is such a poor electrophile in its own right. One might expect that the carbonyl groups of 87 would be electrophilic enough to accept attack by methyllithium to give 9,10-di-(2-propyl-2-ol)anthracene (Figure 38).

Figure 36: Synthesis of 9,10-diacetylanthracene.
Figure 37: $^{13}$C NMR spectra of 9,10-diacetylanthracene.
Figure 38: Attempted formation of 9,10-diisopropylanthracene from 9,10-dicarbomethoxyanthracene.

However, as we have found, 87 is the only product formed in the addition of excess methyllithium to 86. One possible explanation for this observation could be the steric interference caused by the peri hydrogens on the anthracene ring, thus preventing attack at the carbonyl (Figure 39). Due to the steric requirements of the methyl groups, the assumption can be made that each acetyl group actually spends most of its time oriented perpendicular to the anthracene rings, as shown in Figure 39. It is also possible that the methyllithium deprotonates the α-hydrogens on the acetyl groups to form an enolate which is no longer capable of attack on the carbonyl group.

Figure 39: Diagram of 9,10-diacetylanthracene showing steric hinderance of attack by methyllithium
In summary, it has been found that reaction of 9,10-dilithioanthracene with select electrophiles provides access to the previously unknown 9,10-diiodoanthracene and also provides a simple synthesis of seven other 9,10-disubstituted anthracenes. All of the syntheses discussed can be made in one or two step sequences. The results of this work have recently been published.45

Synthesis of 9,10-Difluoroanthracene: Direct Fluorination of Anthracene

As mentioned earlier in this chapter, 9,10-difluoroanthracene was synthesized in 60% yield by reacting 9,10-dilithioanthracene (89) with N-tert-butyl-N-fluoro-benzenesulfonamide (93, Figure 30). This method of synthesis was very useful in that it provided 79 in one step from known compounds, but the major difficulty to be overcome was obtaining 93. As was stated earlier, Aldrich Chemical Co. now sells two different N-alkyl-N-fluoro-toluene-sulfonamides,39 but at the time that this research was being conducted, these compounds were not commercially available.

Up to this time, five syntheses of 79 had been reported in the literature, each of which had its own experimental difficulties. The reaction of 1,4-difluoro-2,5-dibromobenzene with n-butyllithium
followed by trapping of the dehydrobrominated intermediates with furan afforded the bis adduct in 5% yield, which could be hydrogenated and dehydrated to give 79.\textsuperscript{46} Hasek \textit{et al.} found that 9,9,10,10-tetrafluoro-9,10-dihydroanthracene could be formed by reaction of SF$_4$ on anthraquinone,\textsuperscript{46} and later Logothesis discovered that defluorination with iron gauze provided the desired 79 in 5% yield.\textsuperscript{48} In 1971, Anderson and Stock reported a synthesis of 79 involving bromination of 9-fluoroanthracene to give 9-bromo-10-fluoroanthracene, reaction with magnesium to provide the Grignard reagent, and finally reaction with perchloryl fluoride to give 79 in unspecified yield.\textsuperscript{49} Stock and Wasielewski provided a seven step method of synthesis of 79 in 1976, however, the starting material which they used is no longer commercially available.\textsuperscript{50} Finally, 79 can be made by electrolysis of anthracene in an acetonitrile solution of (CH$_3$)$_4$NF·2HF in 0.1% yield.\textsuperscript{51} As can be seen, each of these synthetic methods is wrought with shortcomings. Despite the fact that we had worked out an adequate synthesis of 79, we were open to suggestions for improvement.

In 1986, researchers at the Sagami Chemical Research Center and Onoda Cement Co. in Japan published two articles describing the synthesis and use of N-fluoropyridinium triflates as fluorinating agents.\textsuperscript{52} The compounds they described were capable of fluorinating such compounds as carbanions, aromatics, enol compounds and sulfides under fairly mild conditions. Soon thereafter, Onoda Cement Co. began to market these compounds under the name Onoda
Fluorinates™. By writing directly to the company, we were able to obtain 10-15 g quantities of each of their 3 Onoda Fluorinate FP™ series compounds (see Figure 40). Each of these compounds has varying reactivity: FP-T300 < FP-T500 < FP-T700.

![Chemical structures and reactivity percentages](image)

**Figure 40: Onoda Fluorinate FP™ series.**

With samples of all 3 Onoda Fluorinates™ on hand, attempts were made at reacting 89 with each of the fluorinates (Figure 41). Not unexpectedly, the reaction of 89 with the Onoda Fluorinates™ failed, as it had been previously reported by Umemoto et al. that only lithium salts of active methylene compounds

![Reaction scheme](image)

**Figure 41: Attempted fluorination of 9,10-dilithioanthracene using Onoda-Fluorinates™**
react with Onoda Fluorinates\textsuperscript{\textregistered}.\textsuperscript{53} At the suggestion of Dr. Umemoto,\textsuperscript{53} attempts were made to fluorinate anthracene directly using Onoda Fluorinates\textsuperscript{\textregistered}. The reaction was carried out as shown in Figure 42, and the results of the fluorination are shown in Table 4. As can be seen in Table 4, both FP-T300 and FP-T500 gave 79 in approximately 25\% yield in one step. Some 9-fluoroanthracene (100) was also formed in this reaction. This did not cause a particular problem because the 100 formed could be isolated and subjected to further fluorination to form 79 (see Experimental Section). The yields of the fluorinations could be improved slightly by adding more of the Onoda Fluorinates\textsuperscript{\textregistered} as the reaction proceeds, since some of the fluorinates appear to decompose slightly upon heating. Onoda Fluorinates\textsuperscript{\textregistered} will soon be available for purchase in the United States, therefore, this is the current method of choice for the synthesis of 79.

Xenon difluoride was reacted with 89 and 72 as shown in Figure 43. Analysis of the crude reaction product between XeF\textsubscript{2} and 89 by TLC, mass spectroscopy, and UV spectroscopy showed the presence of 79 and several other products. Unfortunately, all attempts at purification proved futile. Reaction of XeF\textsubscript{2} with anthracene in refluxing CH\textsubscript{2}Cl\textsubscript{2} gave no fluorinated products.
Figure 42: Direct fluorination of anthracene using Onoda-Fluorinates™
Table 4. Results of direct fluorination of anthracene using Onoda Fluorinates™

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Product Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>25% F + 30% F + 45% F + Polyfluorinated products</td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>24% F + 25% F + not isolated + not isolated</td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>&lt;10% F + &lt;10% F + &lt;10% F + major products</td>
</tr>
</tbody>
</table>
Figure 43: Attempted reaction of XeF$_2$ with 9,10-dilithioanthracene and anthracene.
Attempted Synthesis of 9,10-Di-tert-butilanthracene

In order to gain insight into the effect of strain on the retro-Diels-Alder reaction, we attempted to synthesize the reported 9,10-di-tert-butilanthracene.\textsuperscript{54} Synthesis of 9,10-di-tert-butilanthracene has been reported by the reaction of 89 with 2-bromo-2-methylpropane,\textsuperscript{54} and its use in various physical studies has been described.\textsuperscript{55} When we carried out the reaction as shown in Figure 44, the only disubstituted product isolated was 9,10-di-n-butilanthracene (76). The literature reports the melting point of 78 as 105°C, and we found the melting point of 9,10-di-n-butilanthracene to be 105-106°C (see Experimental Section). The only other two compounds isolated from the reaction mixture were shown by TLC and \textsuperscript{1}H NMR to be 9-n-butilanthracene (101) and anthracene (72). It appears that the 9,10-dilithioanthracene formed in the reaction of 89 with butyllithium reacts with some of the n-butilbromide formed as a by-product of the halogen-metal exchange. To verify this possibility, the reaction between 89 and an excess of n-butil bromide was carried out. The major product formed was shown by \textsuperscript{1}H NMR, \textsuperscript{13}C NMR and mass spectroscopy to be 9,10-di-n-butil-anthracene (76), identical to that formed in the reaction shown in Figure 44 (see Experimental Section).

Attempts were also made at dehydrogenating the known trans-9,10-di-tert-butil-9,10-dihydroanthracene with both palladium on carbon and platinum on alumna.\textsuperscript{56} The reactions were carried out
Figure 44: Attempted formation of 9,10-di-tert-butylanthracene using the literature procedure.\textsuperscript{54}
under a variety of conditions ranging from temperatures of 100-250°C, and with both hexane as solvent and in the absence of solvent. In many cases, a small amount of a di-tert-butyl-anthracene (as shown by mass spectroscopy) could be isolated, but $^{13}$C NMR and $^1$H NMR showed the isolated product to be 1,4-di-tert-butyl isomer and not the desired 9,10-isomer. The major product in all cases was anthracene. It seemed unlikely that the tert-butyl groups could be migrating to the 1,4-positions from the 9,10-positions, therefore it was believed that this product was resulting from a small amount of 1,4-di-tert-butyl-1,4-dihydroanthracene contaminant in the starting material. To test this possibility, the known 1,4-di-tert-butyl-1,4-dihydroanthracene (102) was dehydrogenated using Pd/C to give the previously unknown 1,4-di-tert-butylanthracene (103, Figure 45). It was believed that the sample of 9,10-di-tert-butyl-9,10-dihydroanthracene, prepared as shown in Figure 46, was contaminated with 102 even after extensive chromatographic purification.

Figure 45: Dehydrogenation of 1,4-di-tert-butyl-1,4-dihydroanthracene to give 1,4-di-tert-butylanthracene.
Figure 46: Preparation of 9,10-di-tert-butyl-9,10-dihydroanthracene contaminated with 1,4-di-tert-butyl-1,4-dihydroanthracene.\(^6^\)

Indeed, difficulty in separating the 9,10-isomers from the 1,4-isomers has been reported in the literature.\(^6^\)

To circumvent the problem of contamination of 104 by 102, a "pure" sample of 104 was prepared as shown in Figure 47. The alcohol (106) was prepared according to the literature procedure using slight modifications (see Experimental Section).\(^7^\) Alcohol 106 was next reduced with triethylsilane in trifluoroacetic acid to give 107. Conversion of 107 to 104 was carried out using the literature procedure to give pure 104 uncontaminated with other isomers.\(^7^\) Attempted dehydrogenation of this sample of 104 with Pd/C afforded only anthracene as the sole product.

The oxidation of 104 with DDQ was also attempted at room temperature, and resulted in the isolation of starting materials.

When the reaction was carried out at elevated temperatures as shown in Figure 48, analysis of the products by UV spectroscopy, \(^1\)H NMR, and mass spectroscopy, showed the product to be
Figure 47: Preparation of pure trans-9,10-di-tert-butyl-9,10-dihydroanthracene.
9,10-dichloroanthracene. This result seemed strange at first, but there is literature precedence for DDQ acting as a source of electrophilic chlorine at elevated temperatures.\textsuperscript{68}

\begin{center}
\begin{tabular}{c}
\includegraphics[width=0.8\textwidth]{figure48.png}
\end{tabular}
\end{center}

Figure 48: Attempted oxidation of 9,10-di-tert-butyl-9,10-dihydroanthracene with DDQ to give 9,10-dichloroanthracene.

Two other "long shot" attempts at synthesizing 9,10-di-tert-butylanthracene (78) were tried with no success. First, exhaustive methylation of 9,10-anthracene dicarboxylic acid (84) using (CH\textsubscript{3})\textsubscript{3}Al and heating to 110°C using a modification of a literature procedure was unsuccessfully attempted.\textsuperscript{69} Second, attempts were made to couple 2-bromo-2-methylpropane to 9,10-dilithioanthracene (89) using cuprous iodide and molecular oxygen.\textsuperscript{60} This attempt also failed.

It was thus decided that enough time had been devoted to the synthesis of 9,10-di-tert-butylanthracene, and so no further attempts were made towards its synthesis. As will be shown in Chapter V, it would have given some useful data if this compound
could have been synthesized. Based on the data that was accumulated, the literature procedure for the synthesis of 9,10-di-tert-butylanthracene is incorrect, and its synthesis and characterization are left to be completed.

Experimental Section

General. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Microanalyses were carried out at Canadian Microanalytical Service, New Westminster, B.C. Mass spectra were obtained by use of a Kratos-30 mass spectrometer. FT-NMR spectra at 11.75 tesla (500 MHz) or 7.0 tesla (300 MHz) were obtained using equipment funded in part by NIH Grant #1 S10 RR01458-01A1. We thank Mr. Richard Weisenberger and Dr. C.E. Cottrell of The Ohio State University Chemical Instrumentation Center for their assistance in obtaining mass and high-field $^1$H NMR spectra, respectively, and Mr. Carl Engelman for other NMR assistance. All starting materials were purchased from the Aldrich Chemical Co., Milwaukee, WI. Silica gel was Merck, 230-400 mesh flash grade silica. Hexane used for flash chromatography was purchased from OSU lab stores and was distilled through a vigreaux column. Chloroform, methylene chloride and 1,2-dichloroethane were dried by distillation over P$_2$O$_5$ and used immediately. Thionyl chloride was distilled from triphenyl phosphite prior to use. Diethyl ether was distilled from benzophenone ketyl.
9,10-Dimethylantracene (73). 9,10-Dibromoantracene (3.0 g, 8.9 mmol) was placed in a flame dried 50 mL rbf fitted with a condenser and the flask was flushed with argon. Anhydrous diethyl ether (20 mL) was added via syringe. 

n-Butyllithium (10 mL, 2.5 M solution in hexanes, 25 mmol) was added slowly over the course of 10-15 min and the mixture was allowed to stir for an additional 15 min. Iodomethane (2.0 mL, 32 mmol) was added dropwise over 5 min. The solution was heated to reflux for 18 h, allowed to cool, extracted with H₂O (4 x 10 mL), dried over MgSO₄, and finally evaporated to a yellow solid under reduced pressure. The resulting solid was purified by flash chromatography on silica gel eluting with hexane to yield, after pooling and evaporation of the appropriate fractions, yellow crystals (1.08 g, 59%): mp 182.5-184°C (lit. 61 180-181°C); Rf 0.26 (hexane on silica); ¹H NMR (CDCl₃) δ 3.15 (s, 6, CH₃), 7.55 (dd, 4, Ar-H), 8.35 (dd, 4, Ar-H). High resolution mass spectrum: calcd for C₁₈H₁₄O₂, 206.110; measured, 206.112.
9,10-Diethylantracene (74). 9,10-Dibromoantracene (3.0 g, 8.9 mmol) was placed in a flame dried 50 mL rbf fitted with a condenser and the flask was flushed with argon. Anhydrous diethyl ether (20 mL) was added via syringe. n-Butyllithium (10 mL, 2.5 M solution in hexanes, 25 mmol) was added slowly over the course of 10-15 min and the mixture was allowed to stir for an additional 15 min. Iodoethane (3.0 mL, 37 mmol) was added via syringe. The resulting solution was heated to reflux for 15 h, extracted with H₂O (4 x 7 mL), dried over MgSO₄, and finally evaporated under reduced pressure to a thick yellow oil. The oil was subjected to flash chromatography on silica (eluting with hexane) and finally crystallized from absolute ethanol to afford yellow crystals (679 mg, 33%): mp 142-144°C (lit. 144-145°C); Rf 0.29 (hexane on silica); ¹H NMR (CDCl₃) δ 1.39 (t, 6, CH₂CH₃), 3.49 (q, 4, CH₂CH₃), 7.41-7.78 (dd, 4, Ar-H), 8.28-8.63 (dd, 4, Ar-H). High resolution mass spectrum: calcd for C₁₈H₁₈, 234.141; measured, 234.145.

9,10-Di-n-propylantracene (75). 9,10-Dibromoantracene (3.0 g, 8.93 mmol) was placed in a dry 50 mL rbf and the flask was flushed with argon and sealed with septa. Anhydrous diethyl ether (30 mL) was added as solvent and the mixture was allowed to stir while
tert-butyllithium (11 mL, 1.7 M solution in hexanes, 18.7 mmol) was added slowly over the course of 10 minutes. The solution continued to stir for 2 h and then 1-bromopropane (2.0 mL, 32.3 mmol) was added and the resulting solution was brought to reflux for 24 h. The solution was quenched with aqueous NH₄Cl and the ether layer was extracted with H₂O and finally dried over MgSO₄ and evaporated to dryness. Flash chromatography of the solid on silica gel (hexane solvent) gave the desired product as fluorescent needles after recrystallization from methanol (344 mg, 15%): mp 139.5-140.5°C; ¹H NMR (CDCl₃) δ 1.10 (t, 6H, CH₂CH₃), 1.70-1.84 (m, 4H, CH₂CH₂CH₃), 3.45 (t, 4H, CH₂CH₂CH₃), 7.36-7.40 (m, 4H, Ar-H), 8.17-8.23 (m, 4H, Ar-H); ¹³C NMR (CDCl₃) δ 14.8 (CH₂CH₂CH₃), 24.6 (CH₂CH₂CH₃), 30.2 (CH₂CH₂CH₃), 124.7 and 125.3 (aromatic-C-H), 129.5 and 133.7 (quaternary Ar-C); mass spectrum, m/e 262.172 (M⁺, calcd for C₂₀H₂₂, 262.172).

9,10-Di-n-butylanthracene (76). 9,10-Dibromoanthracene (2.0 g, 5.95 mmol) was placed in a dry 50 mL rbf and the flask was fitted with a condenser and sealed with a septa. Anhydrous diethyl ether (30 mL) was added and the solution stirred under argon while n-butyllithium (4.76 mL, 2.5 M solution in hexanes, 11.9 mmol) was added slowly over 5 minutes. The solution stirred for 30 minutes and n-butyl-bromide (1.3 mL, 12 mmol) was added and the solution
was heated to reflux for 15 h. Extraction of the ether layer with 
H\textsubscript{2}O, drying over MgSO\textsubscript{4} and evaporation to dryness resulted in a 
yellow oil. The oil was subjected to silica gel flash chromatography 
(hexane solvent) and the appropriate fractions were pooled and 
evaporated to give a fluorescent oil which crystallized upon 
standing. The solid was recrystallized from methanol to give light 
green fluorescent needles (648 mg, 38\%): mp 104-105°C; \textsuperscript{1}H 
NMR (CDCl\textsubscript{3}) \( \delta \) 1.04-1.52 (t, 6H, CH\textsubscript{3}), 1.57-1.79 (m, 4H, 
CH\textsubscript{2}), 1.80-1.85 (m, 4H, CH\textsubscript{2}), 3.57-3.63 (m, 4H, CH\textsubscript{2}), 7.47-7.51 
(m, 4H, Ar-H), 8.28-8.33 (m, 4H, Ar-H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \( \delta \) 
14.1 (CH\textsubscript{3}), 23.4 (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 27.9 (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 
35.6 (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 124.7 and 125.2 (aromatic-\textsubscript{C}-H), 129.4 
and 133.8 (quaternary Ar-\textsubscript{C}); EI mass spectrum, \textit{m/e} 290.204 (M\textsuperscript{+}, 
calcd for C\textsubscript{22}H\textsubscript{26}, 290.203).

9,10-Diiodoanthracene (82). 9,10-Dibromoanthracene (3.0 g, 8.9 
mmol) was placed in a flame dried 50 mL rbf 
fitted with a condenser and the flask was 
flushed with argon. Anhydrous diethyl ether 
(20 mL) was added via syringe.
n-Butyllithium (10 mL, 2.5 M solution in 
hexanes, 25 mmol) was added slowly over the course of 10-15 min and 
the mixture was allowed to stir for an additional 15 min. Iodine 
crystals (7.5 g, 30 mmol) were added through the top of the condenser 
over the course of 5 min. The mixture was stirred for an additional
15 min until the color was a dark brown, then transferred to a separatory funnel where it was washed 5 times with a 25% (w/w) solution of sodium thiosulfate in water. The crude product was filtered, dried in a vacuum oven at 80°C, and finally recrystallized twice from CCl₄ (100 mL) to give yellow needles (1.82 g, 47%): mp 254-255°C; ¹H NMR (CDCl₃) δ 7.55 (dd, 4, Ar-H), 8.55 (dd, 4, Ar-H); High resolution mass spectrum: calcd for C₁₄H₈I₂, 429.872; measured, 429.873.

Found: C, 39.21; H, 1.90; I, 59.04.

N-Tert-butyl-N-fluoro-benzenesulfonamide (93). The apparatus was set up according to the diagram shown in Appendix A and into the reaction flask was placed 8.5 g (40 mmol) of N-tert-butyl-benzenesulfonamide and 800 mL of dry chloroform. The reaction flask was cooled in a dry ice acetonitrile bath. The fluorine/nitrogen (2.5% F₂) was turned on at an approximate flow rate of 30 mL/min. This was checked by opening the valve on the buret to the atmosphere and then closing it and watching the buret fill with gas again. The fluorination was continued for 12 h and then the flask and lines were flushed with nitrogen. For best results, 5-8 runs were completed and these were pooled for chromatography. The chloroform solution was evaporated in vacuo to give an oily
solid. The oily portion of the product was subjected to flash chromatography on silica gel (hexane:CH$_2$Cl$_2$, 1:1) to give approx. 15% yield of the desired product as an oil identical to that reported in the literature.$^{37}$ $^1$H NMR (CDCl$_3$) $\delta$ 1.45 (d, J = 1.8 Hz, 9, C(CH$_3$)$_3$), 7.50-7.71 (m, 3, Ar-H), 7.95-8.03 (m, 2, Ar-H).

9,10-Difluoroanthracene (79). 9,10-Dibromoanthracene (100 mg, 0.3 mmol) was placed in a flame dried 25 mL rbf along with 10 mL of anhydrous diethyl ether and the flask was flushed with argon and sealed with a septa and finally cooled to 78°C. N-tert-butyl-N-fluorobenzenesulfonamide (0.9 mmol) in 0.5 mL of anhydrous diethyl ether was added. The solution continued to stir and was allowed to warm slowly to room temperature. It was finally quenched with aqueous NH$_4$Cl and the ether layer was given an aqueous workup. The ether layer was dried over MgSO$_4$, evaporated to dryness and the resulting solid was subjected to flash chromatography on silica gel with hexane solvent. The first bright fluorescent band to emerge was collected and pooled to give upon evaporation a yellow crystalline solid (40 mg, 60%) whose NMR spectra and mp are identical with that found in a previous citing: mp 164-165°C (lit.$^{50}$ 164-165°C); $R_f$ 0.56 (hexane on silica); $^1$H NMR (CDCl$_3$) $\delta$ 7.53-7.56 (dd, 4, Ar-H), 8.22-8.27 (m, 4, Ar-H); High resolution mass spectrum: calcd for C$_{14}$H$_8$F$_2$, 214.059; measured, 214.059.
9,10-Dicarbomethoxyanthracene (86). A solution of 9,10-anthracenedicarboxylic acid (1.0 g, 4.4 mmol) and thionyl chloride (50 mL) was brought to reflux for 1.5 h and then the thionyl chloride was removed in vacuo. Anhydrous methanol (60 mL) was added, the solution was heated to reflux for 2.5 h and then evaporated to dryness. The solid was taken up in ether, extracted with aqueous bicarbonate and finally H₂O. The ether layer was dried over MgSO₄ and evaporated to dryness. Recrystallization from methanol yielded yellow crystals (903 mg, 88%): mp 175-176°C; ¹H NMR (CDCl₃) δ 4.15 (s, 6, OCH₃), 7.48-7.65 (dd, 4, Ar-H), 7.94-8.08 (dd, 4, Ar-H); High resolution mass spectrum: calcd for C₁₈H₁₄O₄, 294.0892; measured, 294.0895.

Anal. Calcd for C₁₈H₁₄O₄: C, 73.46; H, 4.79. Found: C, 73.19; H, 4.80.

9,10-Diacetylanthracene (87). To a stirred solution of 9,10-dicarbomethoxyanthracene (100 mg, 0.43 mmol) in anhydrous diethyl ether (25 mL) at -78°C was added methyllithium (1.0 mL of a 1.4 M solution in diethyl ether, 1.4 mmol), and the solution was allowed to warm to ambient temperature overnight. The resulting solution was quenched with ammonium chloride and then worked up with H₂O extraction. The
ether layer was dried over MgSO₄ and evaporated to dryness.

Recrystallization from ethanol afforded yellow crystals (329 mg, 58%): mp 248.5-249.5°C; ¹H NMR (CDCl₃) δ 2.8 (s, 6, CH₃), 7.5-7.7 (dd, 4, Ar-H), 7.8-8.0 (dd, 4, Ar-H); ¹³C NMR (CDCl₃) δ 33.8 (COCH₃), 124.9 and 126.8 (Aromatic C-H), 125.9 (quaternary Ar-C), 138.3 (Aromatic-C=O), 207.4 (C=O). High resolution mass spectrum: calcd for C₁₈H₁₄O₂, 262.099; measured, 262.099.


Direct fluorination of anthracene. A 50 mL flask was flame dried, fitted with a condenser, and flushed with argon. Into the flask was placed anthracene (104 mg, 0.58 mmol) and FP-T500 (300 mg, 1.21 mmol). Dry, degassed 1,2-dichloroethane (35 mL) was added as solvent and the solution was heated at reflux for 5 h. The solution was cooled and quenched with water, then extracted into ether, washed with water (2 x 15 mL), dried over MgSO₄, and evaporated to provide a light yellow solid. The crude product was subjected to silica gel flash chromatography (hexane eluant); the first two fluorescent bands that eluted from the column were collected and pooled to give 9,10-difluoroanthracene (79) (30 mg, 24%) and 9-fluoroanthracene (100) (28 mg, 25%), respectively. The products obtained gave mp, mass spectra, and ¹H NMR identical to those previously reported.⁶₀
Fluorination of 9-fluoroanthracene to give 9,10-difluoroanthracene. 9-Fluoroanthracene (138 mg, 0.7 mmol) was placed in a 50 mL rbf along with 40 mL of dry chloroform. FP-T300 (317 mg, 1.1 mmol) was added and the solution was heated to reflux for 48 h. The solution was cooled and quenched with water, then was extracted into ether, washed with water (2 x 15 mL), dried over MgSO$_4$, and evaporated to provide a light yellow solid. The crude product was subjected to silica gel flash chromatography (hexane eluant); the first two fluorescent bands that eluted from the column were collected and pooled to give 9,10-difluoroanthracene (79) (40 mg, 25%) and unreacted 9-fluoroanthracene (100) (93 mg, 67%), respectively. The products obtained gave mp, mass spectroscopy, and $^1$H NMR identical to those previously reported.$^{50}$

9-Tert-butyl-9-hydroxy-9,10-dihydroanthracene (106). This compound was prepared according to the procedure of Parish and Stock$^{57}$ with two modifications: (1) 2-Bromo-2-methylpropane was substituted for 2-chloro-2-methylpropane in formation of the Grignard and (2) silica gel (230-400 mesh) was used with benzene solvent to purify the compound instead of alumina.
9-tert-Butyl-9,10-dihydroanthracene (107). Into a 100 mL flask was placed 9-tert-butyl-9-hydroxy-9,10-dihydroanthracene (2.0 g, 7.9 mmol) and 
CH$_2$Cl$_2$ (25 mL). The flask was flushed with argon and trifluoroacetic acid (1.3 mL, 17 mmol) was added. The solution turned black as it was allowed to stir for 6 min, and then triethylsilane (2.7 mL, 17 mmol) was added. After 5 min the solution was evaporated in vacuo to a dark oil that was extracted into ether (100 mL) and washed with 20% sodium bicarbonate (2 x 20 mL) and water (2 x 20 mL). The ether layer was dried over MgSO$_4$ and evaporated in vacuo to give a light oil that was chromatographed on silica gel (hexane solvent). Pooling and evaporation of the appropriate fractions gave a colorless solid that was used without further purification (620 mg, 33%): mp 124-125°C (lit.$^6$ 122.5°C); $^1$H NMR (CCl$_4$) $\delta$

0.86 (s, 9, tert-butyl), 3.5 (s, 1, benzylic), 3.9 (q, 2, benzylic), 7.0-7.5 (m, 8, Ar-H).

1,4-Di-tert-butylanthracene (103). A 24.5 cm pressure tube was filled with 1,4-di-tert-butyl-1,4-dihydroanthracene (195 mg, 0.67 mmol), 10% palladium on carbon (256 mg), and hexane (8 mL) as solvent. The tube was heated for 5 h at 200°C, cooled, and filtered through a silica gel plug to remove the palladium on carbon. The hexane
solution was evaporated to dryness and the solid was subjected to silica gel flash chromatography (hexane solvent). The appropriate fractions were pooled and evaporated to give a white solid (164 mg, 86%): mp 123-125°C; $^1$H NMR (CDCl$_3$) $\delta$ 1.79 (s, 18, tert-butyl), 7.47 (s, 2, Ar-H), 7.49-7.56 (m, 2, Ar-H), 8.05-8.10 (m, 2, Ar-H), 9.15 (s, 2, Ar-H); $^{13}$C NMR (CDCl$_3$) $\delta$ 32.11 (C(CH$_3$)$_3$), 35.94 (C(CH$_3$)$_3$), 122.3, 125.3, 126.7, 128.2 (aromatic-C-H), 129.3, 131.5, 144.3 (quaternary Ar-C). High resolution mass spectrum: calcd for C$_{22}$H$_{26}$, 290.203; measured, 290.204.

Attempted dehydrogenation of 9,10-di-tert-butyl-9,10-dihydroanthracene (104). Into a pressure tube was placed 104 (536 mg, 1.82 mmol), 10% palladium on carbon (500 mg), and hexane (8 mL). The tube was sealed and heated in a salt bath at 250°C for 6 h, then removed from the salt bath and allowed to cool. The contents of the tube were passed through a short silica gel plug eluting with hexane to remove the palladium on carbon. The resulting solution was evaporated in vacuo to give a solid that was subjected to silica gel flash chromatography (hexane eluant). Fractions were analyzed by TLC and UV spectroscopy. Pooling and evaporation of the appropriate fractions showed the product composition consisted of anthracene and a trace amount of 103. The products were further characterized using EI mass spectroscopy, $^1$H NMR and $^{13}$C NMR by comparison to authentic samples.
Reaction of 104 with DDQ at high temperature. Into a pressure tube was placed 104 (200 mg, 0.68 mmol) and DDQ (300 mg, 1.32 mmol). Benzene (8 mL) was added as solvent and the tube was sealed and heated at 140°C for 14 h. The contents of the tube were cooled and passed through a short silica gel plug (elution with hexane) to remove the DDQ. TLC of the resulting solution (hexane on silica gel) showed two spots. The solution was evaporated in vacuo to give a light green solid that was dissolved in hexane and subjected to silica gel flash chromatography (hexane solvent). The two bands that eluted from the column were evaporated to remove the hexane; analysis by $^1$H NMR, UV spectroscopy and mass spectroscopy showed the compounds to be 9,10-dichloroanthracene (59 mg, 35%) and anthracene (79 mg, 65%) by comparison to authentic samples.
Chapter IV

Synthesis Of Diels-Alder Adducts Of
9,10-Disubstituted Anthracenes With Ethyl Acrylate

With reasonable sized quantities of each of the 9,10-disubstituted anthracenes on hand, work began toward synthesizing the Diels-Alder adduct of each anthracene with ethyl acrylate. Ethyl acrylate was chosen as the dienophile for 3 reasons: (1) it was readily available and inexpensive, (2) it was fairly easy to work with, and (3) Nanjappan and Czarnik had already shown that rDA reactions of Diels-Alder adducts made between anthracene and methyl acrylate proceeded at a reasonable rate at 200°C, therefore it seemed reasonable that the Diels-Alder adduct with ethyl acrylate would give similar results.

For anthracenes 72, 73, 74, 76, 77, and 83 (Figure 49) the formation of the corresponding Diels-Alder adduct proceeded easily by simply heating the anthracene compound in the presence of ethyl acrylate (54). The compounds were heated in a sealed pressure tube with a small quantity of a radical inhibitor such as BHT to help prevent polymerization of the excess ethyl acrylate. Purification of these adducts (109a-109f) required simple silica gel flash chromatography.
Figure 49: Synthesis of Diels-Alder adducts of 9,10-disubstituted anthracenes with ethyl acrylate.

The $^1$H NMR spectrum of adduct $109e$ ($R = \text{ipr}$) showed a very interesting temperature dependence. When the high field (250 MHz) $^1$H NMR spectra was taken at the usual temperature of 303°K, some of the peaks in the NMR appeared very broad (Figure 50). There are two possible explanations for this trend: (1) the NMR sample was too concentrated, or (2) the compound was experiencing some sort of barrier to rotation. It was shown that possibility 1 was not a factor because only 1-2 mg of $109e$ was dissolved in 1 mL of NMR solvent to take the spectrum thus, there must have been some type of barrier to rotation. When the $^1$H NMR sample was heated and the spectra was taken at 330°K (Figure 51), we could see some peak coalescence, and previously

$$
\begin{array}{ccc}
\text{R} & \text{compound} & \text{adduct} \\
-\text{H} & 72 & 109a \\
-\text{CH}_3 & 73 & 109b \\
-\text{CH}_2\text{CH}_3 & 74 & 109c \\
-\text{CH}_2\text{CH}_2\text{CH}_3 & 76 & 109d \\
-\text{ipr} & 77 & 109e \\
-\text{SCH}_3 & 83 & 109f \\
\end{array}
$$
Figure 50: $^1$H NMR spectrum of 9,10-di-isopropyl-9,10-(11-carboethoxy-ethano)anthracene taken at 303°K in CDCl₃ solvent.
Figure 51: $^1$H NMR spectrum of 9,10-di-isopropyl-9,10-(11-carboethoxy-ethano)anthracene taken at 330°K in CDCl$_3$ solvent.
broad peaks became clear, sharp peaks. Examination of CPK models shows that the isopropyl groups are hindered to rotation by a steric interaction between the methyl groups on the isopropyls and the peri hydrogens on the anthracene portion of the adduct (Figure 52). This interaction would have possibly been most pronounced in the Diels-Alder adduct between 9,10-di-tert-butylanthracene and ethyl acrylate, but as was pointed out in Chapter III a sample of 9,10-di-tert-butylanthracene was not available.

Figure 52: Schematic diagram of 9,10-di-isopropyl-9,10-(11-carboethoxy)ethano)anthracene showing steric interaction of isopropyl groups with anthracene hydrogens.

The 9,10-disubstituted halogen containing anthracenes (79, 80, 81, and 82) did not form Diels-Alder adducts on heating with ethyl acrylate. A variety of attempts were tried under fairly forcing conditions, but no adducts were realized. At the suggestion
of Dr. Hart (OSU), a modification of the procedure was tried that gave very satisfactory results. As is shown in Figure 53, acryloyl chloride (110) was used in place of ethyl acrylate, and then the chlorine atom was simply replaced to the needed ethoxy substituent by refluxing in absolute ethanol. These reactions proceeded where the reaction with ethyl acrylate failed due to the fact that acryloyl chloride is much more reactive as a dienophile than ethyl acrylate.

\[
\begin{align*}
\text{compound} & \quad \text{adduct} \\
R = -F & \quad 79 & 109g \\
-Cl & \quad 80 & 109h \\
-Br & \quad 81 & 109i \\
-I & \quad 82 & 109j 
\end{align*}
\]

Figure 53: Synthesis of halogen-containing Diels-Alder adducts

The Diels-Alder reaction of 9,10-anthracene dicarboxylic acid and 9,10-dicyanoanthracene with the above mentioned dienophiles failed (Figure 54). Attempted reactions between 9,10-anthracene...
Figure 54: Attempted synthesis of Diels-Alder adducts of 9,10-dicyanoanthracene and 9,10-anthracene-dicarboxylic acid.

dicarboxylic acid (84) and ethyl acrylate or acryloyl chloride failed because every attempt resulted in polymerization of the dienophile. One possible reason for this could be due to the presence of the two carboxylic acid groups on 84. These carboxylic acid groups could have been providing acidic enough protons to initiate polymerization of the dienophiles. This polymerization could not be overcome, therefore attempts at forming a Diels-Alder adduct reaction with 84 were abandoned.

Attempts at forming Diels-Alder adducts between 9,10-dicyanoanthracene (85) and ethyl acrylate or acryloyl chloride provided surprising results. In almost every attempt at forming an adduct, only starting materials could be isolated. 9,10-Dicyanoanthracene
(85) appeared to be too unreactive to form an adduct. This was surprising because Chung found that the Diels-Alder adduct between 9,10-dinitroanthracene and ethyl acrylate formed very easily. Intuition tells us that nitro-group are more electron withdrawing than cyano-group, therefore it seemed reasonable that if 9,10-dinitroanthracene entered into a Diels-Alder reaction easily, then so should 85. Only 5 or 6 attempts were made at synthesis of the adduct; however, Chung spent considerable time attempting to synthesize the adduct between 85 and ethyl acrylate, and all of these attempts failed.

Experimental Section

General: Experimental details described in the general Experimental Section of Chapter III also apply here.

9,10-Dihydro-9,10-(11-carboethoxyethano)anthracene (109a).

Anthracene (2.0 g, 11.2 mmol) was placed in a pressure tube along with ethyl acrylate (10 mL), xylene (10 mL) and a few hydroquinone crystals. The tube was sealed and heated to 160°C for 24 h and then evaporated to a thick oil. Crystallization from hexane yielded colorless crystals (2.74 g, 88% yield): mp 98-99°C;
**9,10-Dimethyl-9,10-(11-carboethoxyethano)anthracene (109b).**

9,10-Dimethylanthracene (206.4 mg, 1.0 mmol) was placed in a sealed tube along with 10 mL of ethyl acrylate and a few BHT crystals. The solution was heated with stirring at 110°C for 16 h. It was then cooled, reduced to a thick oil under reduced pressure and purified by silica gel flash chromatography (CHCl₃ solvent). The proper fractions were combined and evaporated to a yellow oil. Recrystallization from hexane yielded colorless crystals (131.2 mg, 71%): mp 101-103°C; ¹H NMR (CDCl₃) δ 1.0-1.2 (t, 6, CH₂CH₃), 1.8-2.1 (m, 2, H-11), 2.0 (s, 6, CH₃), 2.5-2.8 (dd, 1, H-11), 3.8-4.1 (q, 2, CH₂CH₃), 7.0-7.5 (m, 8, Ar-H). EI mass spectrum, m/e 306.1 (M⁺, 1.9), 206 (100), 192 (11.5), 189 (11).
9,10-Diethyl-9,10-(11-carboethoxyethano)anthracene (109c)

9,10-Diethylanthracene (126.3 mg, 0.539 mmol) was placed in a sealed tube along with 11 mL of ethyl acrylate and a few hydroquinone crystals. The tube was heated in an oil bath for 45 h at 100°C.

The resulting solution was evaporated in vacuo to a yellow oil and subjected to silica gel flash chromatography with CHCl₃ as solvent. The appropriate fractions were pooled and evaporated in vacuo. Crystallization from hexane yielded colorless crystals (89.7 mg, 50%): mp 102-103°C; ¹H NMR (CDCl₃) δ 1.0-1.2 (t, 3, CO₂CH₂CH₃), 1.3-1.5 (t, 3, CH₂CH₃), 1.3-1.6 (t, 3, CH₂CH₃), 1.7-2.3 (m, 2, H-12), 2.4-2.7 (q, 2, CH₂CH₃), 2.5-2.8 (q, 2, CH₂CH₃), 2.8-3.1 (dd, 1, H-11), 3.8-4.2 (q, 2, CO₂CH₂CH₃), 7.0-7.4 (m, 8, Ar-H); High resolution mass spectrum: calcd for C₂₃H₂₆O₂, 334.194; measured, 334.194.

Anal. Calcd for C₂₃H₂₆O₂: C 82.60; H, 7.83. Found: C, 82.35; H, 7.75.

9,10-Diisopropyl-9,10-(11-carboethoxyethano)anthracene (109e).

9,10-diisopropylanthracene (153 mg, 0.583 mmol) and ethyl acrylate (50 mL). The flask was sealed with a septum and heated under an atmosphere of argon at 70°C for 5 days. The resulting solution
was cooled and evaporated in vacuo to give a thick oil which was subjected to silica gel flash chromatography (CHCl₃:Hexane, 1:1). Unreacted starting material eluted from the column first and the desired product appeared next. The appropriate fractions were pooled and evaporated to give an oil which was carefully recrystallized from absolute ethanol to yield colorless crystals (85.4 mg, 40%): mp 98-99°C; ¹H NMR at 330°K (CDCl₃)
δ 1.09 (t, 3H, OCH₂CH₃), 1.50-1.67 (m, 14H, CH(CH₃)₂ and CH(CH₃)₂), 2.88-3.01 (m, 2H, 12-H), 3.02-3.16 (m, 1H, 11-H), 3.85-4.04 (m, 2H, OCH₂CH₃), 7.05-7.67 (3 multiplets, 8H, Ar-H).
EI mass spectrum, m/e 362.224 (M⁺, calcd for C₂₅H₃₀O₂, 362.225).

9,10-Di-n-propyl-9,10-(11-carboethoxyethano)anthracene (109d).

9,10-di-n-propylanthracene (100 mg, 0.38 mmol) was placed in a pressure tube along with 10 mL of ethyl acrylate. The tube was sealed and heated at 80°C for 48 h then cooled and evaporated in vacuo to a thick oil. The oil was chromatographed on silica gel (CHCl₃:Hexane, 1:1). The appropriate fractions were pooled and evaporated to a thick oil. Crystallization of the oil from absolute ethanol yielded colorless crystals (110 mg, 80%): mp 83.5-84.5°C; ¹H NMR (CDCl₃) δ 1.11 (t, 3H, OCH₂CH₃), 1.17-1.24 (m, 6H, CH₂CH₂CH₃),
1.73-1.95 (m, 5H, 12-H and CH₂CH₂CH₃), 2.10 (t, 1H, 12-H),
2.32-2.61 (m, 4H, CH₂CH₂CH₃), 2.95 (q, 1H, 11-H), 3.90-4.08
(m, 2H, OCH₂CH₃), 7.05-7.33 (m, 8H, Ar-H); High resolution mass

Anal. Calcd for C₂₅H₃₀O₂: C, 82.83; H, 8.34. Found: C,
82.59; H, 8.30.

9,10-Dithiomethoxy-9,10-(11-carboethoxyethano)anthracene (109f).

9,10-Dithiomethoxyanthracene (500 mg, 0.73
mmol) was placed in a sealed tube with
ethyl acrylate (5 mL). A few hydroquinone
crystals were added and the mixture was
heated for 20 h at 160-170°C with
stirring. The contents of the tube were then cooled and evaporated
under reduced pressure to yield a thick yellow oil, which was
subjected to column chromatography (silica gel, CHCl₃). The
appropriate fractions were collected, pooled, and evaporated under
reduced pressure. The resulting oil was recrystallized from
absolute ethanol to give colorless crystals (0.246 g, 47%): mp
134-137°C; 'H NMR (CDCl₃) δ 1.2 (t, 3, CH₂CH₃),
2.2-2.5 (m, 2, H-12), 2.5 (d, 6, CH₃), 3.11-3.30 (m, 1, H-11),
3.9-4.21 (q, 2, CH₂CH₃), 7.25-7.35 (m, 4, Ar-H), 7.68-7.9 (m, 4,
Ar-H). EI mass spectrum, m/e 325 (M⁺-OEt, 1.5), 270 (100), 255
(44.7), 55 (11.2).

Anal. Calcd for C₂₁H₂₂O₂S₂: C, 68.07; H, 5.98; S,
17.31; Found: C, 68.02; H, 6.01; S, 17.34.
9,10-Difluoro-9,10-(11-carboethoxyethano)anthracene (109g).

9,10-Difluoroanthracene (80 mg, 0.37 mmol) was placed in a pressure tube along with freshly distilled acryloyl chloride (4 mL) and dry xylene (16 mL). Hydroquinone (50 mg) was added and the tube was sealed and heated at 80-90°C overnight. Absolute ethanol (5 mL) was added to the tube and it was heated at 80°C for 1 h. The resulting solution was then evaporated in vacuo to a thick oil that was subjected to silica gel flash chromatography (hexane:CH2Cl2, 1:1). The appropriate fractions were pooled (RF 0.25, silica gel) and evaporated in vacuo to give an oil which resisted all attempts at crystallization (47 mg, 40%): 1H NMR (CDCl3) δ 1.17 (t, 3, OCH2CH3); 2.33-2.41 (m, 2, CH2); 3.16-3.24 (m, 1, H-11); 4.02-4.13 (m, 2, OCH2CH3); 7.24-7.33 (m, 4, Ar-H); 7.44-7.56 (m, 4, Ar-H). High resolution mass spectrum: calcd for C19H16F2O2, 314.1118; measured, 314.1116.

9,10-Dichloro-9,10-(11-carboethoxyethano)anthracene (109h).

A sample of 9,10-dichloroanthracene (1 g, 4.05 mmol) was placed in a sealed tube along with acryloyl chloride (2 mL, 24.6 mmol). Xylene (9 mL) was added as a solvent and a few hydroquinone crystals were added. The tube was then placed in an oil bath and heated at
200°C for 20 h. The tube was allowed to cool, and then it was transferred to a 100 mL rbf. Absolute ethanol (10 mL) was added and the solution was refluxed for one hour. The contents of the flask were then evaporated in vacuo to a dark oil. The oil was subjected to silica gel flash chromatography using CHCl₃ as solvent. The appropriate fractions were pooled together and evaporated in vacuo. The resulting oil was recrystallized twice from absolute ethanol to give colorless crystals (0.66 g, 47%): mp 102-105°C; ¹H NMR (CDCl₃) δ 1.20 (t, 3, CH₃), 2.30-2.75 (m, 2, H-12), 3.14-3.33 (q, 1, H-11), 3.97-4.20 (q, 2, CH₂CH₃), 7.31-7.42 (m, 4, Ar-H), 7.70-7.85 (m, 4, Ar-H); EI mass spectrum, m/e 346 (M⁺, 2.7), 248 (64.7), 246 (100), 202 (11), 130 (23.9).

Anal. Calcd for C₁₉H₁₆Cl₂O₂:  C, 65.72; H, 4.64; Cl, 20.42. Found: C, 65.56; H, 4.72; Cl, 20.52.

9,10-Dibromo-9,10-(11-carboethoxylethano)anthracene (1091).

A sample of 9,10-dibromoanthracene (300 mg, 0.892 mmol) was placed in sealed tube along with of acryloyl chloride (1 mL, 12.3 mmol) Xylene (6 mL) was added as solvent and a few hydroquinone crystals were added. The tube was then heated in an oil bath at 140-150°C for 22 h. The tube was removed from the oil bath and allowed to cool to room temperature, after which time the contents
where transferred to a 50 mL rbf. Absolute ethanol (6 mL) was added and the mixture was refluxed for one hour. The mixture was then cooled and evaporated under reduced pressure to a brown oil. The oil was subjected to silica gel flash chromatography using CHCl₃ as solvent. The appropriate fractions were pooled and evaporated in vacuo. The resulting oil was recrystallized from absolute ethanol to yield colorless crystals (0.258 g, 67%): mp 105-108°C; 

1H NMR (CDCl₃) δ 1.14 (t, 3, CH₂CH₃), 2.40-2.92 (m, 2, H-12), 3.20-3.45 (m, 1, H-11), 4.05 (q, 2, CH₂CH₃), 7.20-7.45 (m, 4, Ar-H), 7.72-7.93 (m, 4, Ar-H). EI mass spectrum, m/e 436 (M⁺, 3), 363 (1.1), 338 (50), 336 (100), 334 (51.33), 281 (1.2), 202 (21).

Anal. Calcd for C₁₉H₁₆Br₂O₂: C, 52.32; H, 3.70; Br, 36.64. Found: C, 52.24; H, 3.76; Br, 36.42.

9,10-Diiodo-9,10-(11-carboethoxyethano)anthracene (109j).

9,10-diiodoanthracene (1 g, 2.33 mmol) was placed in a pressure tube along with acryloyl chloride (2 mL, 24.6 mmol) and 8 mL of xylene. A few BHT crystals were added and the tube was heated with stirring at 130°C for 16 h. The solution was transferred to a rbf and absolute ethanol (20 mL) was added. After refluxing for one hour the solution was evaporated to a yellow oil which was subjected to silica gel flash chromatography using CHCl₃/Hexane as solvent (2:1).
The appropriate fractions were pooled together and evaporated to an oil. The oil was taken up in 7 mL of absolute ethanol 3 times and the ethanol mother liquor was collected and combined and finally evaporated under reduced pressure. The resulting oil was recrystallized from hexane to give light yellow crystals (767.3 mg, 49%): mp 106-107°C; \( ^1H \text{ NMR (CDCl}_3 \) \( \delta \) 1.1-1.3 (t, 3, \( \text{CH}_2\text{CH}_3 \)), 2.6-3.1 (m, 2, H-12), 3.3-3.5 (dd, 1, H-11), 3.9-4.2 (q, 2, \( \text{CH}_2\text{CH}_3 \)), 7.1-7.3 (m, 4, Ar-H), 7.5-7.7 (m, 4, Ar-H); EI mass spectrum, m/e 430.9 (M\(^+\), 24), 430 (100), 403 (41.5), 276 (6), 176 (28).

Anal Calcd. for C\(_{19}\)H\(_{16}\)I\(_2\)O\(_2\); C, 43.05; H, 3.04; I, 47.88,
Found: C, 43.10; H, 3.08; I, 47.81.
Diene Substituent Effects On The Retro-Diels-Alder Reaction

Results and Discussion

Kinetic Method

In order to carry out the cycloreversion reactions depicted in Figure 55, a ~1.2 x 10^{-4} M solution of the adduct in dry diphenyl ether was heated to 200°C in a salt bath. The temperature of the salt bath was controlled to ± 1°C by a Therm-O-Watch™ temperature controller. A 100 mL rbf containing 75 mL of diphenyl ether was placed in the salt bath and allowed to equilibrate, and then to initiate the reaction, 5 mL of a stock solution (~1.92 x 10^{-3} M) of adduct was added. At various times, an aliquot was removed and cooled to room temperature and the concentration of the anthracene product was determined by measuring the solution's absorbance at that anthracene's long-wavelength λ_{max} (shown in Tables 5). The determination of first-order rate constants and kinetic activation parameters (reported as ± 1 standard deviation) was accomplished by using the computer program LSTSQ, available from Serena Software. LSTSQ was run on an IBM-AT microcomputer.
Most of the adducts we examined revealed clean first-order behavior for the anthracene product. No attempts were made to isolate or quantify the dienophile component of the rDA reaction. In two cases (109s and 109t), oxidation of the anthracene under the conditions of the cycloreversion was extremely fast; the formation of oxidized products at 326 and 304 nm, respectively, was monitored instead. Rapid oxidation of anthracenes 111 (R = OH) and 112 (R = NH₂) was confirmed by adding a sample of each anthracene to deoxygenated diphenyl ether at 200°C. The UV spectrum, taken within 15 s, in each case showed no anthracene absorptions, only peaks at 326 and 304 nm respectively.

Results

Table 5 shows the first-order rate constants of the retro-Diels-Alder reaction of 9,10-disubstituted anthracene adducts in diphenyl ether at 200°C. Other data pertinent to our kinetic results are also shown in Table 5. Kinetic activation parameters for some representative substituents are shown in Table 6. Table 7 shows the effects of solvent polarity for some representative diene substituents in the retro-Diels-Alder reactions of anthracene adducts.

Discussion

Inspection of Table 5 shows several trends. First, electron-donating substituents tend to accelerate the cycloreversion reaction. This can be seen by comparing the first order rate
Figure 55: Retro-Diels-Alder reaction used to evaluate diene substituent effects.
Table 5. First-order rate constants of the retro-Diels-Alder reaction at 200°C in diphenyl ether.

<table>
<thead>
<tr>
<th>R</th>
<th>compd</th>
<th>UV of anthracene&lt;sup&gt;a&lt;/sup&gt; (max is underlined)</th>
<th>X of reaction used</th>
<th>constant</th>
<th>10&lt;sup&gt;5&lt;/sup&gt;&lt;sup&gt;k&lt;/sup&gt;&lt;sub&gt;1&lt;/sub&gt;, s&lt;sup&gt;-1&lt;/sup&gt;</th>
<th>half-life, min</th>
<th>rel rate</th>
<th>σ&lt;sub&gt;p&lt;/sub&gt;</th>
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<tr>
<td>H</td>
<td>108a</td>
<td>328, 344, 362, 382</td>
<td>8-98</td>
<td>1.72</td>
<td>672</td>
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<tr>
<td>Me</td>
<td>108b</td>
<td>346, 362, 382, 404</td>
<td>2-85</td>
<td>3.87</td>
<td>289</td>
<td>2.25</td>
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<tr>
<td>Et</td>
<td>109c</td>
<td>346, 362, 382, 404</td>
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<td>34.7</td>
<td>33.0</td>
<td>20.2</td>
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<tr>
<td>n-Pr</td>
<td>109d</td>
<td>346, 364, 384, 404</td>
<td>8-91</td>
<td>34.8</td>
<td>32.0</td>
<td>20.2</td>
<td>(b)</td>
<td></td>
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<tr>
<td>i-Pr</td>
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<td>346, 362, 382, 404</td>
<td>1-94</td>
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<td>84.9</td>
<td>7.91</td>
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<td>109h</td>
<td>346, 366, 386, 406</td>
<td>3-73</td>
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<td>Br</td>
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<td>350, 366, 386, 408</td>
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<tr>
<td>I</td>
<td>109j</td>
<td>356, 372, 392, 416</td>
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<td>825</td>
<td>0.81</td>
<td>0.30</td>
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<tr>
<td>Si(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>109k&lt;sup&gt;c&lt;/sup&gt;</td>
<td>318, 344, 362, 382</td>
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<tr>
<td>CHO</td>
<td>109l&lt;sup&gt;c&lt;/sup&gt;</td>
<td>430 (broad)</td>
<td>17-93</td>
<td>0.32</td>
<td>139</td>
<td>4.84</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>109m&lt;sup&gt;c&lt;/sup&gt;</td>
<td>338, 354, 372, 392</td>
<td>14-80</td>
<td>3.10</td>
<td>372</td>
<td>1.80</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>COOCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>109n&lt;sup&gt;c&lt;/sup&gt;</td>
<td>338, 352, 370, 390</td>
<td>2-88</td>
<td>0.415</td>
<td>2780</td>
<td>0.24</td>
<td>0.39</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Spectrum in diphenyl ether; λ values are reported ±1 nm. <sup>b</sup>No known substituent constant. <sup>c</sup>Adduct synthesized and kinetic data obtained by Yongseog Chung, OSU.
Table 5. Continuation of first-order rate constants of the retro-Diels-Alder reaction at 200°C in diphenyl ether.

<table>
<thead>
<tr>
<th>R</th>
<th>compd</th>
<th>UV of anthracene (a)</th>
<th>% of reaction used to calculate rate constant</th>
<th>$10^5 k_1$, s$^{-1}$</th>
<th>half-life, min</th>
<th>rel rate</th>
<th>$\sigma_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCH$_3$</td>
<td>108p(b)</td>
<td>352, 368, 388, 408</td>
<td>17-86</td>
<td>69.0</td>
<td>16.7</td>
<td>40.1</td>
<td>-0.27</td>
</tr>
<tr>
<td>OPh</td>
<td>108q(b)</td>
<td>304, 364, 384, 406</td>
<td>22-91</td>
<td>168</td>
<td>5.83</td>
<td>115</td>
<td>-0.32</td>
</tr>
<tr>
<td>OSi(C$_2$H$_5$)$_3$</td>
<td>108r(b)</td>
<td>358, 378, 404, 428</td>
<td>14-93</td>
<td>453</td>
<td>2.55</td>
<td>263</td>
<td>(c)</td>
</tr>
<tr>
<td>CH</td>
<td>108s(b)</td>
<td>(d)</td>
<td>(e)</td>
<td>2420</td>
<td>0.48</td>
<td>1410</td>
<td>-0.37</td>
</tr>
<tr>
<td>NH$_2$</td>
<td>108t(b)</td>
<td>382, 402</td>
<td>32-86</td>
<td>4000</td>
<td>0.29</td>
<td>2330</td>
<td>-0.66</td>
</tr>
<tr>
<td>H(C$_2$H$_5$)$_2$</td>
<td>108u(b)</td>
<td>338, 378, 398</td>
<td>4-94</td>
<td>239</td>
<td>ca. 2.2</td>
<td>140</td>
<td>-0.83</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>108v(b)</td>
<td>340, 354, 372, 394</td>
<td>(e)</td>
<td>0.031</td>
<td>37300</td>
<td>0.02</td>
<td>0.78</td>
</tr>
<tr>
<td>-CH$_2$SCH$_2$-</td>
<td>108w(f)</td>
<td>352, 370, 388, 412</td>
<td>8-94</td>
<td>40.3</td>
<td>28.7</td>
<td>38.8</td>
<td>(c)</td>
</tr>
<tr>
<td>-CH$_2$SCH$_2$-</td>
<td>108x(f)</td>
<td>352, 368, 388, 410</td>
<td>15-92</td>
<td>26.1</td>
<td>44.3</td>
<td>25.2</td>
<td>(c)</td>
</tr>
<tr>
<td>CH$_2$SCH$_3$</td>
<td>108y(f)</td>
<td>350, 368, 386, 408</td>
<td>15-95</td>
<td>26.4</td>
<td>43.8</td>
<td>29.2</td>
<td>(c)</td>
</tr>
<tr>
<td>CH$_2$SC(C$_2$H$_5$)$_3$</td>
<td>108z(f)</td>
<td>350, 368, 386, 408</td>
<td>14-87</td>
<td>48.4</td>
<td>23.9</td>
<td>46.5</td>
<td>(c)</td>
</tr>
</tbody>
</table>

(a) Spectrum in diphenyl ether; $\lambda$ values are reported $\pm$1 nm. (b) Adduct synthesized and kinetic data obtained by Yonggeog Chung, OSU. (c) No known substituent constant. (d) Due to rapid oxidation, only a peak at 326 nm due to anthraquinone is observed. (e) $k_1$ was extrapolated from the temperature dependence. (f) Adduct synthesized and kinetic data obtained by P. Namjeppan formerly of OSU.
Table 6. Kinetic Activation Parameters for Some Representative Substituents in the Retro-Diels-Alder Reactions of Anthracene Adducts in Diphenyl Ether

<table>
<thead>
<tr>
<th>compd</th>
<th>$\Delta H^\dagger$ (kcal/mol)</th>
<th>$\Delta S^\dagger$ (eu)</th>
<th>T(avg), °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>109a</td>
<td>34.8 ± 1.4</td>
<td>-7.9 ± 2.7</td>
<td>230</td>
</tr>
<tr>
<td>109b</td>
<td>37.8 ± 1.9</td>
<td>0.4 ± 3.9</td>
<td>223</td>
</tr>
<tr>
<td>109c</td>
<td>36.1 ± 3.5</td>
<td>-0.1 ± 7.2</td>
<td>210</td>
</tr>
<tr>
<td>109e</td>
<td>35.7 ± 0.9</td>
<td>-3.7 ± 1.9</td>
<td>220</td>
</tr>
<tr>
<td>1091(a)</td>
<td>40.0 ± 1.1</td>
<td>6.5 ± 2.3</td>
<td>215</td>
</tr>
<tr>
<td>109p(a)</td>
<td>32.3 ± 1.0</td>
<td>-5.5 ± 2.0</td>
<td>215</td>
</tr>
<tr>
<td>109q(a)</td>
<td>36.2 ± 1.2</td>
<td>4.6 ± 2.6</td>
<td>195</td>
</tr>
<tr>
<td>109s(a)</td>
<td>31.2 ± 1.9</td>
<td>-3.7 ± 4.0</td>
<td>165</td>
</tr>
<tr>
<td>109w(b)</td>
<td>32.6 ± 0.4</td>
<td>-6.0 ± 0.9</td>
<td>210</td>
</tr>
<tr>
<td>109x(b)</td>
<td>37.2 ± 4.2</td>
<td>3.1 ± 8.5</td>
<td>215</td>
</tr>
</tbody>
</table>

(a) Adduct synthesized and kinetic activation parameters were measured by Yongseog Chung, OSU. (b) Adduct synthesized and kinetic activation parameters were measured by P. Nanjappan formerly of OSU.

Table 7. Polar Solvent Effects for Some Representative Substituents in the Retro-Diels-Alder Reactions of Anthracene Adducts

<table>
<thead>
<tr>
<th>compd</th>
<th>rate in diphenyl ether ($10^3 k_1$, s$^{-1}$)</th>
<th>rate in pentadecane ($10^3 k_1$, s$^{-1}$)</th>
<th>reaction temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>109c</td>
<td>34.7</td>
<td>25.1</td>
<td>200</td>
</tr>
<tr>
<td>109u(a)</td>
<td>239</td>
<td>219</td>
<td>200</td>
</tr>
<tr>
<td>109s(a)</td>
<td>628</td>
<td>212</td>
<td>200</td>
</tr>
<tr>
<td>109x(a)</td>
<td>453</td>
<td>381</td>
<td>200</td>
</tr>
</tbody>
</table>

(a) Adduct prepared and solvent effects measured by Yongseog Chung OSU.
constants of compounds 109a-109f and 109p-109u. If compound 109a is set as the reference, the relative rates of compounds 109b-109f and 109p-109u are all greater than that of 109a. Previous studies have shown rate accelerations by methoxy and siloxy substituents,\textsuperscript{27b,69} and so such a trend is not unexpected. Comparison of the $\sigma_p$ constants with the rate of cycloreversion shows a direct relationship. The trend is not linear, however; there does exist a relationship between electron-donating ability and the rate of cycloreversion in the series $R = H < Me < OCH_3 < OH < NH_2$. It is surprising that adduct 109u ($R = NMe_2$) cycloreverts almost 17 times slower than does adduct 109t ($R = NH_2$). Based on the $\sigma_p$ values, one would predict that 109u ($\sigma_p = -0.83$) would cyclorevert faster than 109t ($\sigma_p = -0.66$). This discrepancy can be explained if one considers the relative conjugating ability of 109u compared to 109t. By using CPK models and cyclic voltametry, Chung has found that 109t can occupy a conformation in which the amino group can conjugate with the forming carbon-carbon double bond of the anthracene.\textsuperscript{72} Similar studies of adduct 109u by Chung show steric repulsion by the methyl groups on the amine with the peri hydrogens of anthracene. This steric repulsion forces a conformation of 109u that does not allow nitrogen lone pair conjugation with the forming anthracene $\pi$ bonds in the transition state.
Secondly, electron withdrawing groups do not decelerate
cycloreversion reactions much at all. This is contrary to what
would be predicted, based on the results of electron-donating
substituents. Comparison of adducts 109g-109j and 109l-109m to
the reference adduct 109a shows that reaction rates differ only by
a factor of 5 at most. The only exception to this observation is
adduct 109v, which cycloreverts 46 times more slowly than adduct
109a. The dinitro adduct 109v cycloreverts at 200°C with a
half-life of over 3 weeks whereas the diamino adduct (109t)
cycloreverts with a half-life of 17 s.

Thirdly, steric interactions of the adducts show surprising rate
accelerations. When comparison is made between adducts 109a,
109b and 109c, a 20 fold increase in rate is observed. While
this is a relatively small rate increase, it is much larger than
anything observed by Nanjappan and Czarnik in their dienophile
substituent effects described in Chapter II.³⁰ By moving the
steric bulk from the open and unhindered dienophile to the congested
bridgehead position of the diene, we see a rate acceleration due to
steric interactions. What is most surprising is the rate obtained
for adduct 109e. The adduct containing the isopropyl group
actually shows a rate decrease. This point is shown graphically
in Figure 56. The plot of rate vs. (crudely) steric bulk shown in
Figure 56 reveals a bell-shaped structure-reactivity relationship.
We have concluded, based on molecular mechanics calculations and
examination of CPK models, that increasing the steric bulk of the
Figure 56: Graph of retro-Diels-Alder rate constant as a function of substituent in the alkyl series.
diene substituents results in greater strain energies of both the adducts and parent 9,10-disubstituted anthracenes. Our results show that steric strain in the adducts in which a "gear-like" orientation between substituent and adduct framework can exist, is less than the strain found in the parent anthracenes in which bad contracts with the peri hydrogens cannot be avoided with the isopropyl group. Stated in a different way, the reaction slows because at some point between ethyl and isopropyl groups the generation of strain in the transition structure wins out over the release of strain in the starting material.

Adduct 109d (R = n-pr) in Table 5a shows that this observed rate acceleration is due purely to steric bulk of the substituent. The rate constant for adduct 109d (R = n-pr) is almost identical to that of adduct 109c (R = Et) showing that the steric congestion needed to give a rate acceleration must be close to the bridgehead framework. It would have been optimal to compare these results with the rate constant of the di-tert-butyl adduct, but as was mentioned earlier, we were unable to obtain a sample of 9,10-di-tert-butylanthracene. We may consider the reactivity of the bis(trimethylsilyl) adduct (109k), which is again slower than the diisopropyl adduct 109e. Such a comparison is questionable due to the fact that the Si-C bond is longer than the C-C bond, and so the steric effect of a Si(CH₃)₃ group would be smaller because it would simply be further away from the bridgehead center than a C(CH₃)₃ group would be. Based on their similar σp
values \( \text{Si(CH}_3\text{)}_3, \sigma_p = -0.07 \) and \( \text{C(CH}_3\text{)}_3, \sigma_p = -0.20 \), we would predict that the two groups would have similar inductive effects. It would be difficult, however, to predict what the resonance effect of the vacant silicon d orbital would be, although Nanjappan and Czarnik have previously shown that \( \text{Si(CH}_3\text{)}_3 \) is about 22 times faster as a dienophile substituent than is \( \text{C(CH}_3\text{)}_3 \) (see Table 1, Chapter II or ref. 30).

Based on Nanjappan's work on anthracenophane bridging shown by entries 109w, 109x, 109y and 109z (Table 5), our proposal that strain induced by a bridging alkyl chain would lead to rate accelerations appears to unfounded. Each of these adducts cycloreverts at about the same rate as adducts 109c (R = Et) and 109d (R = n-pr). This indicates no special effect of the anthracenophane bridge at least for these alkyl chain lengths. Rosenfeld has reported that shorter chain lengths than those used in this study have been found to affect both the position of cycloaddition and the DA rates in reactions with tetracyanoethylene.\(^{71}\)

Finally, Table 6 shows kinetic activation parameters for some representative substituents that we studied. As shown in Table 6, most of the activation entropies of the cycloreversion reactions studied fall near 0 eu. This is consistent with the picture of the retro-Diels-Alder reaction transition state structure resembling that of adduct. As would be expected, adduct 109b (R = CH\(_3\)) shows no appreciable changes in rate of cycloreversion upon changing solvent from diphenyl ether to pentadecane. This result
is shown in Table 7. Table 6 and Table 7 both have some noticeable exceptions to the results that have been described here, but these exceptions were discovered by Yongseog Chung and they will be discussed in his dissertation.\textsuperscript{72}

In summary the retro-Diels-Alder reaction of 9,10-disubstituted anthracene adducts is influenced in the following manner: (1) electron-donating substituents increase the rate of cycloreversion, (2) electron-withdrawing groups may decrease or increase the rate of cycloreversion, however, the observed effect is rarely large, (3) steric acceleration due to increasing size of alkyl groups is relatively small and demonstrates an unprecedented bell-shaped structure-reactivity profile.
CHAPTER VI

The Michael/Retro-Michael Reaction

Background

The Michael reaction involves the nucleophilic addition of nucleophiles to the carbon-carbon double bonds of \(\alpha,\beta\)-unsaturated ketones, aldehydes, nitriles, or carboxylic acid derivatives.\(^7^3\) It can also involve any unsaturated system having a functional group capable of stabilizing a carbanionic intermediate. Suitable nucleophiles for the reaction include enolate ions, alkoxide ions, thiols and amines.\(^7^4\) The Michael reaction differs from typical nucleophilic alkylation reactions in the fact that the base which generates the nucleophile is regenerated so that usually only a catalytic amount is required. In certain cases, such as when primary or secondary amines are the nucleophilic species, the amines can act as their own base, and thus no added base is required.\(^7^5\)

The Michael reaction is a reversible process. The use of a full equivalent of base, elevated reaction temperatures, and long reaction times frequently promotes side reactions or reversal of the Michael reaction (referred to as the retro-Michael reaction).\(^7^6\)

Since the retro-Michael reaction may lead to compounds other than
the desired products or to altered starting materials, the retro-
Michael reaction has been generally considered an undesirable
reaction. The retro-Michael reaction has however led to
"interesting" and surprising side reactions, and it has been
used in natural product syntheses. The retro-Michael reaction
has been carried out under a variety of conditions including base
catalysis, acid catalysis, and thermally in the vapor
phase.

Dornow and Boberg in 1952 discovered a Michael/retro-Michael
exchange reaction. The reaction studied by them is shown in
Figure 57, and involves an exchange between ethylcyanoacetate
(113) and nitrostilbene (114) to give phenylnitromethane (115)
and 2-carboethoxycinnamionitrile (116). The reaction was carried
out in good yield over the course of 5 days, and they believed the
reaction proceeded through a Michael addition intermediate. They
based this belief on the discovery that actual Michael addition
intermediates could be isolated in similar studied reactions. These
isolated intermediates provided mechanistic details about the
reaction shown in Figure 57.

Since 1983, Hoffmann et al. have published a series of articles
describing a catalytic cycle based on the Michael/retro-Michael
reaction. Hoffmann found that DABCO could be used to catalyze
the coupling of aldehydes and methyl acrylate as shown in Figure
58. The reactions typically proceeded very cleanly with no
polymerization of methyl acrylate and in good to excellent yields.
The mechanism proposed for the reaction is shown in Figure 59.
Figure 57: Michael/retro-Michael exchange reaction discovered by Dornow and Boberg.\textsuperscript{82}
Figure 58: DABCO catalyzed coupling of aldehydes to methyl acrylate.\textsuperscript{83}
Figure 59: Mechanism of DABCO catalyzed coupling of aldehydes to methyl acrylate.
The forward Michael reaction was not actually "completed" in this system due to the fact that the zwitterion formed (121, Figure 59) in the addition step is never neutralized. Despite this fact, the reaction did demonstrate that the Michael/retro-Michael reaction can be used to form a catalytic cycle. Hoffmann et al. have shown that this reaction has great synthetic utility, and several other experimenters have recently expanded on this work.

Michael/retro-Michael catalysis cycle for $\alpha,\beta$-unsaturated ester hydrolysis in the presence of divalent metal ions

In 1986 Johnson showed that amines could be added to acrylates and $\alpha,\beta$-unsaturated amides at room temperature via a Michael addition reaction. It was further demonstrated by Johnson that the reactions were reversible. Johnson set out to trap the retro-Michael products of an amine and methyl acrylate as shown in Figure 60. He envisioned that a Michael adduct (124) could be allowed to undergo a retro-Michael reaction in the presence of a trapping amine (125), and the trapping amine would add in a Michael reaction to give a new product (127). By studying the ratio of products 124/127 formed at various temperatures, Johnson was able to perform a detailed kinetic analysis of both the forward and reverse reaction of both compounds 124 and 127.
Figure 60: Exchange reaction between methyl acrylate and different amines studied by Johnson.86
Johnson found that the rate constants for the retro-Michael reactions of 124 and 127 were identical \( (k^{-1} = k_2 = 1.8 \times 10^{-8}s^{-1}) \). This indicated that minor changes in the structure of these \(^2\)amines had no effect on the rate constant. Furthermore, Johnson found a \( K_{eq} = 2.0 \times 10^4L \text{ mol}^{-1} \), which showed that at 23°C in methanol, compound 124 was approximately 1% dissociated after 4 h. Stated another way, at 23°C in methanol, the retro-Michael reaction of 124 was about 1% complete after 4 h. These concentrations were detectable by \(^1\)H NMR, enabling Johnson to confirm his calculations experimentally. Johnson also studied a similar reaction in which acrylamide was substituted for methyl acrylate, and he obtained very similar results \( (k^{-1} = k_2 = 8.8 \times 10^{-8}s^{-1}, K_{eq} = 7.3 \times 10^3L \text{ mol}^{-1}) \), retro-Michael reaction is 1% complete at 23°C).

These results were of interest to us because the adducts used by Johnson had an amine \( \beta \) to the acyl group, and the retro-Michael reaction was reversible and proceeding at least to a small extent at 23°C. The \( \beta \)-amino group was of interest because based on the work of Bender and Turnquist we believed that ester adducts with \( \beta \)-amino groups might be subject to metal ion catalysis.\(^9\) The demonstration of reversibility at 23°C was intriguing to us because it showed that the generic catalytic cycle depicted in Figure 16 (Chapter II) could possibly be adapted to fit the Michael/retro-Michael reaction for transacylation reactions. As shown in Figure 61, the Michael/retro-Michael reaction can be applied to Czarnik's catalytic cycle.
Figure 61: Catalytic cycle for acrylate conversion via a Michael/retro-Michael reaction.
In 1987, Min Sok Kang of this group studied the metal ion-promoted hydrolysis of methyl acrylate and metal ion-promoted alcoholysis reactions of acrylamide via a Michael/retro-Michael addition cycle. The potential catalytic cycle studied by Kang is shown in Figure 62 (other cycles studied by Kang are shown in Figure 63 and Figure 64). The Kinetic method which Kang used to study these reactions involved extraction of the organic soluble components from a reaction aliquot, and then quantification by \textsuperscript{1}H NMR. The results of the metal ion-promoted hydrolysis reactions of ester 129 to acid 130 (R = Me, R' = t-Bu, Figure 61) are shown in Table 8. As can be seen in Table 8, the control reaction (which contained no metal ion) showed that non-metal hydrolysis reactions were actually faster than those with added metal ions. This was attributed to the fact that the concentration of the catalytically active complex is negligibly small because the nitrogen of amine 129 is insufficient to provide good coordination for metal ions in a 6 membered chelate. Furthermore, it was proposed by Kang that the favorable inductive effect of a coordinated \(\beta\)-amine would not be expected to be as large as that from an \(\alpha\)-amine, as in the \(\alpha\)-amino acid esters.\footnote{8,9}

Based on the results shown in Table 8, Kang decided that a second binding site located on the amine functionality might provide a greater concentration of the needed catalytically active metal-amine complex. To obtain better binding of a metal, Kang substituted the secondary amine (128) with
Figure 62: Proposed metal ion-promoted hydrolysis of methyl acrylate via a Michael/retro-Michael reaction as first studied by M. S. Kang.86
Table 8. Metal ion-promoted hydrolysis reactions of ester 129 at a pH of 7.55, and 23°C.86

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Co^{+++}</th>
<th>Ni^{++}</th>
<th>Co^{++}</th>
<th>control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>.25</td>
<td>71.7</td>
<td>-</td>
<td>76.9</td>
<td>-</td>
</tr>
<tr>
<td>.5</td>
<td>43.3</td>
<td>71.7</td>
<td>49.2</td>
<td>25.9</td>
</tr>
<tr>
<td>.75</td>
<td>18.3</td>
<td>26.4</td>
<td>21.5</td>
<td>-</td>
</tr>
<tr>
<td>1.0</td>
<td>13.3</td>
<td>11.3</td>
<td>9.2</td>
<td>0</td>
</tr>
<tr>
<td>1.25</td>
<td>5</td>
<td>-</td>
<td>4.6</td>
<td>0</td>
</tr>
<tr>
<td>1.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

trimethylethlenediamine as shown in Figure 63. Amide 135 was refluxed with 2 eq of Cu(ClO\textsubscript{4})\textsubscript{2}·6H\textsubscript{2}O in methanol at 65°C for 32 hours, and no ester was formed. A similar result was found when 1 eq of NaOCH\textsubscript{3} was used under the same conditions. Amide 134 showed no ester formation under similar conditions after 4 days. Kang was able to observe metal ion-promoted hydrolysis of amides 134 and 135, but he was unable to quantify this hydrolysis.

Kang also attempted the metal ion promoted hydrolysis of ester 137 as shown in Figure 64. The results of this hydrolysis in aqueous buffer are shown in Table 9. Table 9 clearly shows that metal ions do give large rate enhancements for the hydrolysis of ester 137. Kang was able to show that the half-life of ester 137 hydrolysis was shortest in the presence of Cu^{++} ions,
Figure 63: Proposed metal ion-promoted alcoholysis reaction of acrylamide via a Michael/retro-Michael reaction as studied by M. S. Kang.86
Figure 64: Proposed metal ion-promoted hydrolysis of methyl acrylate via a Michael/retro-Michael reaction as studied by M. S. Kang.\textsuperscript{86}
Table 9. Metal ion-promoted hydrolysis reactions of ester 137 at a pH of 7.55, and 23°C. 

<table>
<thead>
<tr>
<th>metal ion</th>
<th>time</th>
<th>% ester remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu++</td>
<td>10 min</td>
<td>10.2</td>
</tr>
<tr>
<td>Ni++</td>
<td>90 min</td>
<td>11.8</td>
</tr>
<tr>
<td>Zn++</td>
<td>18.75 hours</td>
<td>14.7</td>
</tr>
<tr>
<td>control (Na+)</td>
<td>9.15 days</td>
<td>27.2</td>
</tr>
</tbody>
</table>

(no metal t₁/₂ = 29 h, 2 eq of Cu++ t₁/₂ = 2 min). Kang further found that increasing the pH of the reaction resulted in a rate increase for the Cu²⁺ promoted hydrolysis reaction of ester 137. At pH 9.0 however, the rate of Cu²⁺ promoted hydrolysis was found to decrease. The proposed explanation for this observation was that up to pH 8.5, metals exist as complex ions with organic ligands. Above pH 8.5, the concentration of hydroxide is larger, and at the higher pH, metal hydroxides form that prefer to come out of the polydentate coordination sites of the ester. This results in an elimination of the catalytic ability of the metal ions and thus a deceleration of the rate of hydrolysis.
Based on his own observations and those of previous studies, Kang concluded that reactions using alcohol as a final acyl group acceptor are much slower than those using water. For example, Kang found the metal ion-promoted hydrolysis reaction of ester 137 at 25°C to be very fast; $t_{1/2}$ at pH 7.55 = 2 min and $t_{1/2}$ at pH 8.5 = 35 s. However, when ester 137 was subjected to ethanolysis in the presence of Cu$^{++}$ at 65°C, the reaction was much slower; $t_{1/2}$ = 3 hours. Furthermore, metal ion-promoted hydrolysis of amides 134 and 135 were slow but observable, whereas metal ion-promoted alcoholysis of these amides was too slow to be detected.

Lastly, Kang studied the reactivity of ester 139 and acid 141 (Figure 65) towards the retro-Michael reaction. The retro-Michael reaction of ester 139 proceeded to equilibrium in complete analogy to the work of Johnson. Kang found that the retro-Michael reaction of ester 139 proceeded to an equilibrium point of 50% consumption of ester 139 in 6 h. The retro-Michael reaction of acid 141 was too slow to be seen in preliminary experiments. One reason for this observation could have been the method used to quantify the products. The method of detection used in this study as well as all other studies by Kang is shown schematically in Figure 66. Because Kang was using an extraction technique to quantify products, it was possible that some of the products were not observed because they were present only in minute quantities.
Figure 65: Attempted retro-Michael reactions of ester 139 and acid 141.\(^{86}\)
Figure 66: Reaction work-up steps used by Kang for quantification of reaction products.88
Nature Of The Problem

Based on the work by Kang on the catalytic cycle using a Michael/retro-Michael reaction, the following questions were left to be answered:

1. Can the entire cycle be carried out in an aqueous environment and in one reaction vessel?

2. Can the cycle be monitored in such a way that all three steps can be observed at the same point in time?

3. Are the hydrolysis or catalysis reactions promoted or catalyzed by metal ions?

4. What conditions of pH and temperature are required to effect the retro-Michael reaction?

5. How do metal ions affect the forward and retro-Michael reaction?

The remaining two chapters will discuss the methods we used to answer these questions, and the results we obtained using such methods.
CHAPTER VII

The Michael-Cycle Catalytic System

Compound Choice and Instrumentation

As discussed in Chapter VI, the method of detection used by Kang presented several experimental challenges. Kang's method of product detection method was quite laborious and very time consuming. Furthermore, the method allowed only for the detection of organic soluble products, leaving the water soluble products undetected.

To solve these problems, we decided that the ethylenediamine group used should be redesigned so that a different method of detection could be used. UV spectroscopy and High Performance Liquid Chromatography were the two methods of detection available to us. Due to its ability to quantify virtually all types of compounds, we decided that reverse-phase HPLC would be the method of choice for product detection and quantitation.

The HPLC instrument we used contained a UV detection system that monitored the absorbance at 256 nm, and so any compounds we wished to quantify needed to have a light absorbing chromophore attached to them. Therefore, our ethylenediamine molecule needed to
have some type of chromophore attached to it in such a way that the chromophore would not affect the reactions of interest in any way. The compound chosen for our purposes was N'-benzyl-N,N-dimethylethylenediamine (143, Figure 67). This compound was suitable for our needs because the chromophore was attached to the ethylenediamine molecule in such a way that it was far removed from the chelating amines. Secondly, the compound was readily available from several chemical companies at reasonable cost.

![Figure 67: N'-Benzyl-N,N-dimethylethylenediamine](image)

Purification of N'-Benzyl-N,N-dimethylethylenediamine

N'-Benzyl-N,N-dimethylethylenediamine (143) was purchased from Aldrich Chemical Co. in 25 g quantities that were reported by Aldrich Chemical Co. to be technical grade (95% pure), but actual analysis showed the purity to be much lower. It is a high
boiling liquid that is not stable upon prolonged exposure to air. In order for 143 to be useful for our studies, it was necessary that it be as close to analytically pure as possible. This requirement provided us with several experimental challenges. Numerous attempts were made to purify 143 by vacuum distillation, but by this method we achieved only 95% purity as shown by $^1$H NMR. As mentioned above, compound 143 was unstable upon exposure to air and it underwent air oxidation easily. This resulted in a rapid drop in purity soon after distillation. To prevent this oxidation and to purify 143 to analytical purity, it was decided to attempt to purify 143 by forming either a metal chelated solid or a salt of some kind.

The first method of purification attempted was formation of a zinc chloride chelate as shown in Figure 68. Freshly distilled 143 was mixed with ZnCl$_2$ in isopropanol to give almost pure 144. Recrystallization provided 144 in pure form as shown by $^1$H NMR and $^{13}$C NMR. Compound 144 was immune to further oxidation and had an indefinite shelf life. To remove the ZnCl$_2$ from 144, a modification of a procedure developed by Kang was used (Figure 68). The zinc ion was removed from 144 by extraction with pH 11.0 EDTA, and then 143 was removed from the EDTA solution in pure form by extraction with chloroform (see Experimental Section for complete details). This method provided 143 in pure form, but a second method of purification offering different advantages was also developed.
Figure 68: Purification of N'-benzyl-N,N-dimethylethylenediamine by formation of a zinc chloride complex and then removal of the zinc chloride to give pure amine.
N'-Benzyl-N,N-dimethylethylenediamine (143) could also be purified by formation of the HBr salt as shown in Figure 69. This method of purification proved somewhat simpler than the previously described method in that no anhydrous zinc chloride was needed, and the HBr was readily available from OSU Lab Stores. The HBr salt of 145 was formed under conditions similar to that used for the formation of 144, and the removal of the HBr required simple extraction as shown in Figure 69 (see Experimental Section for sample procedure). This method of reisolation of 143 was easier with compound 145 due to the fact that no special solutions such as EDTA were needed. By forming an HBr salt, it was possible to coordinate the diamine salt (143) in such a way that it was indefinitely stable. The diamine salt (143) could then be extracted with base in a matter of minutes to provide pure 143.

Synthesis of Other Michael-Cycle Compounds

With a means of obtaining pure 143 in hand, work was next begun toward independently synthesizing the other two intermediates (146 and 147) of the catalytic Michael-Cycle shown in Figure 70. Benzyl-3-((2-(dimethylamino)ethyl)methylamino)propionate (146) was synthesized in a straightforward manner by mixing pure 143 with excess methyl acrylate (118), adding methanol as solvent and stirring under argon for 2-3 days. Addition of methanol before methyl acrylate resulted in a yellow color in the product that could not be eliminated. Evaporation in vacuo to remove excess methyl acrylate (118) and methanol provided analytically pure 146.
Figure 69: Purification of $N'$-Benzyl-$N,N$-dimethylethlenediamine by formation of the HBr salt, and then removal of the HBr to give pure amine.
Figure 70: Michael catalytic cycle for the hydrolysis of methyl acrylate.
(see Experimental Section). Compound 146 was sensitive to air oxidation, but it was found that 146 could be stored under vacuum for up to 3 weeks with little decomposition. To minimize any extraneous results due to decomposition, fresh 146 was synthesized as needed every couple of days. Storage of 146 under an atmosphere of argon or nitrogen did not prevent decomposition as well as storage under vacuum, and so storage under vacuum was the method of choice.

Benzyl-3-((2-(dimethylamino)ethyl)methylamino)propionic acid (147) was also synthesized and isolated as its ditriflate salt (150) in a straightforward manner as shown in Figure 71. Synthesis of the tert-butyl ester (149) required simple mixing of 143 and tert-butyl acrylate (148), allowing the resulting solution to stir for 1-2 days. Evaporation of excess 148 in vacuo gave pure 149 (as shown by \(^1\)H NMR), which was hydrolyzed in refluxing trifluoroacetic acid. Simple evaporation in vacuo did not remove all the excess trifluoroacetic acid; however, it was found that the trifluoroacetic acid could be removed by forming an azeotrope with water and then evaporation in vacuo. Multiple evaporations (5-10) with water resulted in a thick oil of pure 150 that crystallized very slowly upon standing. By knowing the number of moles of 143 that were started with, it was possible to calculate the molecular weight of 150. In this way it was found that 150 was isolated as the bis-trifluoroacetic acid salt. Subsequent microanalysis confirmed the elemental composition of this sample,
Figure 71: Formation of 3-((2-(Dimethylamino)ethyl)benzylamino)propionic acid
The HPLC Solvent System

A considerable amount of time was devoted to developing a suitable solvent system for product separation and working out a standardized method to quantify the products, and so it bears mention here. The equipment list (instrument, column type, injection loop size etc.) are described in the General Experimental Section of this chapter, and therefore will not be listed here.

With authentic samples of compounds 143, 146 and 147 available, the task of finding a HPLC solvent system that allowed good separation of all three compounds was conducted. Because all three compounds contained the ethylenediamine functionality, a pH 2.0, 0.2 N phosphoric acid/KOH buffer was chosen as one of the solvents. The 0.2 N buffer was strong enough to protonate both amine groups and decompose any metal ion complexes. Care was taken to make sure that the pH of the buffer system was not below pH 2.0 to prevent decomposition of the column. The nature of the compounds required that the HPLC solvent contain an organic phase, and methanol proved to be suitable. By trial and error, it was found that a methanol/buffer (7/4) solvent system with a flow rate of 1.0 mL/min provided separations of compound 143, 146 and 147 as shown in Figure 72. This figure shows that compounds 143 and 147 gave good separation with sharp, well defined peaks on the chromatogram. The peak corresponding to ester 146 was not as well defined, but very reproducible peaks were obtained, and so the decision was made to use the solvent system described above rather
Figure 72: Sample HPLC chromatogram showing separation of compounds used in the catalytic Michael-cycle.
than a gradient solvent system. A gradient solvent might have led to a sharper peak for 146, however it would have greatly increased the time between sample injections on the HPLC. A gradient solvent system would also have required a washing period between sample injections, which the chosen solvent system described above did not require.

One final very important point concerning this HPLC solvent system needs to be mentioned. It was imperative that the HPLC column be flushed thoroughly after every day's use with a suitable storage solvent such as methanol/water (7/3). Without this washing after every use the column would rapidly degrade and would be rendered useless. In most cases, the column was washed overnight at a flow rate of 0.5 mL/min, and with this washing system our column provided good separation for over 1 year.

Choosing an Internal Standard

The method of choice for quantitative analysis involved the use of an internal standard because it minimized system and procedural variations thus eliminating deviations in precision as a function of sample size. For the use of an internal standard, several requirements concerning the choice of internal standard should be met:
1. It should be completely resolved.
2. It should not elute on or over another component, yet elute as close to the peak of interest as possible.
3. It should have similar chemical properties to eliminate or reduce differences in detector response between itself and the components of interest.
4. It should be prepared at the same concentration level as the sample.
5. It should be of good purity to prevent adding contamination and spurious peaks to the chromatogram.
6. It should be chemically inert.

Due to the nature of the compounds we were studying and the type of HPLC solvent system used to separate them, finding a suitable internal standard proved to be very challenging. The most important problem that was encountered involved water solubility. One of the ultimate goals of the project was to carry out all transformations in an aqueous buffered solution. It was hoped that a water soluble internal standard could be found that met all of the above mentioned criteria. However, all water soluble compounds evaluated for use eluted too close to the compounds of interest (see Table 10). Table 10 shows some of the compounds that were evaluated as internal standards, and as can be seen, each compound evaluated proved unsuitable for one reason or another.
Table 10. Compounds evaluated as internal standards.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention Time (min)</th>
<th>Problem With Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzyl trimethylammonium chloride</td>
<td>4.80</td>
<td>retention time too low</td>
</tr>
<tr>
<td>benzyl triethylammonium chloride</td>
<td>5.50</td>
<td>very broad peak</td>
</tr>
<tr>
<td>benzyl tributylammonium chloride</td>
<td>6.96</td>
<td>decomposes on heating</td>
</tr>
<tr>
<td>aniline</td>
<td>3.50</td>
<td>retention time too low</td>
</tr>
<tr>
<td>diethyl aniline</td>
<td>3.58</td>
<td>retention time too low</td>
</tr>
<tr>
<td>4-nitrophenol</td>
<td>3.94</td>
<td>retention time too low</td>
</tr>
<tr>
<td>nitrobenzene</td>
<td>4.70</td>
<td>retention time too low</td>
</tr>
<tr>
<td>p-bromodimethyl aniline</td>
<td>9.47</td>
<td>not soluble in buffer</td>
</tr>
<tr>
<td>chlorobenzene</td>
<td>10.03</td>
<td>not soluble in buffer</td>
</tr>
<tr>
<td>o-dichlorobenzene</td>
<td>11.50</td>
<td>not soluble in buffer</td>
</tr>
<tr>
<td>veratrol</td>
<td>10.30</td>
<td>evaporates</td>
</tr>
<tr>
<td>benzoic acid</td>
<td>4.61</td>
<td>retention time too low</td>
</tr>
<tr>
<td>benzyl alcohol</td>
<td>4.14/4.67</td>
<td>impure</td>
</tr>
</tbody>
</table>

It was thus decided that a different method must be chosen for quantification. To accomplish our goals, an addition method was chosen for product quantification. This method involved removal of a precisely measured aliquot of the reaction solution and addition of this aliquot to a precisely measured aliquot of HPLC solvent solution containing a suitable internal standard. The compound chosen as the standard was chlorobenzene. Chlorobenzene proved suitable due to the fact that it eluted far away from the desired compounds (see Figure 72), and it was chemically inert in our system under the conditions employed.

Each aliquot removed from the reaction solution was 1.0 mL, and to measure this quantity rapidly and reproducibly, a Gilson P1000 pipetman™ was used. This 1.0 mL aliquot was added to 2.0 mL
of HPLC solvent (methanol buffer, 7/4) containing $3.093 \times 10^{-3}$ M chlorobenzene. The 2.0 mL quantity of HPLC solvent was measured with a standard glass pipet. For best results the solution containing chlorobenzene was made up fresh each day of use by standard dilution techniques. To test the suitability of this method, considerable time was devoted to testing its reproducibility. By using a digital analytical balance, it was found that both 1.0 mL and 2.0 mL quantities could be measured and added together with high reproducibility. This method was finally tested with the compounds of interest by using samples with known concentrations of 143, 146 and 147, and adding 1.0 mL aliquots of these solutions to 2.0 mL quantities of HPLC solvent containing chlorobenzene. It was found that by injecting these samples into the HPLC and integrating, reproducible peaks were obtained on the chromatograms. Furthermore, the integration showed that the samples could be made up with a reproducibility of ± <1%. This addition method allowed us to obtain least squared analyses of our data that always had a minimum correlation coefficient of 0.98, and in most cases correlation coefficients of 0.99 were obtained. This method was periodically tested with solutions of known concentration to judge the precision of the mixing method and of peak integration. The following Experimental Section gives a sample procedure for the addition method, and the method of preparation of the chlorobenzene solution.
**Experimental Section**

**General**

Experimental conditions described in earlier Experimental Sections in previous chapters also apply here. HPLC was carried out on an IBM LC/9533 system using an IBM C-18 reversed-phase column and a 20-μL injection loop. Elution was carried out at a flow rate of 1.0 mL/min with continuous UV detection of eluant at 254 nm. The buffer referred to for HPLC solvent was a pH 2.0 aqueous buffer of 0.2 N phosphoric acid and KOH. The water used to make the HPLC solvent buffer and the methanol used as HPLC solvent were HPLC grade solutions purchased from Fisher Scientific, Cincinnati, OH. pH measurements were determined on a Fisher Accumet pH meter, model 810. Standardized solutions for the pH meter were obtained through OSU Lab Stores, and the pH meter was standardized before each use.

**N’-Benzyl-N,N-dimethylethylenediamine-zinc chloride chelate (144)**

Into a 500 mL rbf was placed anhydrous zinc chloride (3.53 g, 25.9 mmol) and 400 mL of isopropanol. The solution was heated with stirring until the zinc chloride dissolved and then freshly distilled N’-benzyl-N,N-dimethylethylenediamine (4.61 g, 25.9 mmol) was added. The solution continued to stir for 3 min, and
was then allowed to cool. The solid that formed was collected by filtration and recrystallized from isopropanol/hexane (2/1) to give colorless crystals (4.14 g, 51%): mp 179-180°C; H NMR (CDCl₃) δ 2.52 (s, 6, N(CH₃)₂), 2.09-2.93 (br-multiplet, 4, NCH₂CH₂N), 3.45-3.60 (m, 1, NH), 3.68-4.20 (br-singlet, 2, benzylic), 7.24-7.43 (m, 5, Ar-H); C NMR (CDCl₃) δ 44.683, 47.443, 53.468, 58.518, 128.380, 128.842, 129.178, 135.177. EI mass spectrum, m/e M⁺-ZnCl₂ (178, 57%)

Anal. Calcd for C₁₁H₁₇N₂Cl₂Zn: C, 42.14; H, 5.46; N, 8.93; Cl, 22.61. Found: C, 42.02; H, 5.75; Cl, 22.65.

**Extraction of 144 with EDTA to remove ZnCl₂**

Into a 50 mL flask was placed 144 (600 mg, 1.91 mmol) and to this was added 40 mL of a 0.25 mM solution of EDTA, pH 11.0. The solution was stirred until all 144 had dissolved and then it was transferred to a separatory funnel where it was extracted with chloroform (2 x 20 mL). The chloroform was dried over MgSO₄, filtered and evaporated to give pure 143 as a colorless oil (269 mg, 79%): H NMR (CDCl₃) δ 2.14 (s, 6, N(CH₃)₂), 2.36 (t, 2, CH₂), 2.63 (t, 2 CH₂), 3.74 (s, 2, benzylic), 7.14-7.27 (m, 5, Ar-H); C NMR (CDCl₃) δ 45.153, 46.350, 53.745, 58.800, 125.433, 127.745, 127.935, 140.213.
N'-Benzyl-N,N-dimethylethylenediamine·HBr salt (145)

Into a 250 mL rbf was placed 200 mL of isopropanol and freshly distilled N'-benzyl-N,N-dimethylethylenediamine (9.22 g, 51.7 mmol). The solution was heated to about 60°C with stirring and then HBr (18 mL) was added. The solution continued to stir for 3 min and it was then removed from the heat and allowed to cool whereupon a white solid formed. The solid was collected by filtration and recrystallized by dissolving it in hot methanol and then adding about 5% (v/v) diethyl ether. Upon cooling colorless needles formed (12.1 g, 69%): mp 198-200°C.

Extraction method to remove HBr from 145

The free amine of N'-benzyl-N,N-dimethylethylenediamine was obtained from the HBr salt by dissolving 145 (3 g, 8.8 mmol) in 100 mL of H₂O and then adding KOH to basify the H₂O to a pH of about 11 (pH was checked by pH paper). The solution was next extracted with CHCl₃ (3 x 30 mL) and the CHCl₃ layers were pooled and dried over MgSO₄. The chloroform was finally evaporated in vacuo to give pure 143 as a colorless oil with ¹H NMR and ¹³C NMR spectral data identical to that reported above (1.33 g, 85%).
Methyl-3-((2-(dimethylamino)ethyl)benzylamino)propionate (146)

Pure N'-benzyl-N,N-dimethylethylene diamine (4.2 g, 23.3 mmol), isolated by one of the described methods, was placed in a 100 mL rbf along with methyl acrylate (2.1 mL, 23.3 mmol). Methanol (30 mL) was added and the solution was stirred under argon for 48 h. The solution was then evaporated in vacuo to give a light oil in quantitative yield.

$^1$H NMR (CDCl$_3$) $\delta$ 2.32 (s, 6, N(CH$_3$)$_2$), 2.34-2.56 (m, 6, NCH$_2$CH$_2$N and NCH$_2$CH$_2$CO$_2$CH$_3$), 2.81 (t, 2, NCH$_2$CH$_2$CO$_2$CH$_3$), 3.78 (s, 2, benzylic), 3.60 (s, 3, OCH$_2$), 7.43 (m, 5, Ar-H); $^{13}$C NMR (CDCl$_3$) $\delta$ 32.309 (t), 45.670 (q), 49.611 (t), 51.205 (q), 51.631 (t), 57.390 (t), 58.680 (t), 126.680 (d), 127.948 (d), 128.532 (d), 139.131 (s), 172.758 (s); High resolution mass spectrum calcd for C$_{15}$H$_{26}$O$_2$N$_2$, 264.1837; measured, 264.1821.

Anal. Calcd for C$_{15}$H$_{24}$N$_2$O$_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 67.81; H, 8.94; N, 10.59.
3-((2-(Dimethylamino)ethyl)benzylamino)propionic acid (150)

Pure N'-benzyl-N,N-dimethylethlenediamine (5.305 g, 18.54 mmol) first isolated by one of the above described methods was placed into a 250 mL rfb along with tert-butyl-acrylate (10 mL, 8.83 g, 69 mmol) and then methanol (150 mL) was added. The flask was flushed with argon and stirred for 48 h at room temperature. The contents of the flask were next evaporated in vacuo to give the tert-butyl ester (149) as a thick oil in quantitative yield. The oil was shown to be pure 149 by 1H NMR (CDCl₃) δ 1.4 (s, 9, t-bu), 2.15 (s, 6, N(CH₃)₂), 2.23-2.51 (m, 4, NCH₂CH₂N), 2.60-2.91 (m, 4, NCH₂CH₂COOH), 3.5 (s, 2, benzylic), 7.20-7.35 (m, 5 Ar-H).

To the same flask containing (149) was added trifluoroacetic acid (50 mL) and CH₂Cl₂ (100 mL). The solution was heated to reflux for 24 h and the solution was evaporated in vacuo to give a thick colorless oil. Water was added (150 mL) and the solution was evaporated in vacuo; this procedure was repeated until the CCF₃COOH quartets in the 13C NMR did not decrease in intensity (5-10 rotoevaporations): 1H NMR (D₂O) δ 2.70 (t, 2, CH₂N), 2.79 (s, 6, N(CH₃)₂), 3.40 (t, 2, CH₂COOH), 3.50 (s, 4, NCH₂CH₂N), 4.33 (s, 2, benzylic), 7.35-7.43 (m, 5, Ar-H); 13C NMR (D₂O) δ 28.477 (t), 40.859 (s), 43.237 (q), 47.155 (t), 49.115 (t), 50.816 (t), 58.522 (t),
116.201 (quartet of singlets), 129.931 (d), 130.554 (d), 130.873 (d), 162.993 (quartet of singlets), 173.793 (s); EI Mass spectrum, m/e 192.1033 (32.95, M⁺-CH₂N(CH₃)₂), 178.1409 (1.78, M⁺-CH₂CH₂N(CH₃)₂).

Anal. Calcd for C₁₈H₂₄F₆O₆N₂: C, 45.19; H, 5.06; N, 5.86. Found: C, 45.38; H, 4.65%; N, 5.77.

Preparation of HPLC solvent solution containing chlorobenzene as internal standard

A 100 mL volumetric flask was placed on a digital balance and then 435.2 mg of chlorobenzene was added by using a 100 μL HPLC syringe. The chlorobenzene was diluted to 100 mL with methanol and the resulting stock solution was used to make the standard solution each day. On each day, 4 mL of the stock solution was placed in a 50 mL volumetric flask and diluted to 50 mL with HPLC solvent (methanol/buffer, 7/4).
CHAPTER VIII

The Michael Catalytic Cycle For Ester Hydrolysis:

Results and Discussion

General Experimental Conditions

All metal ions used were hydrated perchlorate salts purchased from GFS Chemical Co., Columbus, Ohio. The determination of first-order rate constants was accomplished using the previously described LSTSQ computer program (see Experimental Section of Chapter V). The following buffers were used: KCl/HCl, for pH 1.0-1.5, KCl/KOH for pH 2.0, H₃PO₄/KOH for pH 2.5-3.0, CH₃COOH/KOH for pH 3.5-5.5, 2-(N-morpholino)ethanesulfonic acid (MES) for pH 6.0-6.5, N-(2-hydroxyethyl)piperazine-N'-2-ethanesulfonic acid (CHES) for pH 9.0, 3-cyclohexylamino-1-propanesulfonic acid (CAPS) for pH 11.0 and KH₂PO₄/KOH for pH 6.0-8.0 in special cases. 4-Ethylmorpholine was used for pH 7.0 in the retro-Michael reaction at 85°C in the presence of metal ions. All buffers were purchased from Aldrich Chemical Co, Milwaukee, WI., and the buffer strength was 0.1 M unless stated otherwise. Other pertinent information will be listed under the individual Kinetic Method sections to which they apply.
Hydrolysis of
Methyl-3-((2-(dimethylamino)ethyl)benzylamino)propionate

Kinetic Method

For all metals except copper, the following general procedure applies: a -0.0018 M solution of 146 was prepared in the desired buffer, and then the hydrolysis was initiated by adding the metal in the appropriate quantity as a solid. At timed intervals a 1.0 mL aliquot was removed and added to 2.0 mL of HPLC solvent containing 3.093 x 10^-3 M chlorobenzene. The resulting solution was mixed by shaking, and then a 100 μL HPLC syringe was filled and the sample was injected into the HPLC for quantification. The conditions of flow rate and solvent conditions were as previously described in Chapter VII.

For concentrations of Cu^{2+} of 1.25 mol % (0.01-0.25 equivalents) the procedure used was the same as that described above. Due to the rapid rate of the copper catalyzed hydrolysis of 146, a modification of the above procedure was used for Cu^{2+} ion concentrations of greater than 25 mol %. A stock solution of buffer containing 0.0036 M 146 was prepared. A second stock solution containing Cu(ClO_4)_2·6H_2O in the desired buffer was prepared in such a way that 20 mL of this buffer contained twice the desired concentration of Cu^{2+} ion. Into a 50 mL rbf was placed 20 mL of the ester stock solution and the solution was stirred
rapidly while 20 mL of the Cu\(^{+2}\) stock solution was added with a pipet having a 23 s delivery time. Time zero was taken at the moment of delivery of the Cu\(^{+2}\) ion solution and at the desired time a 1.0 mL aliquot was removed and added to 2.0 mL of HPLC solvent containing 3.093 x 10\(^{-3}\) M chlorobenzene. The solution was shaken and a 100 \(\mu\)L HPLC syringe was filled with the resulting solution which was then injected into the HPLC. Total time from removal of an aliquot of the reaction solution to injection into the HPLC was 30 s, and care was taken so that this time interval did not vary. A separate run was made for each time point using the original stock solutions.

Results

The hydrolysis of methyl-3-((2-(dimethylamino)ethyl)-benzylamino)propionate (146) to 3-((2-(dimethylamino)ethyl)-benzylamino)propionic acid (147) is shown schematically in Figure 73. All of the hydrolyses studied gave clean first order behavior for both the disappearance of ester 146 and appearance of acid 147. For reactions containing >25 mol % Cu\(^{+2}\) relative to ester 146, the appearance of acid 147 could not be monitored, but for all other cases the disappearance of 146 was followed as well as the appearance of 147. Kinetic analyses obtained on the disappearance of ester 146 and the appearance of acid 147 were in good agreement with each other.
The results of the hydrolysis of 146 with various metals are shown in Table 11. The ester hydrolysis reaction was carried out in the absence of metal ions, and with increasing concentrations of Cu^{++} from 0.01-5.0 equivalents. The hydrolysis reaction was also carried out using from 1-10 equivalents of Ni^{++}, Co^{++} and Zn^{++}. The buffer concentration was increased to 0.25 M for the reactions containing 5 and 10 equivalents of Zn^{++} because the zinc ion lowered the pH of the 0.1 M buffer solution. By increasing the buffer strength no change in pH was observed upon adding Zn^{++}. Table 12 shows the effect of pH on the hydrolysis of ester 146 in the presence of 0.25 equivalents of Cu^{++}. The concentration of 0.25 mol % Cu^{++} was chosen due to the fact that the Cu^{++} catalyzed reaction was found to proceed at an easily measured rate at pH 7.50. Therefore, based on the work of Kroll and Kang, we believed the reaction should show an increase in rate at higher pH's. Table 13 shows the results of a survey of the effect on hydrolysis of a variety of metal ions.

Figure 73: Hydrolysis of Methyl-3-((2-(dimethylamino)ethyl)-benzylamino)propionate to form 3-((2-(dimethylamino)-ethyl)benzylamino)propionic acid.
Table 11. Hydrolysis of Methyl-3-((2-(dimethylamino)ethyl)benzylamino)propionate (146) in 0.1 M HEPES, pH 7.50 at 23°C.

<table>
<thead>
<tr>
<th>Metal</th>
<th># of Equivalents</th>
<th>$k_1 10^3$(min$^{-1}$)</th>
<th>$t_{1/2}$(min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
<td>0.1134</td>
<td>6108</td>
</tr>
<tr>
<td>10% EDTA</td>
<td>-</td>
<td>0.0618</td>
<td>11206</td>
</tr>
<tr>
<td>Cu$^{++}$</td>
<td>0.01</td>
<td>0.3754</td>
<td>1346</td>
</tr>
<tr>
<td>Cu$^{++}$</td>
<td>0.05</td>
<td>1.596</td>
<td>434</td>
</tr>
<tr>
<td>Cu$^{++}$</td>
<td>0.10</td>
<td>2.925</td>
<td>237</td>
</tr>
<tr>
<td>Cu$^{++}$</td>
<td>0.15</td>
<td>3.591</td>
<td>193</td>
</tr>
<tr>
<td>Cu$^{++}$</td>
<td>0.20</td>
<td>7.353</td>
<td>94</td>
</tr>
<tr>
<td>Cu$^{++}$</td>
<td>0.25</td>
<td>17.04</td>
<td>41</td>
</tr>
<tr>
<td>Cu$^{++}$</td>
<td>0.50</td>
<td>87.54</td>
<td>7.9</td>
</tr>
<tr>
<td>Cu$^{++}$</td>
<td>1.0</td>
<td>370.8</td>
<td>2</td>
</tr>
<tr>
<td>Cu$^{++}$</td>
<td>5.0</td>
<td>951.6</td>
<td>0.73</td>
</tr>
<tr>
<td>Ni$^{++}$</td>
<td>1.0</td>
<td>0.7276</td>
<td>953</td>
</tr>
<tr>
<td>Ni$^{++}$</td>
<td>2.0</td>
<td>2.274</td>
<td>305</td>
</tr>
<tr>
<td>Ni$^{++}$</td>
<td>5.0</td>
<td>4.59</td>
<td>151</td>
</tr>
<tr>
<td>Ni$^{++}$</td>
<td>10.0</td>
<td>9.673</td>
<td>72</td>
</tr>
<tr>
<td>Co$^{++}$</td>
<td>1.0</td>
<td>0.2387</td>
<td>2903</td>
</tr>
<tr>
<td>Co$^{++}$</td>
<td>5.0</td>
<td>0.5152</td>
<td>1345</td>
</tr>
<tr>
<td>Co$^{++}$</td>
<td>10.0</td>
<td>1.009</td>
<td>687</td>
</tr>
<tr>
<td>Zn$^{++}$</td>
<td>1.0</td>
<td>0.2507</td>
<td>2765</td>
</tr>
<tr>
<td>Zn$^{++}$(a)</td>
<td>5.0</td>
<td>0.3446</td>
<td>2011</td>
</tr>
<tr>
<td>Zn$^{++}$(a)</td>
<td>10.0</td>
<td>0.3058</td>
<td>2266</td>
</tr>
</tbody>
</table>

(a) Buffer strength 0.25 M.
Table 12. Effect of pH on the hydrolysis of Methyl-3-\((2-(\text{dimethylamino})\text{ethyl})\text{benzylamino})\text{propionate} \ (146) \ with \ 25 \ \text{mol \ % \ Cu}^{++} \ in \ \text{pH} \ 7.50 \ \text{HEPES.}

<table>
<thead>
<tr>
<th>pH</th>
<th>Buffer</th>
<th>(k_1 \times 10^3 \text{(min}^{-1}))</th>
<th>(t_{1/2} \text{(min)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.0</td>
<td>KH(_2)PO(_4)/KOH</td>
<td>0.900</td>
<td>752</td>
</tr>
<tr>
<td>6.5</td>
<td>KH(_2)PO(_4)/KOH</td>
<td>5.22</td>
<td>133</td>
</tr>
<tr>
<td>7.0</td>
<td>KH(_2)PO(_4)/KOH</td>
<td>16.50</td>
<td>42</td>
</tr>
<tr>
<td>7.5</td>
<td>KH(_2)PO(_4)/KOH</td>
<td>35.0</td>
<td>19.8</td>
</tr>
<tr>
<td>8.0</td>
<td>KH(_2)PO(_4)/KOH</td>
<td>68.6</td>
<td>10.1</td>
</tr>
<tr>
<td>9.0(a)</td>
<td>CHES</td>
<td>325.8</td>
<td>2.12</td>
</tr>
</tbody>
</table>

(a) At this pH the Cu\(^{++}\) ion is not stable in this buffer and it begins to precipitate out as a brown solid in about 90 min.
Table 13. Ester hydrolysis using various metals in HEPES buffer at 25°C.

<table>
<thead>
<tr>
<th>Metal(a)</th>
<th>% hydrolysis after 12 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu^{++}</td>
<td>100(b)</td>
</tr>
<tr>
<td>Ni^{++}</td>
<td>&gt;98</td>
</tr>
<tr>
<td>Zn^{++}</td>
<td>75</td>
</tr>
<tr>
<td>Pb^{++}</td>
<td>71</td>
</tr>
<tr>
<td>Cd^{++}</td>
<td>67</td>
</tr>
<tr>
<td>Gd^{+++}</td>
<td>65</td>
</tr>
<tr>
<td>Co^{++}</td>
<td>61</td>
</tr>
<tr>
<td>Eu^{+++}</td>
<td>56</td>
</tr>
<tr>
<td>Li^{+}</td>
<td>54</td>
</tr>
<tr>
<td>Ca^{++}</td>
<td>53</td>
</tr>
<tr>
<td>Na^{+}</td>
<td>53</td>
</tr>
<tr>
<td>Mg^{++}</td>
<td>52</td>
</tr>
<tr>
<td>Sr^{++}</td>
<td>50</td>
</tr>
<tr>
<td>Ag^{+}</td>
<td>46</td>
</tr>
<tr>
<td>Mn^{++}</td>
<td>45</td>
</tr>
<tr>
<td>Hg^{+}</td>
<td>44(c)</td>
</tr>
<tr>
<td>Hg^{++}</td>
<td>41</td>
</tr>
<tr>
<td>Al^{+++}</td>
<td>40(d)</td>
</tr>
<tr>
<td>Fe^{++}</td>
<td>40(d)</td>
</tr>
<tr>
<td>Fe^{+++}</td>
<td>40(d)</td>
</tr>
<tr>
<td>Sn^{++}</td>
<td>40(d)</td>
</tr>
<tr>
<td>In^{+++}</td>
<td>40(d)</td>
</tr>
</tbody>
</table>

(a) All metals used were perchlorate salts except for SnCl_2. (b) The ester hydrolysis was complete in less than 24 h. (c) The ester hydrolysis proceeded to give a peak on HPLC corresponding to the acid, but another larger peak formed indicating some type of side product formation. (d) The control experiment of the ester hydrolysis with no metals became contaminated and therefore is not available, however these values are indicative of an uncatalyzed reaction.
Discussion

The results shown in Table 11 demonstrate several important points. First, all of the metals examined in Table 11 show an acceleration of the rate of hydrolysis over the uncatalyzed rate. This was not particularly surprising to us because Cu++, Ni++, Co++ and Zn++ have all previously been shown to accelerate ester hydrolysis reactions. All of the metals studied showed acceleration of the rate of ester hydrolysis with increasing metal ion concentration except for Zn++. The rate of hydrolysis in the presence of 1, 5 and 10 equivalents of Zn++ showed no significant changes in rate despite the greater quantity of Zn++ present. Similar results have previously been observed by Wells and Bruice for Zn++ promoted ester hydrolysis of 2-(2'-hydroxyphenol)-4(5)-methyl-5(4)-(2",2"-dimethylacetate)imidazoles. Wells and Bruice found that Zn++ ions formed dimeric complexes of the type (ligand)_{2}Zn which were not particularly labile to hydrolysis. We can thus propose that dimeric complexes of 146 and Zn++ could be formed as shown in Figure 74. Complexes of this type would be resistant to hydrolysis as has been demonstrated by Wells and Bruice. As has been shown by Groves and Chambers for amide hydrolysis, and by Wells and Bruice for ester hydrolysis, the proposed active species in these reactions is a metal-bound hydroxide ion. Dimeric complexes of the type shown in Figure 74 would prevent formation of a metal bound hydroxide because all sites on the Zn++ are occupied. The lack of formation of
metal bound hydroxides would thus prevent significant rate acceleration. Meriwether and Westheimer have reported that at pH >7.1 there is significant precipitation of zinc hydroxides from buffered solutions containing Zn^{++}. These hydroxides are unreactive toward hydrolysis and therefore do not participate in the hydrolysis. Under the conditions used, no zinc hydroxides were observed in the reaction mixtures, however, this does not conclusively prove that they did not lead to some or all of the observed rate changes in the Zn^{++} ion hydrolysis reactions.

Inspection of Table 11 shows that addition of 5 equivalents of Cu^{++} results in a ~15400-fold increase in the rate of hydrolysis over the rate of the ester hydrolysis containing 10% EDTA.
This rate acceleration is greater than that reported by Kang, but it is not qualitatively similar to the results of Bender and Turnquist for the Cu++ catalyzed hydrolysis of D,L-phenylalanine ethyl ester. As was pointed out by Kang, metal ions generally coordinate in 5 membered rings (depending on the metal), and in the ester studied (146), the metal must coordinate in a 6 membered ring as shown in Figure 75. The fact that Bender and Turnquist observed a 10^6-fold increase in the rate of hydrolysis of D,L-phenylalanine ethyl ester is possibly due to the fact that D,L-phenylalanine ethyl ester is capable of forming 5 membered metal chelates. It should also be pointed out that Westheimer and Shookhoff reported that introduction of a positive charge two atoms away from the carboxyl group of an ester leads to an increase in rate of 10^3. The amino of ester 146 is three atoms away from the carbonyl. Either of these proposals or a combination of both could explain why rate accelerations for the Cu++ catalyzed hydrolysis were not identical to the accelerations observed for the hydrolysis of D,L-phenylalanine ethyl ester.

Lastly and possibly most importantly, inspection of Table 11 shows that the Cu++ ion is truly catalytic in the hydrolysis reaction with respect to ester 146. As little as 1 mol % of Cu++ is capable of very significant rate accelerations, and all Cu++ ion catalyzed reactions proceed to 100 % completion. The reaction with as little as 1 mol % Cu++ proceeded with absolutely no change in rate throughout the entire hydrolysis. We have
therefore shown that the Cu\textsuperscript{++} ion is capable of turnover, and under the experimental conditions used, no poisoning of the Cu\textsuperscript{++} ion was observed. The hydrolysis reaction does appear to be approaching saturation with respect to Cu\textsuperscript{++} ion when 5 equivalents of Cu\textsuperscript{++} are added, but due to the rapid rate of hydrolysis of 146 with >5 equivalents of Cu\textsuperscript{++}, this saturation effect was not studied in detail.

![Chemical Structure](image)

**Figure 75:** Structure of Methyl-3-((2-(dimethylamino)-ethyl)benzylamino)propionate metal complex.

Table 12 shows that an increase in pH results in significant increases in the rate of Cu\textsuperscript{++}-catalyzed hydrolysis of 146. Potassium hydrogen phosphate buffer was used in place of the biological buffers to eliminate any differences in rate due to the buffer. Therefore, the results in Table 12 are not directly comparable to those in Table 11. The results shown in Table 12 are very similar to the results found by Kroll and later by Fife and
Przystas. It is also interesting to note that we do not observe a 10-fold increase in rate with each 1 pH unit change which would be indicative of simple specific base catalysis. It should be noted that as is shown in Table 12, at high pH the Cu$^{++}$ ion begins to decompose, therefore it is not advantageous to carry out Cu$^{++}$ catalyzed hydrolyses at a pH greater than about 8.0. It was found that for best results and stability of Cu$^{++}$, a pH of 7.0-7.5 should be used. Furthermore, as was reported by Kang, at high pH the formation of insoluble hydroxides becomes important, and the formation of metal hydroxides has been proposed by Kang to lead to a decrease in the catalytic activity of the metal ions.

As was reported in Chapter I, Cu$^{++}$, Zn$^{++}$, Co$^{++}$ and Ni$^{++}$ have all been found to accelerate the rate of ester hydrolysis. Similar effects have also been observed for Hg$^{++}$, Pb$^{++}$ and Cd$^{++}$ on other systems. Up to the present time however, no survey of the effects of different metals has been carried out on the same ester hydrolysis system.

We therefore decided to survey the effect of 22 different metal ions on the rate of hydrolysis of 146. The results of this survey are quite interesting (Table 13). Table 13 shows that Pb$^{++}$, Cd$^{++}$ and Gd$^{+++}$ all accelerate the rate of hydrolysis of 146 to some extent. This is a novel finding, as many very recent studies on ester hydrolysis have not included these metal ions. It is easy to reason that because cadmium and mercury lie directly below zinc in the periodic table, these two metal ions might give at
least some rate acceleration similar to that seen by zinc. Previous experimenters have used Na⁺ in hydrolysis experiments as a control or for increasing ionic strengths of solutions. However, based on the results shown in Table 13, this was perhaps a poor choice of metal ion. It is possible that the rate accelerations of hydrolysis could be due to such factors as ionic strength, catalysis by the counter ion or any number of other possibilities. These factors however were not evaluated in this study but present interesting avenues to pursue in future studies.

The retro-Michael Reaction of 3-((2-(Dimethylamino)ethyl)benzylamino)propionic acid

Kinetic Method

The retro-Michael reaction was carried out by filling a 100 mL rbf with 80 mL of a buffered solution containing ~1.8 x 10⁻³ M 150 and the appropriate concentration of metal ion where required. The flask was fitted with a condenser and deoxygenated by bubbling argon through the solution overnight. The condenser was fitted with a "Tee" gas inlet adapter so that a steady stream of argon could constantly pass over the reaction solution. The flask was next placed in an oil bath at either 100°C or 85°C (± 1°C) depending on the reaction, and at various timed intervals an aliquot was removed and cooled to room
temperature. A Gilson P1000™ pipet was used to transfer 1.0 mL of this solution into 2.0 mL of HPLC solvent containing chlorobenzene as internal standard, and the resulting solution was analyzed by HPLC as has been described in the Experimental Sections of this chapter.

In order to determine that the retro-Michael reaction was proceeding as shown in Figure 76, the reaction was run to determine that N'-benzyl-N,N-dimethylthelyenediamine (143) and acrylic acid (131) were the products formed. Unfortunately, only 143 could be isolated and characterized by the procedure used. Based on the HPLC and ¹H NMR results described below, we are confident that the retro-Michael is proceeding to give the 143.

Figure 76: Retro-Michael reaction of 3-((2-(dimethylamino)ethyl)benzylamino)propionic acid.
Retro-Michael reaction of 147 on large scale for product identification

Into a pressure tube was placed the trifluoroacetic acid salt of 3-((2-(dimethylamino)benzylamino)propionic acid (200 mg, 0.419 mmol) and 13 mL of pH 7.50, 0.6 N HEPES buffer. The tube was sealed and heated for 2 h at 160°C. The tube was cooled, and analysis by HPLC of the contents showed that all of the acid (147) had been converted to products. The contents of the tube were transferred to a separatory funnel and 75 mL of H₂O was added. The solution was basified to pH 11 with KOH (pH checked by pH paper) and then extracted with CHCl₃ (3 x 20 mL). The CHCl₃ solutions were pooled, dried over MgSO₄, filtered and finally evaporated in vacuo to give N'-benzyl-N,N-dimethylethylenediamine (143) that was shown to be pure by both HPLC and ¹H NMR.

Results

Table 14 shows the first order rate constants of the retro-Michael reaction at various pH values. The rate constants were obtained using the computer program LSTSQ previously described. The last two entries of Table 14 show the effect of changing the type and strength of buffer on the retro-Michael reaction. Figure 77 shows a graph of rate vs. pH of the retro-Michael reaction.
Table 14. pH Dependence of the Retro-Michael Reaction

<table>
<thead>
<tr>
<th>pH</th>
<th>Buffer</th>
<th>$10^3 k_1$(min$^{-1}$)</th>
<th>$t_{1/2}$(min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>KCl/HCl</td>
<td>1.297</td>
<td>534</td>
</tr>
<tr>
<td>1.5</td>
<td>KCl/HCl</td>
<td>1.960</td>
<td>354</td>
</tr>
<tr>
<td>2.0</td>
<td>HCl/KOH</td>
<td>6.582</td>
<td>105</td>
</tr>
<tr>
<td>2.5</td>
<td>H$_3$PO$_4$/KOH</td>
<td>11.309</td>
<td>61.3</td>
</tr>
<tr>
<td>3.0</td>
<td>H$_3$PO$_4$/KOH</td>
<td>15.463</td>
<td>44.8</td>
</tr>
<tr>
<td>3.5</td>
<td>CH$_3$COOH/KOH</td>
<td>14.735</td>
<td>47.0</td>
</tr>
<tr>
<td>4.0</td>
<td>CH$_3$COOH/KOH</td>
<td>7.672</td>
<td>90.0</td>
</tr>
<tr>
<td>4.5</td>
<td>CH$_3$COOH/KOH</td>
<td>3.897</td>
<td>177</td>
</tr>
<tr>
<td>5.0</td>
<td>CH$_3$COOH/KOH</td>
<td>2.490</td>
<td>278</td>
</tr>
<tr>
<td>5.5</td>
<td>CH$_3$COOH/KOH</td>
<td>0.674</td>
<td>1028</td>
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<tr>
<td>6.0</td>
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<td>0.561</td>
<td>1234</td>
</tr>
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<td>6.5</td>
<td>MES</td>
<td>0.354</td>
<td>1959</td>
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<tr>
<td>7.0</td>
<td>HEPES</td>
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<td>3853</td>
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<tr>
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<td>HEPES</td>
<td>0.086</td>
<td>8014</td>
</tr>
<tr>
<td>2.5</td>
<td>Citric acid/KOH</td>
<td>11.27</td>
<td>61.4</td>
</tr>
<tr>
<td>3.0</td>
<td>0.2N H$_3$PO$_4$/KOH</td>
<td>14.82</td>
<td>46.8</td>
</tr>
</tbody>
</table>
Figure 77: Graph of pH vs. Rate of the retro-Michael reaction shown in Figure 71.
Discussion

As can be seen from the rate constants in Table 14 and from the graph shown in Figure 77, the retro-Michael reaction of 147 at 100°C shows a sharp increase in rate between pH 1.0-3.0, and then a sharp decrease in rate at pH >3.5. As previously mentioned, the retro-Michael reaction has been found to be acid catalyzed. In view of this fact, our results of increased rate at lower pH are not surprising. What is surprising is the fact that a rate maximum is reached between pH 3.0-3.5, and that there is a rate decrease below pH 3.0. The decrease in rate was not due to an effect by the buffer because a citric acid/KOH buffer of pH 2.5 gave an almost identical rate constant as the H₃PO₄/KOH buffer. The observed rate changes must be arising from a change in protonation state of 147. We therefore propose that at pH <3.5, there exist two sites of protonation as shown in Figure 78. As the pH is increased from 1.0 to 3.5 there will be a greater probability of the dimethylamino group of 154 being unprotonated. Therefore there would be a rate acceleration reflecting this fact because the electrons on the dimethylamino group will be available for abstraction of a proton as shown in Figure 78. At pH >3.5 the carboxylic acid group becomes completely deprotonated, and as such it makes abstraction of the α-hydrogen by the dimethylamino group more difficult. This results in a decrease in the rate above pH 3.5. Furthermore, above pH 3.5 total deprotonation of both amine groups as well as the carboxylic acid group is achieved making the
Figure 78: Various forms of the diprotonated state of 3-((2-(dimethylamino)ethyl)benzylamino)propionic acid. Structure 154 is proposed as the kinetically competent form for rapid retro-Michael reaction via intramolecular general base catalysis.
secondary amine group of the ethylenediamine fragment a poorer
leaving group. Lastly, the change in rate is not believed to be
affected by buffer strength because doubling the buffer
concentration at pH 3.0 had no significant effect on the rate of the
retro-Michael reaction (see the last two entries of Table 14).

A brief study of the retro-Michael reaction was conducted at pH
8.0-12.0. The reactions were followed only long enough to observe
that there was no increase in rate above pH 8.0. This finding is
somewhat surprising based on the fact that there are several
examples of base-catalyzed retro-Michael reactions in the
literature. However, as has been mentioned above, secondary
amines are poor leaving groups at high pH, and so these results are
within intuitive reason.

To evaluate the effect of metal ions on the retro-Michael
reaction, a brief study was conducted of the retro-Michael reaction
in the presence of 2 eq of Cu++, Ni++, Co++ and Zn++. The
reaction was carried out at 100°C in 0.1 M HEPES, pH 7.50, and
at 85°C with 0.1 M 4-ethylmorpholine buffer. In all cases
little (<15%) or no accelerations of rate were observed for the
retro-Michael reactions. This was surprising because it could be
intuitively reasoned that a metal ion chelated to
3-((2-dimethylamino)ethyl)benzylamino propionic acid (147) (see
Figure 79) should decrease the electron density on both amine groups
and thus make a better leaving group of the developing secondary
amine.
One possible explanation for this lack of observed acceleration could be the high temperatures used for this reaction. At high temperatures (85°C and 100°C), the metal-ion coordination of a metal to the amino acid (146) would be expected to be weak. The metal ion would thus not be coordinated to the amine groups very strongly, and would therefore be unable to exert any effect. We did not conduct experiments at temperatures lower than 85°C because the reactions would have been too slow to observe at reasonable temperatures.

Mention should be made of a very puzzling impurity that sometimes appeared during the course of the retro-Michael reaction. At certain times during the course of the reaction, an impurity appeared on the HPLC chromatogram at a retention time of ~4.67 min. What was surprising was that this impurity disappeared when the
reaction flask was thoroughly flushed with argon. All attempts to prepare and characterize this impurity failed. By thoroughly deoxygenating the buffers used and by keeping the reaction solution under a steady stream of argon, this impurity disappeared and therefore did not affect the reaction kinetics.

The Forward Michael Reaction

Kinetic Method

The forward Michael reaction was carried out as shown in Figure 80 by first isolating pure $N'$-benzyl-$N,N$-dimethylethylenediamine (143) from either the zinc chloride complex (144) or the HBr salt form (145) as previously described (see Experimental Section of Chapter VII). A stock solution of ~0.0018 M 143 was prepared in the desired buffer solution, and 80 mL of the stock solution was placed in a 100 mL rbf. The desired amount of metal was added as a solid, then 155 $\mu$L (10 eq) of methyl acrylate (118) was added to initiate the reaction. At the desired time intervals, a 1.0 mL aliquot was withdrawn and added to 2.0 mL of HPLC solvent containing $3.093 \times 10^{-3}$ M chlorobenzene. The resulting solution was mixed well and finally analyzed by HPLC as previously described. The reaction was followed by monitoring the disappearance of the peak corresponding to (143). The appearance of a peak corresponding to ester (154) could not be followed due to the simultaneous hydrolysis reaction of the ester (154) to the acid (147). The forward Michael reaction containing no metal ions followed
first-order kinetics throughout the entire reaction. However, the reactions containing metal ions showed non-pseudo-first order behaviour in the second half of the reaction; therefore only the first 50% of the reactions were used to calculate initial rate constants.

Table 15 shows the results of the forward Michael reaction in the presence and absence of added metal ions. The first entry in Table 15 shows that the forward Michael reaction proceeds rapidly at pH 7.50 with a reaction half-life of ~263 min. The Michael reaction is thus complete in less than 48 h when N'-benzyl-N,N-dimethyl-ethylenediamine (143) is the limiting reagent and there is a >10-fold excess of methyl acrylate (pseudo-first order conditions). Examination of Table 15 shows that all metal-ion containing forward Michael reactions show a decrease in rate compared to the
non metal containing reaction. As was mentioned above, the reaction rate decreased as the reaction proceeded in the presence of added metal ions.

Table 15. Forward Michael reaction using various metals in HEPES buffer at pH 7.5.

<table>
<thead>
<tr>
<th>Metal</th>
<th># of equiv</th>
<th>$10^3k_1$ (min$^{-1}$)</th>
<th>$t_{1/2}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>0</td>
<td>2.639</td>
<td>263</td>
</tr>
<tr>
<td>Cu$^{++}$</td>
<td>0.25</td>
<td>1.68</td>
<td>412</td>
</tr>
<tr>
<td>Zn$^{++}$</td>
<td>2</td>
<td>1.242</td>
<td>557</td>
</tr>
<tr>
<td>Co$^{++}$</td>
<td>2</td>
<td>1.383</td>
<td>501</td>
</tr>
<tr>
<td>Ni$^{++}$</td>
<td>2</td>
<td>0.4722</td>
<td>1476</td>
</tr>
</tbody>
</table>

One possible explanation for these observations is shown in Figure 81. It can be proposed that metal complex 157 forms in the reactions containing metal ions. This complex would then probably not enter into the forward Michael reaction with methyl acrylate for two possible reasons: (1) the metal complexed amines (157) would be too sterically encumbered or (2) decreased nucleophilicity of the secondary amine in 143 due to an inductive effect of the metal ion. It can thus be proposed that the free diamine (143) is the reactive species that participates in the Michael reaction. However, as the ester (146) is formed, it chelates a metal ion that then catalyzes the hydrolysis to acid.
Figure 81: Proposed equilibrium reactions of the Michael reaction.
metal-ion complex 156. As has been shown above for ester hydrolysis, the metal-ion in complex 156 can detach from acid 156 to give free acid 147 and complexed metal ion. All three equilibrium constants are estimated to be roughly equal ($K_{eq1} = K_{eq2} = K_{eq3}$), so the driving force for the decrease in rate must involve $K_{eq1}$. The free metal ion can re-enter the first equilibrium ($K_{eq1}$), effectively driving it to the side of 157 because each metal ion formed in $K_{eq3}$ would be able to consume two molecules of 143, therefore slowing the overall forward Michael reaction. The net effect is that free metal-ions drive the equilibrium between 143 and 157 towards the side of 157, therefore decreasing the rate as the reaction proceeds.

Uncatalyzed Hydrolysis of Methyl Acrylate: How Slow Can It Go?

Background

A survey of the literature shows that there has been little data gathered on the uncatalyzed hydrolysis of esters at neutral pH. One possible reason for this lack of information is the fact that these reactions are very slow. In 1929, Zahorka et al. calculated a rate constant for the hydrolysis of methyl acetate that had a reaction half-life of 75 years! Because of this lack of available information concerning $\alpha,\beta$-unsaturated ester hydrolysis, we
conducted a set of experiments on the hydrolysis of methyl acrylate at various pH values. We found that separation and detection of methyl acrylate (118) and its hydrolysis product, acrylic acid (131), was possible with our HPLC solvent system, and a sample chromatogram showing the separation of these compounds is shown in Figure 82.

Kinetic Method

The reaction was carried out as shown in Figure 83 by preparing a 6.0 x 10^{-4} M solution of methyl acrylate (118) in the desired buffer. Each reaction flask was stored in the dark and every 7-12 days the reaction was monitored by removing a 1.0 mL aliquot and treating this aliquot in the same manner described above. Attempts were made to carry out the reaction at pH 7.0 and 7.5 with 2 eq of Cu^{++}, but after about 3 weeks the Cu^{++} precipitated out as a brown solid.

Results

The estimated first order rate constants for the hydrolysis of methyl acrylate at various pH's are shown in Table 16. The rates of hydrolysis of 118 were very slow at all the pH's examined, and thus the first order rate constants are ± 50%. The reaction at pH 8.0 was followed to ~70% completion; however, the hydrolysis at pH 5.0 was only 5% complete at the termination of this experiment (2000 h).
Figure 82: Sample HPLC chromatogram showing separation of methyl acrylate and acrylic acid along with chlorobenzene as a standard.
Figure 83: Hydrolysis of methyl acrylate to form acrylic acid.

<table>
<thead>
<tr>
<th>pH</th>
<th>Buffer</th>
<th>$10^3k_1$ (min$^{-1}$)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>CH$_3$COOH/KOH</td>
<td>0.6</td>
<td>19000</td>
</tr>
<tr>
<td>5.5</td>
<td>CH$_3$COOH/KOH</td>
<td>2.3</td>
<td>5100</td>
</tr>
<tr>
<td>6.0</td>
<td>KH$_2$PO$_4$/KOH</td>
<td>11.0</td>
<td>1100</td>
</tr>
<tr>
<td>6.5</td>
<td>KH$_2$PO$_4$/KOH</td>
<td>10.0</td>
<td>1200</td>
</tr>
<tr>
<td>7.0</td>
<td>KH$_2$PO$_4$/KOH</td>
<td>8.0</td>
<td>1400</td>
</tr>
<tr>
<td>7.5</td>
<td>KH$_2$PO$_4$/KOH</td>
<td>11.0</td>
<td>1000</td>
</tr>
<tr>
<td>8.0</td>
<td>KH$_2$PO$_4$/KOH</td>
<td>13.0</td>
<td>900</td>
</tr>
<tr>
<td>7.50</td>
<td>HEPES</td>
<td>11.0</td>
<td>1000</td>
</tr>
</tbody>
</table>
Discussion

Examination of the results in Table 16 reveals that from pH 5.0-8.0 the rate constants deviate from linearity. This result is most probably due to experimental error introduced due to the length of the reaction time. The two rate constants observed for pH 7.50 in the two buffer systems studied do show reasonable agreement with each other. As was mentioned above, we have observed a ~15400-fold rate of acceleration for the hydrolysis of ester 146 to acid 147 (see previous discussion of hydrolysis of 146). If we now compare the rate of hydrolysis of methyl acrylate (118) in pH 7.5 HEPES buffer to the rate of hydrolysis of methyl acrylate covalently bound to \(N'-\text{benzyl-}N,N\text{-dimethylethylenediamine}\) in the presence of \(\text{Cu}^{++}\) ion, we observe a ~90000-fold rate of acceleration. This acceleration is still slightly less than similar accelerations observed by Bender and Turnquist,\(^9\) however, these results are now becoming quantitatively similar. Future work in the Czarnik group will hopefully approach the rates of acceleration observed by Bender and Turnquist.

Conclusions

In summary, it can be shown that the catalytic cycle based on the Michael/retro-Michael reaction shown in Figure 70 (Chapter VII) takes place in buffered solution. The forward Michael reaction (step 1) proceeds at reasonable rates both in the presence of and
absence of added metal-ions. The hydrolysis of the ester formed in the Michael reaction is the fastest step of the cycle when carried out in the presence of 5 eq of Cu^{++} \left( t_{1/2} = 43 \text{ s} \right). The retro-Michael reaction (step 3) is the slowest reaction of the cycle, and future work on this cycle will be directed toward accelerating this reaction. One possible means of accomplishing this goal would be to modify the secondary amine group of N'-benzyl-N,N-dimethylethylenediamine to make it a better leaving group.
LIST OF REFERENCES


44. Kamiya, I.; Sugimoto. T. Photochemistry and Photobiology, 1979, 30, 49.


64. Yongseog Chung, OSU, personal communication.

65. Diphenyl ether was freshly distilled from stannous chloride.

66. Temperature was maintained at ± 1°C by an internal thermometer connected to a Therm-O-Watch controller, model number LG 10000S, I2R Inc, 108 Franklin Ave, Cheltingham, PA. 19012.

67. The UV spectrometer used was a Hewlett Packard 8451A Diode Array Spectrometer.

68. Serena Software, 489 Serena Lane, Bloomington, IN. 47401.


70. Molecular mechanics programs adapted from Allinger's "MMPI" were obtained from Serena Software, 489 Serena Lane, Bloomington IN, 47401; this version (name: "MMPM") with the accompanying graphics routine was run on an IBM-AT microcomputer.

71. S. Rosenfeld, Smith College, unpublished results.


88. This compound was not further characterized due to the fact that it was further derivatized.


91. Gilson International, Middleton, WI.

92. This analysis is off from the accepted value of ± 0.40 %. Attempts will be made to get this compound's analysis within the accepted limits before publication.


99. See ref 94 for a similar use of this buffer for metal ion containing reactions at 85°C.

a. Chromatography column containing H₂O and KI
b. Buret turned upside down to measure gas flow rate
c. Tygon tubing to carry gas
d. Glass tubing the same diameter as a thermometer
e. 24/40 vacuum thermometer adapter
f. Septum
g. 1000 ml 3 neck flask
h. 4 cm diameter glass tube with 24/40 joint on top (female) and inlet that tygon tubing will fit onto on the bottom
i. Sodium fluoride to remove HF
j. Glass wool
k. 1/4 inch copper tubing
l. 1/4 inch brass “tee” available at any hardware store
m. Fluorine/Nitrogen tank
n. 3 way stopcock

Apparatus for the fluorination of N-tert-butyl-N-benzenesulfonamide