

12-1-2012

Activation of Alcohols Toward Nucleophilic Substitution: Conversion of Alcohols to Alkyl Halides

Amani Atiyalla Abdugadar

Follow this and additional works at: <http://digscholarship.unco.edu/theses>

Recommended Citation

Abdugadar, Amani Atiyalla, "Activation of Alcohols Toward Nucleophilic Substitution: Conversion of Alcohols to Alkyl Halides" (2012). *Theses*. Paper 22.

This Text is brought to you for free and open access by the Student Research at Scholarship & Creative Works @ Digital UNC. It has been accepted for inclusion in Theses by an authorized administrator of Scholarship & Creative Works @ Digital UNC. For more information, please contact Jane.Monson@unco.edu.

© 2012

Amani Abdugadar

ALL RIGHTS RESERVED

UNIVERSITY OF NORTHERN COLORADO

Greeley, Colorado

The Graduate School

ACTIVATION OF ALCOHOLS TOWARD NEOCLEOPHILIC
SUBSTITUTION: CONVERSION OF ALCOHOLS
TO ALKYL HALIDES

A Thesis Submitted in Partial Fulfillment
of the Requirements for the Degree of
Master of Science

Amani Abdugadar

College of Natural and Health Sciences
Department of Chemistry and Biochemistry

December, 2012

This Thesis by: Amani Abdugadar

Entitled: *Activation of Alcohols Toward Neocleophilic Substitution: Conversion of Alcohols to Alkyl Halides*

has been approved as meeting the requirement for the Master of Science in College of Natural and Health Sciences in Department of Chemistry and Biochemistry

Accepted by the Thesis Committee

Michael D. Mosher, Ph.D., Research Co-Advisor

Richard W. Schwenz, Ph.D., Research Co-Advisor

David L. Pringle, Ph.D., Committee Member

Accepted by the Graduate School

Linda L. Black, Ed.D., LPC
Acting Dean of the Graduate School and International Admissions

ABSTRACT

Abdugadar, Amani. *Activation of Alcohols Toward Nucleophilic Substitution: Conversion of Alcohols to Alkyl Halides*. Published Master of Science thesis, University of Northern Colorado, 2012.

The conversion of alcohols into alkyl halides is one of the most important reactions in organic chemistry. Development of new methodology is still desirable in academic research. Unfortunately, the hydroxyl group of the alcohol is relatively difficult to replace under normal conditions. That necessitates the conversion of alcohols to a more activated functionality before nucleophilic substitution becomes viable. Under vigorous conditions, the replacement is straightforward. Procedures for the generation of halides from alcohols have been extensively examined, e.g., using HX or Mitsunobu inversion. However, these methods require time, strong acid, or catalysis to proceed. These classical methods suffer from issues surrounding the toxicity of the reagents used or the difficult purification of the products. This research provided a new technique for promoting nucleophilic chlorination of primary, secondary, and tertiary alcohols by the aromatic cationic activation of the hydroxyl group of the alcohols. The chemical conditions for this transformation are relatively benign and the reaction proceeds rapidly. The kinetics of the reaction were studied by both infrared and ultraviolet-visible spectroscopy. The reaction order was determined and the rate constants were calculated for this halogenation reaction.

ACKNOWLEDGEMENTS

It would not have been possible for me to earn this degree without the help and support of kind people around me. I found it difficult to impart a significant acknowledgment to those who most deserve it in few sentences.

My husband, Habib, supported me through good and bad days. He has been a source of strength. Above all, I would like to thank him and my daughter, Taiba, for being patient while I was away from them. I wish to thank my parents and family for their support and encouragement.

This work would not have been possible without the support and patience of my supervisors, Professor Michael D. Mosher and Professor Richard W. Schwenz. I would like to thank them for guiding me through this research.

It gives me great pleasure to acknowledge the chemistry department at the University of Northern Colorado (UNC). It has been an honor to study at UNC. I wish to thank Professor Richard Hyslop for advising and inspiring me. I wish to thank Professor David Pringle as well; he is not just a professor but he showed that he truly cares about me by continually asking about me and my country.

I would like to express my appreciation to the graduate students at UNCO for all of their support.

The Center of International Education (CIE) supported me at all times, especially during the Libyan war.

I would like to acknowledge the financial support of the Libyan government and Benghazi University (Almarj Branch).

I want to give thanks to God for helping me reach this point in my life.

I really want to thank every person who supported me. I gratefully acknowledge the Libyan youth for the revolution to gain our freedom. May God bless the martyrs.

TABLE OF CONTENTS

CHAPTER I. INTRODUCTION	1
Alcohol Activation for Nucleophilic Substitution	1
Aromatic Cationic Activation of Alcohols.....	4
The Halogenation Reaction and Mechanism	5
Introduction to Substitution Reactions.....	7
Infrared Spectroscopy: The General Principles	11
Instrumentation for Infrared Spectroscopy: Typical System Components	11
Fourier Transform Infrared Spectroscopy.....	12
Infrared Spectra for Alcohols.....	14
Ultraviolet-Visual Spectroscopy	15
CHAPTER II. LITERATURE REVIEW	18
Non-Phosphorus Activation of Alcohols	20
Phosphorus Chemistry	24
CHAPTER III. METHODOLOGY	34
Beer's Law	37
Data Analysis	42
CHAPTER IV. RESULTS AND DISCUSSION.....	44
Reaction of 9,9-Dichloroxanthene and Alcohols	44
Determining Dilution Effects.....	52
Verification of the Beer-Lambert Law	53
Determining Reaction Order for a Primary Alcohol, 1-Butanol.....	53
Determining Reaction Order for a Secondary Alcohol, 2-Butanol.....	56
Determining Reaction Order for a Tertiary Alcohol, 2-Methylpropan-2-ol	59
Repetition of the Reaction	61
Calculating k Values	61
Discussion	63

CHAPTER V. CONCLUSION	66
Conclusion	66
Recommendations/Proposals for Future Work	68
REFERENCES	71

LIST OF TABLES

1.	Dilution Effects	52
2.	Example Primary Alcohol Reaction Data	56
3.	Example Secondary Alcohol Reaction Data	57
4.	Example Tertiary Alcohol Reaction Data	60
5.	Rate Constants for the Primary Alcohol	62
6.	Rate Constants for the Secondary Alcohol	62
7.	Rate Constants for the Tertiary Alcohol.....	62
8.	Rate Constants for the Butanols.....	63

LIST OF FIGURES

1.	Classical reagents for halogenation of alcohols.....	1
2.	Thionyl chloride-mediated halogenation of alcohols	4
3.	Mechanistic design for alcohol activation by cyclopropenium ion	5
4.	Mechanism for chlorination reaction.....	7
5.	S _N 1 mechanism	9
6.	S _N 2 mechanism	10
7.	Interpretation of interferograms into infrared spectra.....	13
8.	Michelson interferometer.....	14
9.	A schematic diagram of a stopped-flow spectrophotometer.....	17
10.	Activation of alcohols by <i>in situ</i> generation of halide ion	20
11.	Conversion alcohols into iodides using thiominium salt	21
12.	Nucleophilic attack of the alcohol on the thiominium salt	21
13.	Pivaloyl chloride-mediated alcohol activation.....	22
14.	Pivaloyl chloride-mediated alcohol activation mechanism	22
15.	Chlorination of alcohols via the Lewis acid, AlCl ₃	23
16.	Corresponding iodides produced by treatment of alcohols with NaI supported on KSF clay	24
17.	Postulated mechanism for the Mitsunobu reaction.....	25
18.	Developed Mitsunobu reaction	27

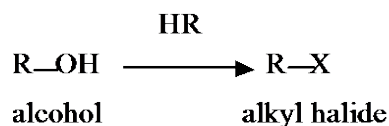
19.	N-Halosaccharine mediated halogenations of alcohol mechanism	27
20.	Appel reaction mechanism.....	28
21.	Cleavage of the phosphorus-oxygen double bond forming two carbonyl groups.....	30
22.	Chlorination of alcohol	31
23.	Reactions with carbaphosphazenes.....	32
24.	Alternative pathway for alcohol activation.....	33
25.	Converting alcohols and thiols to iodides and bromides	33
26.	Preparation of the chlorinating reagent 9,9-dichloroxanthene.....	34
27.	A halogenation reaction for a polymer-bound xanthone.....	35
28.	Beer-Lambert curve	38
29.	First-order reaction.....	40
30.	A plot of reciprocal of concentration versus time (second-order plot)	41
31.	Concentration versus time (zero-order plot)	41
32.	2-Butanol infrared spectrum	47
33.	2-Butanol infrared spectrum during the reaction	48
34.	2-Butanol infrared spectrum after the reaction	49
35.	Xanthone ultraviolet visual spectra.....	50
36.	Dichloroxanthene/alcohol ultraviolet visual spectra.....	51
37.	Determining dilution effects	52
38.	Primary alcohol (1.00E-06 M)	55
39.	Secondary alcohol (4.00E-06 M)	57
40.	Tertiary alcohol (1.00E-06 M)	59

CHAPTER I

INTRODUCTION

Alcohol Activation for Nucleophilic Substitution

The substitution of activated alcohols is a frequently used approach not only in organic synthesis but also for preparing active pharmaceutical ingredients.¹ Substitution of the hydroxyl group in alcohols by nucleophiles intrinsically requires some type of activation. Since the hydroxyl group is a poor leaving group, it generally should be activated before treatment with a chlorination reagent. This transformation must be accomplished before nucleophilic substitution becomes feasible. Many reagents have been employed to carry out this transformation (see Figure 1). Some of the methods developed for this purpose utilize reagents such as PCl_3 , HCl , and PPh_3 /diethyl azodicarboxylate (DEAD). Development of an alternative strategy is still needed.



$\text{HR} = \text{Halogenation Reagent} = \text{HX}, \text{PX}_3, \text{SOCl}_2, \text{PX}_5, \text{or } \text{POCl}_3$

$\text{X} = \text{Cl}, \text{Br}, \text{I}$

$\text{ROH} = 1^\circ, 2^\circ \text{ or } 3^\circ \text{ Alcohols}$

Figure 1. Classical reagents for halogenation of alcohols.

Alkyl halides are very useful reagents in organic chemistry as well as in chemical and molecular biology. The alkyl halides have been utilized in the synthesis of many effective drugs. They are useful in nanomaterial fabrication and nanotechnologies.² Halogenated compounds also play a significant role in organic synthesis. They react with nucleophiles to give the corresponding products and can be lithiated to work as electrophiles. The alkyl iodides possess an important role in the formation of carbon-carbon bonds by free-radical and organometallic reactions.³

Activation of alcohols towards nucleophilic substitution can occur by converting them into alkoxyphosphonium ions. Activating the alcohols using a combination of triphenyl phosphine and diethylazodicarboxylate (DEAD) is known as the Mitsunobu reaction, which occurs by the formation of a phosphorus ester that activates the hydroxyl group in the reaction. Inversion of stereochemistry in this reaction indicates an S_N2 mechanism for the final step in the process. Another method to activate the alcohols is based on *in situ* generation of chlorophosphonium ions. This process involves formation of chlorophosphonium ions and can occur by the reaction of triphenylphosphine with carbon tetrachloride.⁴

The classical conversion of primary alcohols to chlorides involves the use of hydrogen chloride gas in the presence of a catalytic quantity of zinc chloride as a catalyst. This is known as the Lucas reagent. The use of aqueous hydrochloric acid, however, is less suitable because of the poor yield and the large amount of zinc chloride required. To overcome this difficulty, phase-transfer catalysts in a heterogeneous system have been used.⁵ Tertiary alcohols react readily with concentrated hydrochloric acid, but primary and secondary alcohols react so slowly that a catalyst is needed. Usually, unsaturated

alcohols are converted to saturated alkyl halides.⁶ Because the use of HCl shows poor results for the conversion of an alcohol to an alkyl chloride, a catalyst such as the zinc used in the Lucas reagent is required. This reaction was improved by adding zinc chloride and had the advantage of milder conditions and commercial availability, making it an efficient reagent system in industry. One way to prepare this reagent is by bubbling hydrogen chloride gas into a solution of zinc chloride to get a 1:1 solution of ZnCl_2 : HCl.⁷ This process results in converting the poor hydroxyl leaving group to a better one. By protonating an alcohol, the hydroxyl group is converted to H_2O , making the alcohol active toward nucleophilic substitution reactions.

Another general method for converting alcohols to halides involves reactions of alcohols with halides of certain nonmetallic elements. Thionyl chloride and phosphorus trichloride are the most common representatives of this group of reagents. For example, primary and secondary chlorides can be synthesized from their corresponding alcohols by a 1:1 mixture of thionyl chloride and benzotriazole in an inert solvent such as dichloromethane as shown in Figure 2.⁸

Conversion of alcohols into iodides using potassium iodide in a phosphoric acid/phosphorus pentoxide mixture is a well-established transformation in organic chemistry. It is a very convenient reaction for unfunctionalized primary, secondary, and tertiary alcohols.⁶

Fluorination of alcohols is also possible and can be achieved by the reactions of dialkylaminosulfur trifluorides (DAST) with alcohols. For instance, the reaction of DAST with an alcohol can replace the hydroxyl group of the alcohol with fluoride. Other reagents used for the same purpose include SF_4 , SeF_4 /pyridine, or HF.⁹

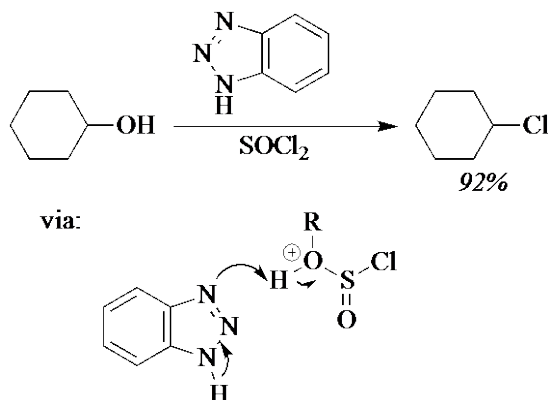


Figure 2. Thionyl chloride-mediated halogenation of alcohols.

The typically used reagents discussed above are either toxic or they need vigorous conditions to be used. For example, the use of phosphorus reagents, e.g., Mitsunobu reagents, is complicated because the resulting reaction mixture contains the product and byproducts (triphenylphosphine oxide and hydrazine dicarboxylate). Purification of the halide product from these byproducts requires additional processing. In addition, DEAD, one of the Mitsunobu reaction's starting materials is explosive, expensive, and its hydrazine byproduct is toxic. For these reasons, commercial use and production of the Mitsunobu reaction has been limited.¹⁰ The use of HCl in this reaction is also limited to acid-stable, saturated, unfunctionalized alcohols.⁶ Moreover, some of these methods are only applicable for either primary, secondary, or tertiary alcohols. Therefore, development of a new procedure to convert primary, secondary, and tertiary alcohols to their corresponding alkyl halides is still needed.

Aromatic Cationic Activation of Alcohols

As mentioned above, alcohols must be converted to a more active functionality before nucleophilic substitution becomes viable. One possible strategy for the activation

of alcohols was proposed by Kelly and Lambert¹¹ and is based on the formation of activated aromatic cations. The aromatic starting material was cyclopropene. The activation of alcohols should be possible through the mechanism proposed in Figure 3.

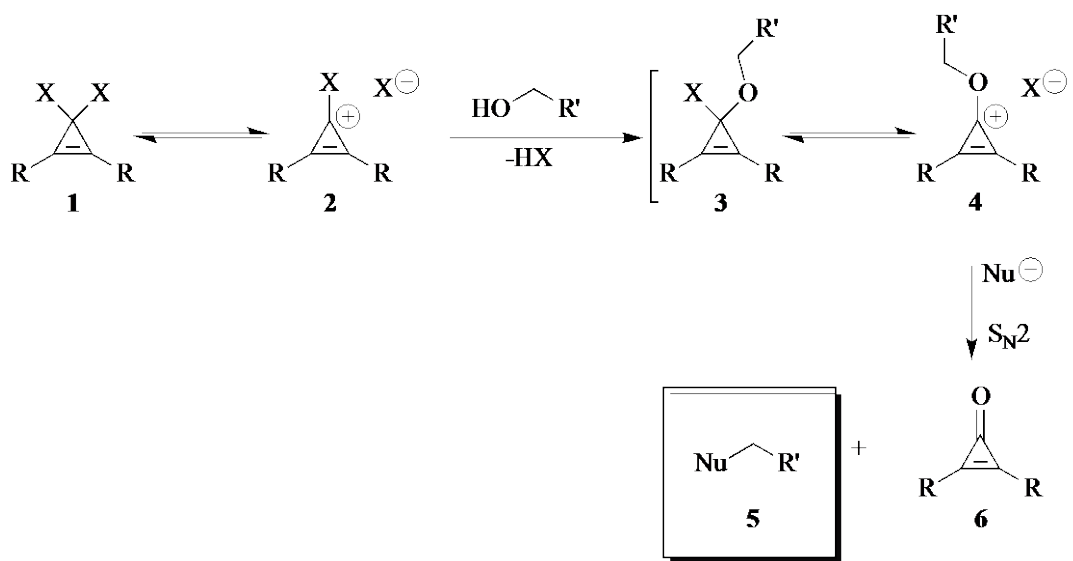


Figure 3. Mechanistic design for alcohol activation by cyclopropenium ion.

A cyclopropene **1** with two geminal substituents (X) may exist in equilibrium with cyclopropenium salt **2**. In the presence of an alcohol, the cyclopropenyl ether **3** is formed and then re-ionizes via the dissociation of the remaining halogen to give the highly activated alkoxy-substituted cyclopropenium ion **4**. Nucleophilic substitution in a final step is then possible, and the product **5** would be synthesized along with cyclopropenone **6**.¹¹

The Halogenation Reaction and Mechanism

In the present study, a procedure was investigated for an efficient conversion of alcohols to their corresponding chlorides under neutral conditions by treatment with 9,9-dichloroxanthene. The conversion of primary, secondary and tertiary alcohols into

chlorides was studied using dichloroxanthene in toluene as the chlorinating reagent. The reaction was very convenient and a rapid and efficient conversion to chlorides was achieved. The chlorination reagent was efficient and was able to activate the hydroxyl group of the alcohol by forming aromatic cation intermediates. The relative unknown reaction provided a one-pot conversion of an alcohol to the corresponding alkyl halide.

By applying the mechanism described by Kelly and Lambert¹¹ to the reaction between primary, secondary, and tertiary butanols with 9,9-dichloroxanthene, the chloride ion represents the nucleophile in the reaction. Thus, the chloride ion attacks the activated alcohol after its liberation from the dichloroxanthene. As a result, the butanols are converted into butyl chlorides.

The reaction pathway for this reaction is presented in Figure 4. It was reasoned that the activation of the hydroxyl group of the alcohol toward nucleophilic displacement should be possible via this mechanistic design. 9,9-Dichloroxanthene (**7**) might exist in equilibrium with its salt (**8**). Addition of an alcohol to this salt would produce an ether (**9**) that re-ionizes via dissociation of the remaining chloride ion. This cationic ether (**10**) was believed to be a highly activated aromatic intermediate. The facile loss of the chloride allows the hydroxyl group of the alcohol to be activated and then replaced by the chloride ion present in the solution via a nucleophilic substitution reaction.

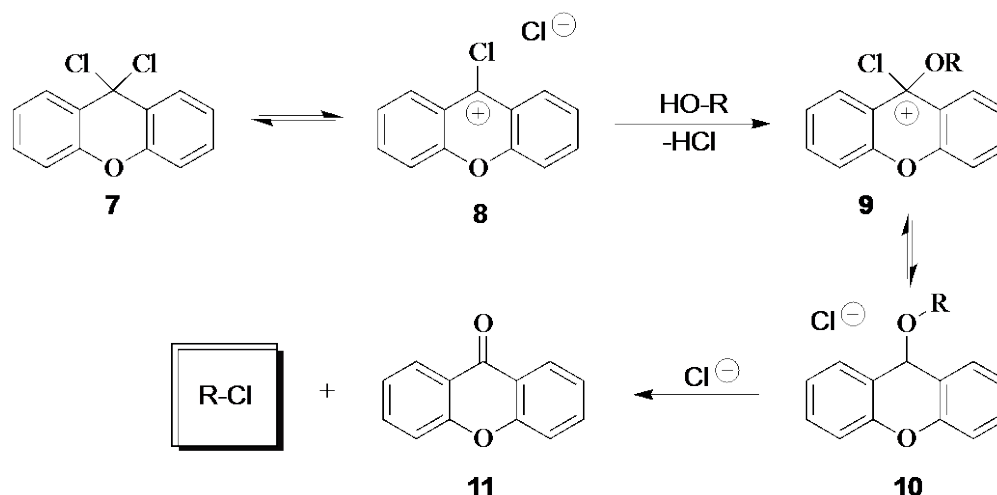


Figure 4. Mechanism for chlorination reaction.

This research explored the kinetics of the transformation of alcohols to their corresponding alkyl chlorides using this novel technique. This reaction was studied to determine the rate of the process, which should be different for primary, secondary and tertiary alcohols. The main purpose of this research was to study the kinetics of this reaction by determining the rate constant for each reaction and determining the order of the halogenation reaction.

Introduction to Substitution Reactions

Substitution reactions are chemical reactions wherein one group or atom is substituted for another group or atom. Sometimes, the new group takes the same structural position of the leaving group. Substitution reactions involve the formation of a new bond and the breaking of an old one. According to the nature of the reagent and the nature of the site of substitution, these reactions can be classified as electrophilic, nucleophilic, or radical.¹²

Nucleophilic substitution reactions are chemical reactions for aliphatic compounds in which the leaving group is attached to an sp^3 -hybridized carbon atom. They are one of the most important reactions in aliphatic organic chemistry. Fortunately, the mechanisms of nucleophilic substitution reactions are well understood. There are two main mechanisms: S_N1 and S_N2 , where S stands for ‘substitution’ and N for ‘nucleophilic’. The “1” and “2” refer to the molecularity of the reaction as either unimolecular or bimolecular in the rate-determining step of the mechanism.

The mechanism for a given transformation depends upon the structure of the alkyl group bearing the leaving group. Primary and secondary substrates tend to react by the bimolecular S_N2 route where the incoming nucleophile attacks at the same time as the leaving group departs, resulting in Walden inversion at the carbon atom to which the halide was attached. On the other hand, tertiary substrates tend to follow S_N1 reaction mechanisms.¹² The main pathways for the conversion of alcohols to alkyl halides are either S_N1 or S_N2 mechanisms.

S_N1 Mechanism

The S_N1 mechanism is a unimolecular, multi-step reaction. Heterolytic cleavage of the carbon-leaving group bond forms an intermediate carbocation. This step is considered the rate-determining step. This step is followed by the addition of a nucleophile to the carbocation. The reaction is first order in the substrate and independent in the nucleophile concentration.¹⁶ Substitution reactions on tertiary alcohols tend to follow the S_N1 reaction mechanism due to their ability to form stable carbocation intermediates. The high degree of steric constraint on the back side of the tertiary alcohol

also prohibits the approach of the nucleophile prior to the formation of the flat sp^2 -hybridized carbocation (see Figure 5).

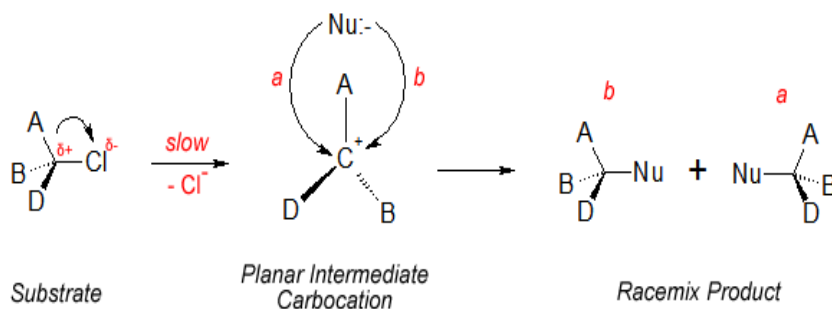


Figure 5. S_N1 mechanism. Attack of the nucleophile on the planar carbocation can occur via pathway “a” or “b” resulting in the corresponding product “a” or “b.”

Evidence for the S_N1 mechanism exists. For example, a chiral substrate would be expected to generate a racemic product mixture after the reaction. However, some studies have indicated that loss of the leaving group physically restricts the addition of the nucleophile to the front side of the carbocation. Thus, a completely racemic product mixture is rarely observed. More often than not, the inversion product resulting from more backside attack than front-side attack predominates. In any case, scrambling of the stereochemistry at the reaction center occurs.¹⁴ The kinetics of the S_N1 mechanism are first-order in the substrate and zero order in the nucleophile. This can be determined by a linear relationship between the natural logarithm of the concentration of the substrate versus time for the reaction. The rate constant for the reaction is equal to the negative of the slope of that linear relationship.¹⁵

S_N2 Mechanism

Unlike the S_N1 mechanism, the S_N2 mechanism is a bimolecular reaction, and it is a one-step process. A typical feature of this mechanism is the backside attack that results

in a Walden inversion. In the S_N2 mechanism, the old bond is broken and the new bond is formed in a concerted fashion. The nucleophile attacks the substrate from the opposite side of the leaving group, leading to a transition state where the carbon atom has adopted an sp^2 -like geometry. After completion of the reaction, a product with inverted chemistry is formed, known as Walden inversion.¹⁶ Primary and secondary alcohols are expected to follow this route because of the ease of approach of the nucleophile to the backside of the substrate. Moreover, a step-wise release of the leaving group from the substrate would not be preferred as it would generate a primary or secondary carbocation that is relatively unstable (see Figure 6).

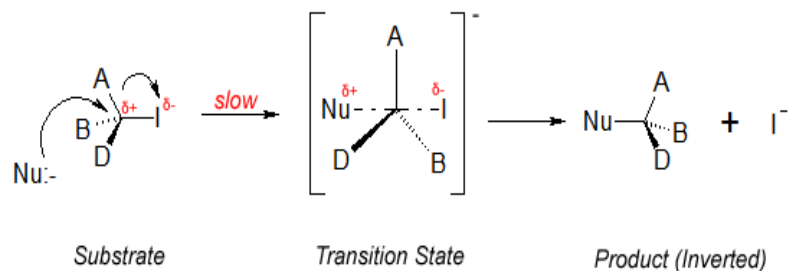


Figure 6. S_N2 mechanism. Approach of the nucleophile only occurs on the backside of the carbon-leaving group bond and results in inversion of the stereochemistry in the product molecule.

The kinetics of the S_N2 mechanism are first-order in the substrate and first order in the nucleophile. This can be determined by keeping the concentration of one of the two reactants (substrate or nucleophile) large. The resulting rate law would then be described as a pseudo-first order reaction in the other reactant. Thus, if the concentration of nucleophile is kept large, a plot of the natural logarithm of the concentration of the substrate versus time for the reaction would result in a linear relationship. The rate

constant for the pseudo-first order reaction is equal to the negative of the slope of the linear relationship.¹⁷

Infrared Spectroscopy: The General Principles

The spectroscopic technique that uses infrared light to examine or quantify chemicals is called infrared spectroscopy.¹⁸ IR spectroscopy is the measurement of the interactions of waves of the infrared portion of the electromagnetic spectrum with matter. The infrared (IR) spectrum starts beyond the red region of the visible spectrum at a wavelength of 700 nm and extends to the microwave region at wavelength of 0.1 cm.

The observed interactions in the IR spectrum involve the energies associated with a change in the vibrational states of the molecule. The absorption of the IR energy follows the Beer-Lambert Law in dilute solutions; therefore, infrared spectroscopy is useful for both elucidation of molecular structure and the quantification and identification of different species in a sample.¹⁹ If a molecule absorbs infrared radiation, a change in the energy due to vibrations or rotations occurs in the molecule.¹⁸ In organic chemistry techniques, IR spectra are mostly represented as a plot of percent transmittance (% T) versus wavenumber (in cm^{-1}). However, IR spectra utilized in many other disciplines are plotted in terms of absorbance (A) versus wavelength (in units of micrometers). The relationship between absorbance and % T is related by the following equation:

$$-\log T = A \quad (1)$$

Therefore, the conversion from A to % T is relatively straightforward.²⁰

Instrumentation for Infrared Spectroscopy: Typical System Components

A source of infrared energy (IR light), a means for separating the IR light into different wavelengths, a sample holder, and a detector are required in IR spectroscopy.

The IR light source is usually an inert rod that is heated. The heated material, often silicon carbide, SiC, (producing a device called a globar), or a mixture of rare-earth oxides (giving a device called a Nernst glower), is used to generate the infrared energy. Ionic salts such as NaCl, KBr, and CsBr, which are transparent to the IR radiation, are used to construct the IR sample holder. These ionic salts are soluble in water. They can be replaced by less soluble, yet more expensive salts such as CaF₂ and AgCl depending on the sample.²¹

Fourier Transform Infrared Spectroscopy

Fourier Transform Infrared Spectroscopy (FT-IR spectroscopy) is a measurement technique frequently used to identify chemicals. Because absorptions in IR spectroscopy follow the Beer-Lambert Law, the technique can be used to study chemical reactions as a function of time.

The FT-IR was developed to overcome the limitation encountered with the continuous wave IR spectrometer. The FT-IR spectrometer differs from the continuous wave IR spectrometer since it allows all IR radiation wavelengths to interact with the sample simultaneously instead of scanning through the individual wavelengths. The absorbances by a molecule are obtained by a device known as an *interferometer*, which is a very simple optical device that causes negative and positive interference to occur. The major advantage of the FT-IR spectrometer is the speed by which the spectrum is obtained (typically a few seconds), which allows large amount of data to be gathered in a short time period. FT-IR is preferred over continuous wave, dispersive or filter methods of infrared spectral analysis because it is a non-destructive technique and provides a precise measurement with no external calibration.²² The spectrum of a beam of incident

IR radiation in FT-IR is obtained by generating an interferogram with Michelson interferometer. Subsequently, the interferogram is inverted by means of a cosine Fourier transform in the spectrometer.²³ As the interferogram is measured, all frequencies are measured simultaneously. To plot IR spectra, the interferogram has to be interpreted (see Figure 7). A means of decoding the individual frequencies is accomplished by a mathematical technique called the Fourier transformation.²²

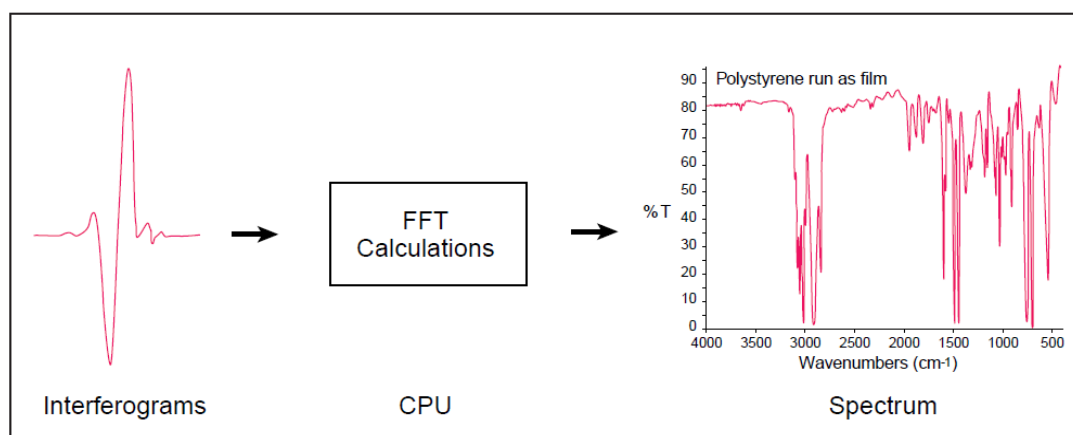


Figure 7. Interpretation of interferograms into infrared spectra.

Most interferometers used today for infrared spectrometry are based on the two-beam type originally designed by Michelson in 1891.²⁴ The Michelson interferometer is a device where light strikes a partially reflecting plate and the beams are recombined and interfered either destructively or constructively at the plate. The Michelson interferometer, which uses two mirrors (or other reflecting surfaces) as shown in Figure 8, divides an incoming beam of radiation into two equal parts with each part continuing along a separate path. As one mirror moves, the detector records the interference pattern

produced by the superposition of the two beams, which are split and recombined by the beam splitter. When the two beams are recombined, a condition is created under which interference can take place. That interference depends upon the speed and displacement or movement of one of the mirrors. Interference occurs when two beams of radiation are added together or combine to form one summation signal.²⁵

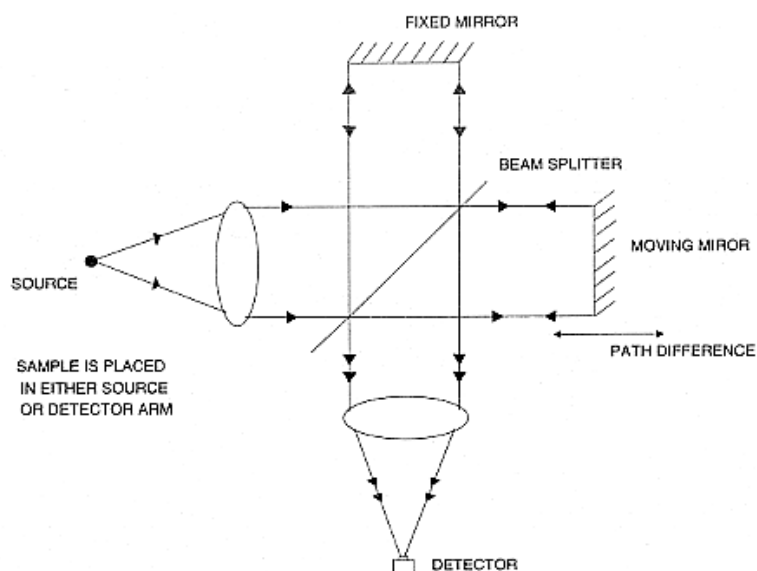


Figure 8. Michelson interferometer.

Infrared Spectra for Alcohols

Molecules generally have many bonds and each bond may be a part of an IR-active vibrational mode. The fact that specific bonds within the molecules reproducibly absorb specific wavelengths of IR energy makes the use of IR spectra very helpful for identifying compounds. This can be done by identifying specific absorbances in the IR spectrum and relating those to the structure of a molecule or by comparing the spectra with authentic samples in a method known as fingerprinting.²⁶ For example, a strong,

broad band between 3500 and 3200 cm^{-1} is due to the hydrogen-bonded O-H stretching mode of an alcohol.²⁷ In some cases, it is possible to observe an O-H stretch that is not participating in hydrogen bonding. Such a signal occurs as a sharp absorbance at 3600 cm^{-1} .²⁶ The weakening of the hydrogen-oxygen bond, as a consequence of the hydrogen bonding, causes this shift from 3600 cm^{-1} to approximately 3300 cm^{-1} .

Ultraviolet-Visual Spectroscopy

Ultraviolet visual spectroscopy (UV-Vis spectroscopy) is a common method for analyzing molecules. This technique is defined as a type of spectroscopy used to examine the interaction of the analyte with ultraviolet or visible light through absorption.²⁸ The absorption of ultraviolet (UV) radiation by atoms and molecules involves transitions of the electrons to highly excited energy levels. The UV spectral region extends from about 400 nm to the side of the X-ray region at ~ 10 nm.²⁹ Visible light spans wavelengths of energy from 400-700 nm. The absorption of ultraviolet and visible light, especially in the range of 200-780 nm, often involves electronic transitions in molecules by π electrons or nonbonded electrons (n) as they transition to an excited electron state, usually the π^* orbitals within a compound. In other words, π to π^* and n to π^* transitions predominate in the UV-vis spectrum. Because of that, organic compounds with only single bonds and no π or nonbonded electrons tend not to absorb in this region of the UV-vis spectrum. This means that saturated hydrocarbons cannot be observed, measured, or evaluated by UV-Vis spectroscopy.²⁸ UV-Vis absorptions are particularly sensitive for unsaturated organic compounds, mainly those containing aromatic or carbonyl groups, where the π to π^* transition is very easy to accomplish.³⁰ Therefore,

9,9-dichloroxanthene, an aromatic compound, can be considered a very good UV-vis reagent.

A plot of absorbance versus wavelength is known as a UV-vis spectrum. The x -axis for a typical UV-vis absorption spectrum is commonly expressed in nanometers. The y -axis is often plotted in terms of absorbance at each wavelength.³¹ Most UV-vis spectra are obtained by measuring the intensity of monochromatic radiation across a range of wavelengths passing through a solution in a cuvette.³²

Instrumentation for Ultraviolet-Visual Spectroscopy: Typical System Components

The instrument used to examine the absorption of light in UV-Vis spectroscopy is known as a UV-Vis spectrophotometer. The spectrophotometer has four basic components: a source of light, a monochromator for selecting the wavelength of the radiation for analysis, a sample holder (a cuvette), and a detector. A common source for visible light is a tungsten lamp.³¹ Materials such as quartz or glass can be used to construct the UV-vis cuvette.²¹

Techniques for Very Fast Reactions

Some reactions are so fast that special techniques have to be employed. The main reason why conventional techniques lead to difficulties for very rapid reactions is the usual time it takes to mix reactants might be significant in comparison with the half-life of the reaction. This difficulty can be surmounted by using special techniques for bringing the reactants very rapidly into the reaction vessel and for mixing them. Usually, it takes several seconds to a minute to bring a mixture of gases or liquids into a reaction vessel and to have it completely mixed using conventional techniques. This time can be

reduced greatly by using methods such as stopped-flow techniques, one form of which is shown schematically in Figure 9.³³

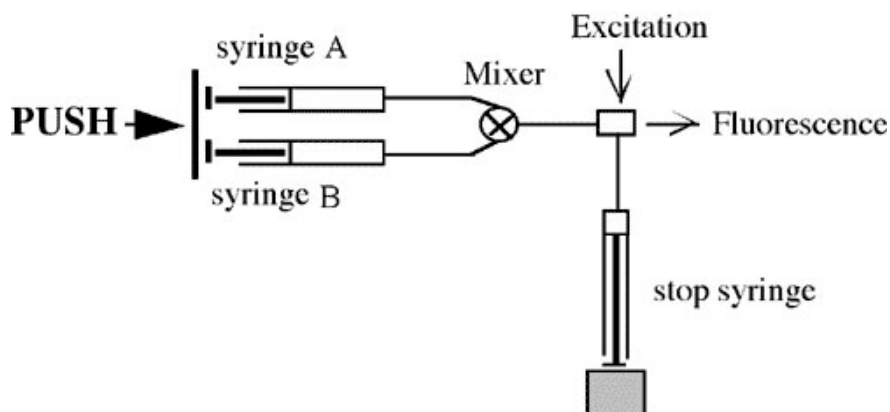


Figure 9. A schematic diagram of a stopped-flow fluorescence spectrophotometer.³⁷

Stop-flow mixing has the advantage that only small samples are required. The apparatus acts as an efficient and very rapid mixing device. Stop-flow methods always require an inline timing device because the time analysis must be very rapid. Spectroscopic methods using pulsed radiation are used as stop-flow devices because they can be both analytical and timing devices. Two solutions are rapidly forced through a mixing chamber from which there is an exit into a tube.³⁶ Two syringes actuate the flow manually or automatically. The flow is then suddenly stopped. Measurements of the reaction system are taken when the fluid is stationary.

CHAPTER II

LITERATURE REVIEW

The direct conversion of alcohols to alkyl halides is a transformation widely utilized in organic synthesis, and there are a number of reagents that are used for this purpose. Because of the poor leaving group ability of the hydroxyl group, the activation has to occur before nucleophilic substitution by the chloride anion.³⁸ To accomplish this goal, many reagent systems have been utilized. The most commonly used reagents that convert the hydroxyl group of an alcohol into a good leaving group are based on phosphorus chemistry. These procedures often generate stoichiometric quantities of triphenylphosphine oxide or diphenyl methylphosphanate, which can cause difficulties in product separation. For example, alkyl iodides can be synthesized by the reaction of alcohols with phosphorus triiodide. This reaction produces the toxic byproduct H_3PO_3 .²

In spite of the difficulties involved, the most common precursors for the preparation of alkyl halides are the corresponding alcohols; a variety of techniques have been developed to obtain this conversion. Typically, the overall conversions occur via nucleophilic substitution using several reagents.³⁹ However, halide ions are not strong enough nucleophiles to replace the hydroxyl group under normal conditions. The hydroxyl group can be converted to a halogen by adding either a strong acid such as HX , inorganic acids such as SOCl_2 , or by some other activation of the hydroxyl group toward nucleophilic substitution.

Tertiary halides are easily made via a first-order process in the reaction of the corresponding tertiary alcohols with concentrated HX. For example, *tert*-butanol reacts readily with hydrobromic acid to give the corresponding bromide predominantly by the S_N1 mechanism. In this mechanism, the alcohol is protonated first to improve the nature of the leaving group, the hydroxyl group. Water rather than the -OH group leaves, allowing the formation of a stabilized carbocation.⁴⁰

Primary and secondary alcohols react slowly in hydrohalic acids, so a catalyst is often employed. Rearrangement does not appear to be a problem for the primary alcohols, indicating that the reaction proceeds primarily via an S_N2 mechanism. For example, unsubstituted primary alcohols can be converted to the corresponding alkyl bromides using hot, concentrated hydrobromic acid. Unfortunately, these methods are applicable only to acid-stable, unfunctionalized, simple alcohols.⁶ In another example, primary alcohols can be converted into alkyl chlorides by either using either gaseous hydrogen chloride or aqueous concentrated hydrochloric acid in the presence of zinc chloride as a catalyst. In this last example, a large amount of zinc chloride is necessary for adequate conversion to the alkyl chloride.⁵

As mentioned previously, the use of agents other than hydrohalic acids for the conversion of alcohols to alkyl halides is common, i.e., the reaction of alcohols with the halides of nonmetallic elements such as SOCl₂ or PBr₃. Primary and secondary alcohols are typically transformed using these reagents. The mechanisms tend to follow second order kinetics to replace the alcohol. These methods are useful for alcohols that are neither acid sensitive nor prone to rearrangement.⁸ Making primary, secondary, and

tertiary iodides is possible by using phosphoric acid-phosphorus pentoxide mixtures with potassium iodide.⁶

Non-Phosphorus Activation of Alcohols

While the hydrogen halide is commonly used as the reagent for this transformation, it is often generated *in situ* from the halide ion and an acid such as phosphoric or sulfuric acid. For instance, *in situ* generation of hydrogen iodide from a methanesulphonic acid/sodium iodide mixture was found to be an efficient reagent system for the conversion of various alcohols to their corresponding alkyl iodides (see Figure 10). The key in this conversion is the protonation of the alcohol by HI formed *in situ*, leading to conversion of the hydroxyl group to a better leaving group; water.⁴¹

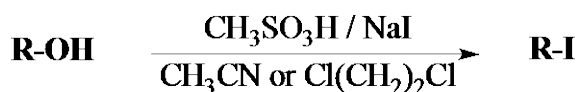


Figure 10. Activation of alcohols by *in situ* generation of halide ion.

Treatment of a range of primary and secondary alcohols with a thioiminium salt affords the corresponding iodides in excellent yields with straightforward purification. For example, primary and secondary alcohols can be converted to their iodides by treating them with the stable thioiminium salt *N,N*-dimethyl-*N*-(methylsulfanylmethylene)ammonium iodide as represented in Figure 11. The alkyl iodide product is readily isolated from the byproducts. The activation of the alcohols in this reaction occurs by converting them to alkoxyiminium ions.

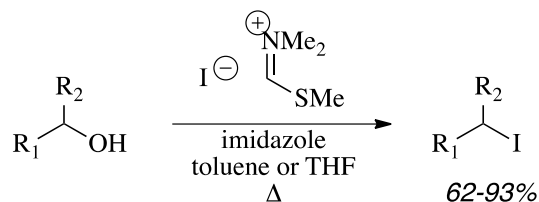


Figure 11. Conversion of alcohols into iodides using thioiminium salt.

In Figure 12, the nucleophilic attack of the alcohol (**12**) on the thioiminium salt results in the formation of the intermediate I (**13**), which led to the formation of the alkoxyiminium ion (**14**), a species that is highly activated toward nucleophilic substitution reactions.³⁸

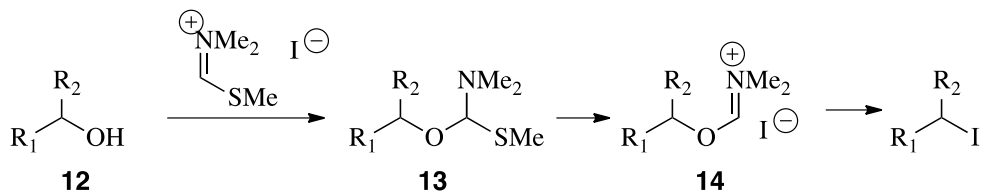


Figure 12. Nucleophilic attack of the alcohol on the thioiminium salt.

Some limitations of these methods reduce their ability to be scaled up for use in industrial scale production. Those limitations include difficult product separation, high material cost, and large amounts of wastes for disposal. In this context, development of a new procedure to accomplish the conversion of an alcohol to an alkyl halide is still desirable in industry as well as in academia.

The pivaloyl chloride\dimethylformamide complex is found to be an attractive reagent system for smooth conversion of primary, secondary, allylic, homoallylic, and

benzylic alcohols into chlorides. It is a mild, relatively non-toxic, and inexpensive reagent system. When alcohols are treated with a mixture of pivaloyl chloride/DMF in dichloromethane, alkyl chlorides are formed in moderate to good yields as depicted in Figure 13.

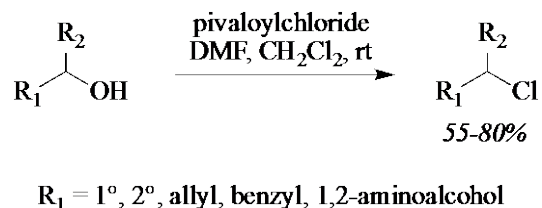


Figure 13. Pivaloyl chloride-mediated alcohol activation.

The reactive intermediate in this reaction, a Vilsmeier-Haack-type complex, adds to the hydroxyl group of the alcohol, forming a cationic species. Nucleophilic attack of the chloride ion on the cationic species by $\text{S}_{\text{N}}2$ kinetics produces the corresponding chloride compounds. This mechanism is shown in Figure 14.³⁹

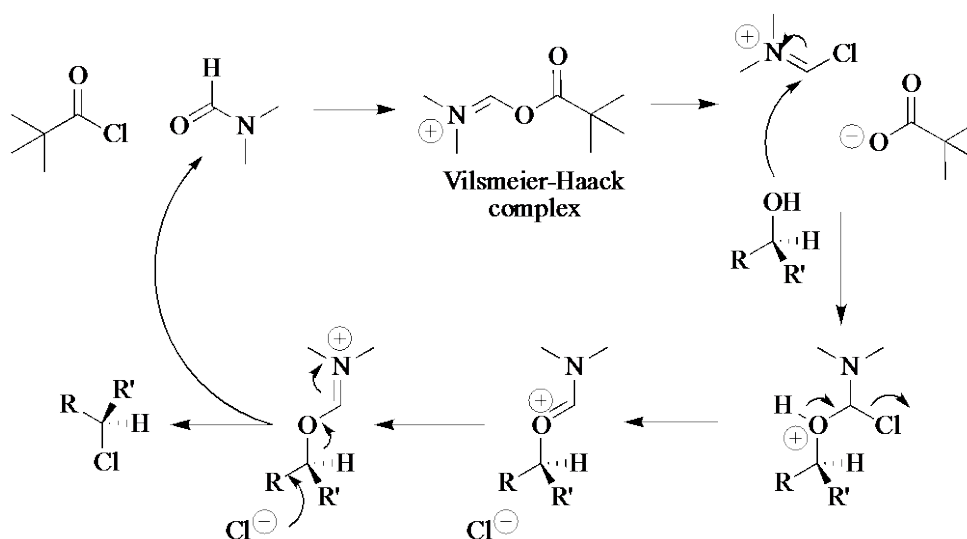


Figure 14. Pivaloyl chloride-mediated alcohol activation mechanism.

Alkali metal iodides in conjunction with Lewis or Brønsted acids can function as efficient reagent systems for the conversion of alcohols to alkyl halides. For example, halogenated aluminates, AlCl_3 , can be used as efficient reagents for the conversion. AlCl_3 has advantages over other metal halides such as commercial availability and low cost. The reaction proceeds by activation of the hydroxyl group of the alcohol by the strong Lewis acid AlCl_3 . Figure 15 describes a possible mechanism for this conversion. In this reaction, AlCl_3 reacts with the OH bond of the alcohol and leads to the formation of an intermediate that decomposes either concertedly by an $\text{S}_{\text{N}}2$ -type mechanism or by forming a carbocation following $\text{S}_{\text{N}}1$ -type kinetics and forming the corresponding alkyl chloride. The regenerated aluminum salt precipitates from the reaction and can be separated by simple filtration. This feature is attractive because the amount of waste disposal typically produced by traditional chlorination reactions can be reduced.⁴²

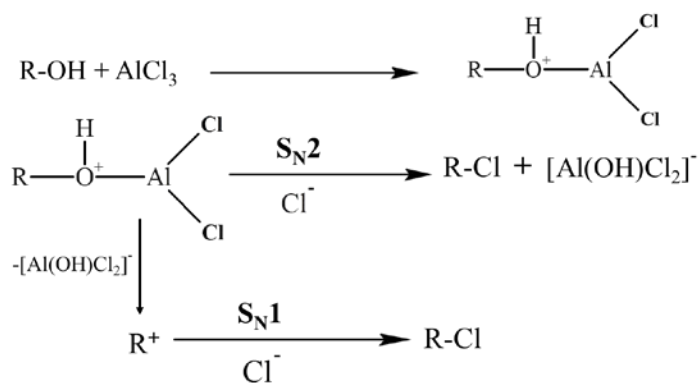
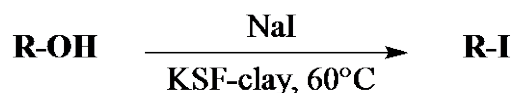


Figure 15. Chlorination of alcohols via the Lewis acid AlCl_3 .

Tajbakhsh and coworkers in 2005 reported a simple and efficient procedure for the conversion of alcohols to alkyl halides. Treatment of alcohols with NaI supported on KSF clay under mild conditions can produce the corresponding iodides as shown in Figure 16. The KSF clay most likely acts as a mild Lewis Acid in the procedure.



R = alkyl, allyl, benzyl

Figure 16. Corresponding iodides produced by treatment of alcohols with NaI supported on KSF clay.

Phosphorus Chemistry

Reactions coupled with conversion of phosphorus(III) compounds to phosphorus(V) compounds have been widely applied in organic synthesis. Quaternary phosphonium intermediates are believed to be involved in these types of reactions.⁴ Because of the wide variety of reactions, phosphorus-containing compounds play a significant role in chemistry and biological sciences. The high nucleophilicity of phosphine compounds and the ability to adopt different oxidation states are two important features of phosphorus-containing reagents. The Mitsunobu reaction and Appel reaction are two representative examples employing this type of reagent. van Kalker, Leenders, Hommersom, Rutjes, and van Delft⁴³ noted that phosphorus-mediated reactions are attractive owing to their broad substrate scope and mild reaction conditions.

Mitsunobu Protocol

The intermolecular dehydration reaction occurring between alcohols and acidic components on treatment with diethylazodicarboxylate (DEAD) and triphenylphosphine was first described by Oyo Mitsunobu.⁴⁴ The reaction takes place under mild conditions with complete inversion of the alcohol hydroxyl group configuration, indicating the overall mechanism follows S_N2-type kinetics. This reagent system is widely utilized in

the synthesis and transformation of various kinds of organic compounds. The Mitsunobu reaction falls under the category of redox reactions in which the DEAD is reduced to hydrazinedicarboxylate while triphenylphosphine is oxidized to triphenylphosphine oxide.

In the Mitsunobu reaction, alcohols are activated by the formation of alkoxyphosphonium ions. This reaction is carried out at room temperature or below; the solvent used is an anhydrous polar aprotic solvent such as tetrahydrofuran.

The reaction is believed to proceed through a four step mechanism as shown in Figure 17. The first step includes the addition of triphenylphosphine to diethyl azodicarboxylate, giving a quaternary phosphonium salt (**15**). The second step is protonation of the produced phosphonium intermediate. The third step forms an alkoxyphosphonium salt (**16**) through the addition of an alcohol substrate. The final step is the nucleophilic substitution reaction of the resulting species, displacing the triphenylphosphine oxide leaving group.⁴

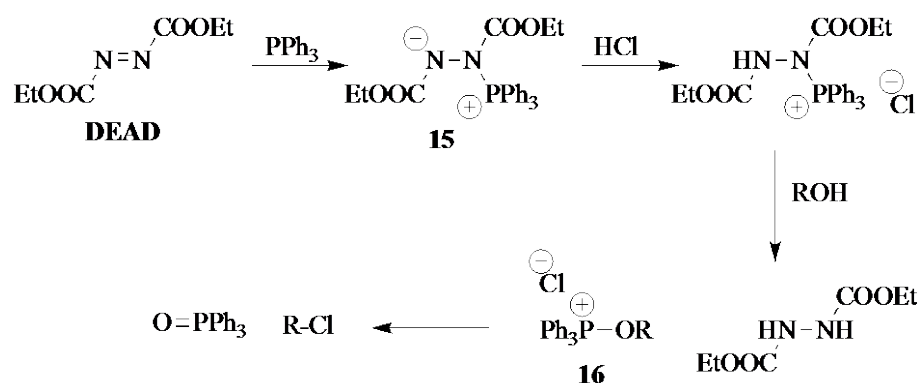


Figure 17. Postulated mechanism for the Mitsunobu reaction.

The Mitsunobu reaction provides a useful synthetic method for many products, but the resulting reaction mixture containing the product and byproducts such as triphenylphosphine oxide and hydrazine dicarboxylate as well as unreacted starting materials complicates the use of this method. Removal of these byproducts requires additional processing often including chromatography. In addition to the high cost, the typically used starting material in the Mitsunobu reaction, DEAD, can be explosive and its hydrazine byproduct is toxic. Thus the reaction requires care in reagent handling as well as disposal. Moreover, the product purification is complicated because of the amount of waste typically produced by the Mitsunobu reaction. For these reasons, commercial use of the Mitsunobu reaction has been limited.¹⁰

Alternative reagent systems have been introduced to resolve the problem of separating products from the byproducts. Kiankarimi, Lowe, McCarthy, and Whitten⁴⁵ reported an improved procedure for the Mitsunobu protocol that uses diphenyl-2-pyridylphosphine and di-*tert*-butylazodicarboxylate. These reagents and their byproducts are either soluble during acidic workup or are converted to gaseous byproducts and water soluble materials on treatment with an acid. For instance, treatment of the commercially available *tert*-butyl azodicarboxylate with mineral acids results in rapid decomposition to give carbon dioxide and nitrogen. Thus, the problem of separating products from the byproducts is solved.

Another method developed to facilitate easier purification is based on incorporating the starting material triphenylphosphine into a resin polymer. The use of polystyrene-supported triphenylphosphine can enable the isolation of triphenylphosphine

oxide by simple filtration techniques.⁴⁶ Reduction of the polymer supported triphenylphosphine oxide can regenerate the triphenylphosphine for future use.

Another method that further developed the Mitsunobu reaction was introduced by Firouzabadi, Iranpoor, and Ebrahimzadh.⁴⁷ Triphenylphosphine was combined with N-halosaccharine. It would be expected that the interaction of triphenylphosphine with N-halosaccharine would generate the halophosphonium salt as the reactive phosphonium species in the same manner as in the Mitsunobu reaction. This transformation is carried out at room temperature under mild conditions. The reaction and its mechanism are illustrated in Figures 18 and 19.⁴⁷

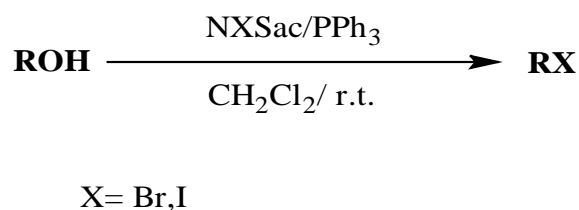


Figure 18. Developed Mitsunobu reaction.

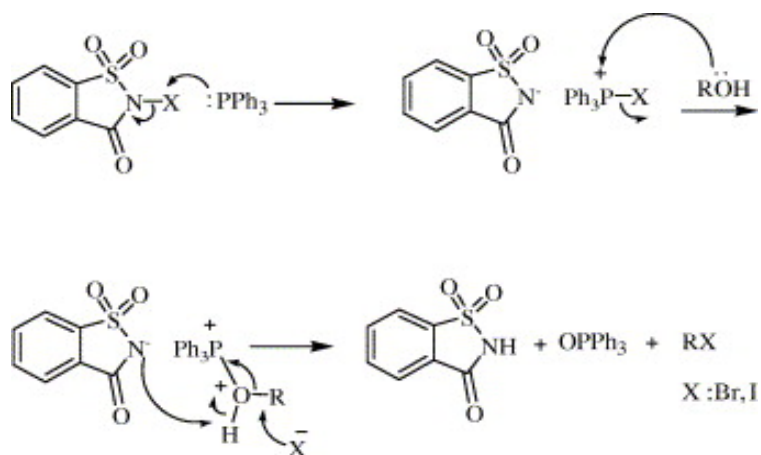


Figure 19. N-Halosaccharine mediated halogenation of alcohol mechanism.

Appel Reaction

The Appel reaction is an organic reaction that converts alcohols to the corresponding stereochemically inverted halides with the involvement of halophosphonium salts. Typically, the use of the triphenylphosphine/carbontetrahalide complex provides a facile means of purifying the desired alkyl halide from the phosphine oxide byproduct. This reagent system has found a widespread application in halogenation reactions and has become a widely utilized method to achieve the alcohol to alkyl halide transformation. The reaction is very convenient except that it is often carried out at reflux temperatures and is found to produce stoichiometric amounts of byproducts that need to be disposed of.⁴⁶

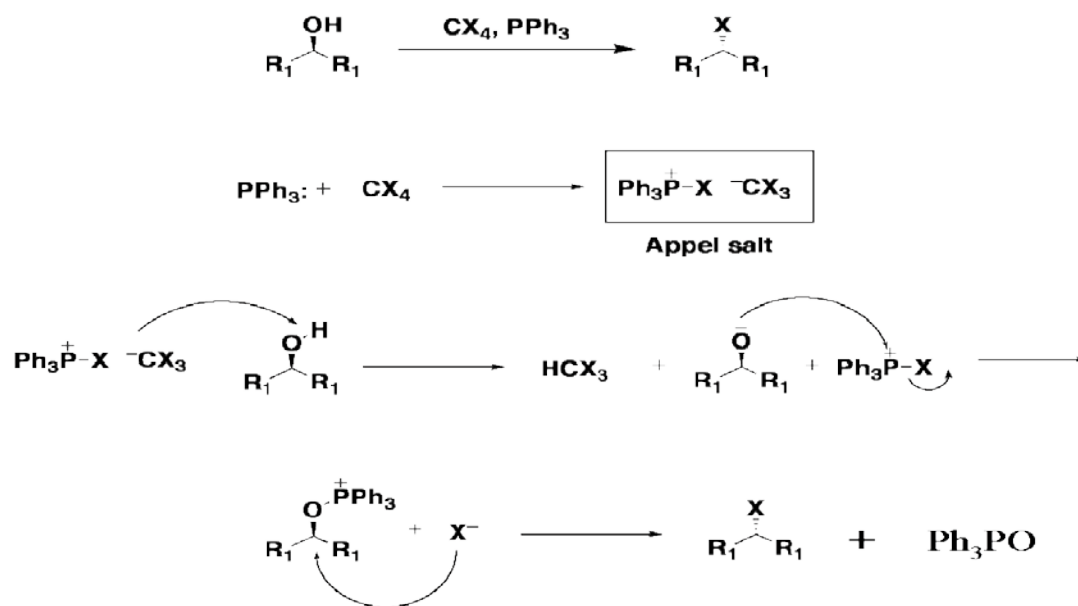


Figure 20. Appel reaction mechanism.

The Appel reaction involves formation of chlorophosphonium ions salts (the so-called Appel salts) via the halogenation of triphenylphosphine by carbon tetrachloride. The hydroxyl group of the alcohol then attacks the chlorophosphonium ions, releasing the halide leaving group. In an S_N2 fashion, the halide subsequently attacks the carbon, displacing the triphenylphosphine oxide leaving group and resulting in the final alkyl halide product with inverted stereochemistry. The mechanism of this reaction is outlined in Figure 20.⁴

One of the drawbacks to the use of this reagent system is the co-production of stoichiometric amounts of the triphenylphosphine oxide byproduct, which makes it difficult to purify the desired halide product. As mentioned above, one solution to this purification is the use of polymer-supported triphenylphosphine. Another solution involves replacing the triphenylphosphine typically used in Mitsunobu and Appel reactions with an alternative phosphine source whose oxide byproduct can easily be separated from the halide product. For example, 1,2-bis(diphenylphosphino) ethane, abbreviated as diphos, in methylene chloride as a solvent can be used as an alternative phosphine source. The resulting phosphine oxide precipitates from the reaction and can be readily removed by filtration.⁴⁸

The problem that triphenylphosphine oxide possesses a polarity that is very similar to the alkyl halide product of the reaction has been addressed. In fact, many strategies have been developed to remove the phosphine oxides from the reaction mixture and thereby eliminate any purification issues. Toto and Doi⁴⁶ investigated the use of bifunctional tertiary phosphines to halogenate primary and secondary alcohols using carbon tetrachloride and the solid bifunctional alkyldiphenylphosphine; 1,3-

bis(diphenylphosphino)propane (2-PEDP). Using the 2-PEDP reagent allows the removal of all phosphorus-containing products; excellent yields of the product alkyl halide were obtained with only minor purification. Therefore, using this reagent system enabled the ease of product isolation, leading to an efficient procedure for halogenation reactions of alcohols.

Improvements in both reaction times and product isolation methods have been reported. For example, triphenylphosphine oxide is often regarded as an unreactive molecule. However, *in situ* generation of chlorophosphonium ions from triphenylphosphine oxide is possible despite the strength of the phosphorus-oxygen double bond. Denton et al.⁴⁹ developed a procedure that made the active intermediate in the Appel reaction catalytically accessible from the byproduct triphenylphosphine oxide Figure 21. Thus, triphenylphosphine oxide becomes a catalyst instead of being a waste byproduct.

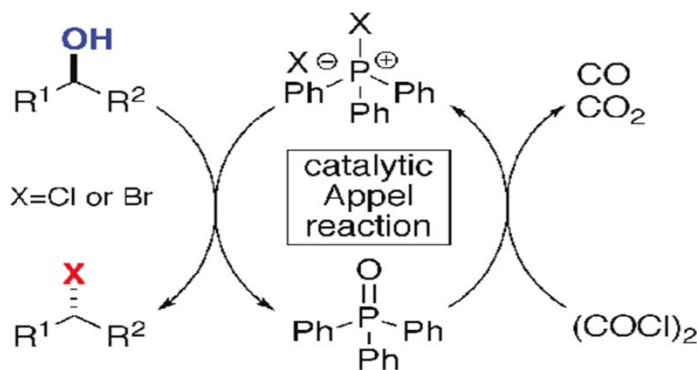


Figure 21. Cleavage of the phosphorus-oxygen double bond forming two carbonyl groups.

This occurs by the activation of the triphenylphosphine oxide by using oxalyl chloride, giving an acylphosphonium intermediate that can be converted to the chlorophosphonium salt by the loss of carbon monoxide and carbon dioxide. This procedure applies oxalyl-mediated chlorophosphonium regeneration from the byproduct triphenylphosphine oxide. Oxalyl chloride (COCl_2) is used as the consumable stoichiometric reagent for the Appel halogenation reaction. The cleavage of the phosphorus-oxygen double bond forms two carbonyl groups, which will be converted to carbon monoxide and carbon dioxide. This conversion was confirmed to be effective by the chlorination of decanol in CDCl_3 shown in Figure 22.

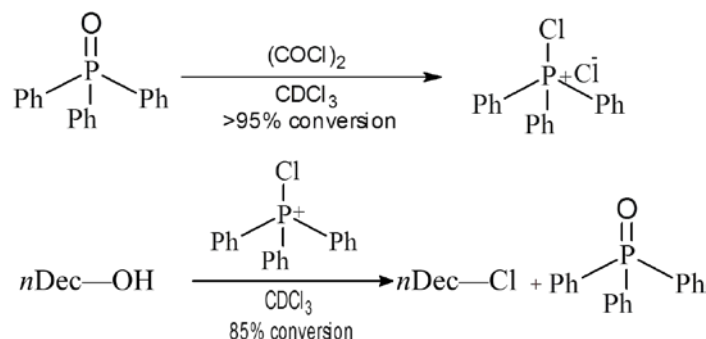


Figure 22. Chlorination of decanol.

Cyclophosphazenes have not only been in use as precursors for many inorganic polymers but also for the formation of unique heterocyclic frameworks that are useful for several applications. For example, reactions of carbaphosphazene with dimethylformamide as shown in Figure 23 afford an efficient conversion of alcohols to their corresponding chlorides at room temperature. The reaction proceeds through the

formation of alkoxyulfonium and imidinium salts of the carbaphosphazene as possible intermediates.⁵⁰

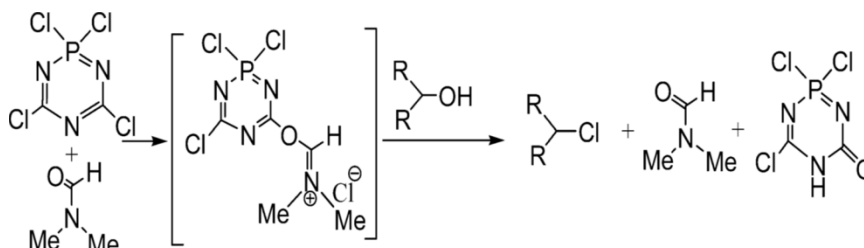


Figure 23. Reactions with carbaphosphazenes.

Hamid, Slatford, and Williams⁵¹ provided an alternative method for activation of alcohols by converting them to other functionality. This alternative pathway involved the temporary oxidation of the alcohols to their aldehydes or ketones since carbonyl compounds have a much wider range of reactivity than alcohols. The additional reactivity of carbonyl compounds over alcohols was exploited by different ways, include imine formation and then reduction to an amine, alkene formation and reduction to alkane, or enolization, followed by reduction back to a functionalized alcohol (see Figure 24).⁵¹

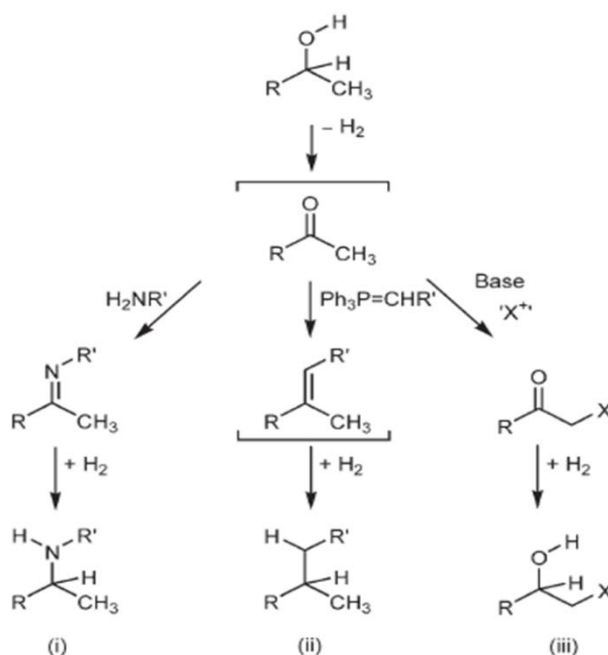


Figure 24. Alternative pathway for alcohol activation.

Silicaphosphine (silphos), $[\text{P}(\text{Cl})_{3-n}(\text{SiO}_2)_n]$, is a heterogeneous reagent capable of converting alcohols to their halides in high yields. This reagent in the presence of liquid bromine or solid iodine can convert alcohols and thiols to their corresponding bromides or iodides in refluxing acetonitrile (CH_3CN) as shown in Figure 25. The big advantage of this method over others is the ease of separation of the byproduct, silphos oxide, by simple filtration.⁵²

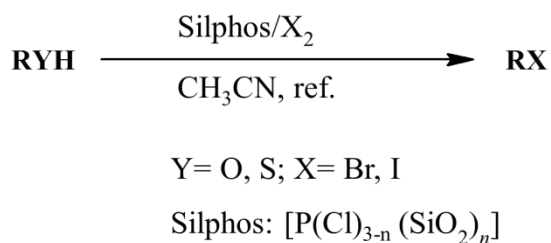



Figure 25. Converting alcohols and thiols to iodides and bromides.

METHODOLOGY



Xanthone + $\text{SOCl}_2 \longrightarrow$ 9,9-Dichloroxanthene (DCX)

reaction can be applied to xanthenes that are part of larger macromolecules. For example, the starting material, xanthone, could be part of a resin polymer. Then, halogenation with thionyl chloride would provide a polymer-supported chlorinating agent. The first step would be to bind a peptide resin polymer to xanthone using, for example, aluminum trichloride via an intermolecular Freidel-Crafts alkylation. The polymer-bound xanthone could be treated with thionyl chloride (SOCl_2) to make polymer-bound 9,9-dichloroxanthene. Addition of an alcohol to this activated resin would give the corresponding alkyl chlorides. Figure 27 illustrates these reactions.

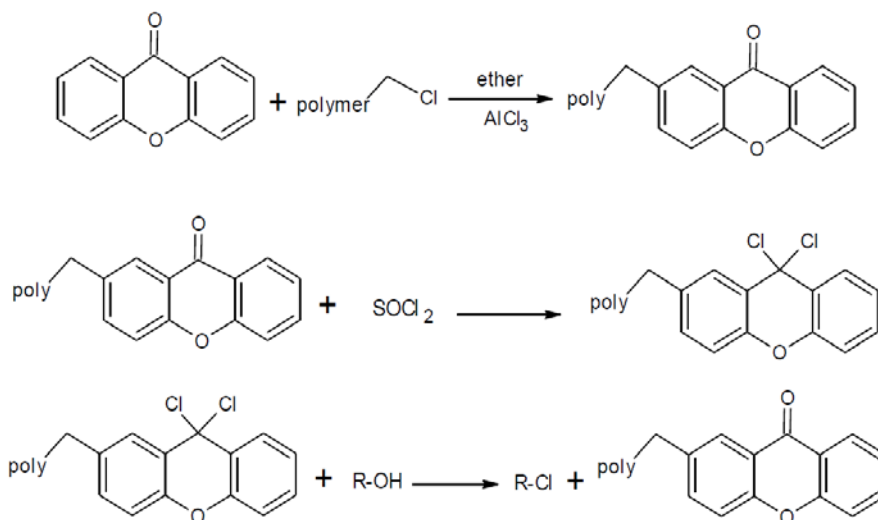


Figure 27. A halogenation reaction for a polymer-bound xanthone.

In the project reported here, 9,9-dichloroxanthene was not converted to a polymer-supported agent. It was instead diluted with toluene to the appropriate concentrations for evaluation. A stock solution was refrigerated to be used as needed for the dilutions. The stock solution and all dilutions were destroyed and re-made every two weeks. This was done to ensure the dichloroxanthene had not decomposed before studying its reaction with other compounds. Alcohols, as dilute solutions in toluene, were then mixed with the diluted solutions of chlorinating reagent; 9,9-dichloroxanthene.

A reaction between the dichloroxanthene and the alcohol proceeded by conversion of the alcohols into xanthene ethers making them highly activated toward nucleophilic displacement by liberated chloride ion. The kinetics of the halogenation reaction were explored by using Infrared and UV-vis spectroscopy.

The halogenation reaction of an alcohol can be monitored by observing a change in the intensity of the IR absorbance of the alcohol in this region. As the reaction proceeds, this signal disappears, indicating the alcohol has reacted and is no longer

present in the reaction mixture. When the alkyl halide is formed, the OH peak will disappear, indicating that the alcohol has converted into an alkyl halide. Therefore, the conversion of the alcohols to the corresponding alkyl halides can be confirmed by using FT-IR. In the present study, a dilute solution of the alcohol was injected into an IR cell and the appropriate amount of diluted chlorinating reagent was then added to give a molar ratio of 1:1. By comparing the absorbance at 3300 cm^{-1} of the alcohol before and after the mixing, it was obvious that the chlorination reagent was effective.

Primary, secondary, and tertiary alcohols were investigated by this method. The primary alcohol chosen for analysis was 1-butanol, the secondary alcohol was 2-butanol, and the tertiary alcohol was 2-methyl-2-butanol. These alcohols were chosen because they are soluble in toluene at the concentrations used in the study. In addition, these alcohols were chosen because they do not possess spectroscopic signals that overlap the region of data analysis. The ready availability and inexpensive cost of the alcohols made them ideal choices for the study of this reaction.

The reaction, unfortunately, was too fast to be evaluated by FT-IR. This was due to either problems of diffusion of the dichloroxanthene through the alcohol solution in the solution cell and/or to the rapid kinetics of the reaction. Attempts were made to dilute the alcohol and dichloroxanthene in an effort to observe the reaction in the absence of the diffusion, but this did not result in any useful information. As the dilution of the solution progressed, the absorbance intensity decreased. Eventually, the OH absorption was too small to be observed, yet the reaction still appeared to be as fast as the diffusion process.

In the present research, UV-Vis spectroscopy was used to monitor the halogenation reaction. Because 9,9-dichloroxanthene is a colored solution (green-

brownish), it was a good UV-vis reagent. Toluene solutions of xanthone do not possess the same color. Several concentrations of primary, secondary, and tertiary alcohols were prepared and mixed with dichloroxanthene. A 0.00021 M toluene solution of 9,9-dichloroxanthene was first injected in a quartz cuvette, the absorbance at 412 nm measured, and then the appropriate amounts of the diluted toluene solutions of the alcohols were added. The reaction was repeatedly done with different xanthene: alcohol ratios. UV-vis allowed using lower concentrations than IR because the absorbance of UV-vis light at this wavelength had a greater molar absorptivity than the OH absorbance in the IR spectrum. Therefore, the concentration problem was solved by using UV-vis spectroscopy.

As noted before, the dichloroxanthene possesses an absorption in the UV-vis spectrum at 412 nm. This signal was present in the dichloroxanthene but absent in the xanthone product. Therefore, the reaction was monitored by observing a change in the absorbance at this wavelength. In addition to the high concentrations conflict in IR, mixing of the two samples was incomplete in the thin IR cell. That diffusion of the two reagents in the UV-vis still existed, though it was hypothesized that the solutions could be diluted enough to slow the reaction but still present an observable signal. In the future, to completely avoid the problems associated with mixing, it should be possible to run the reaction using stop-flow techniques.

Beer's Law

The fundamental relationship between an absorbance and concentration is described by the Beer-Lambert Law (Beer's Law). Beer's Law defines the relationship between absorbance (A) and concentration (c). It states that the absorbance of a

substance in a solution is directly proportional to the concentration of that solution as seen in Equation 2.⁵³

$$A = \epsilon b c \quad (2)$$

where ϵ is molar absorptivity ($\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$),

c is molar concentration (mol dm^{-3}), and

b is path length (cm).

Beer's Law is valid for only relatively low concentrations when all of the absorbing species in the sample act independently of each other.²⁸ By plotting the absorbance against concentration, a linear plot is obtained.⁵³ In the research conducted here, different concentrations of the dichloroxanthene were prepared, the UV-vis absorbance at 412 nm was measured, and then was plotted. A linear relationship was observed when small concentrations were used (see Figure. 28).

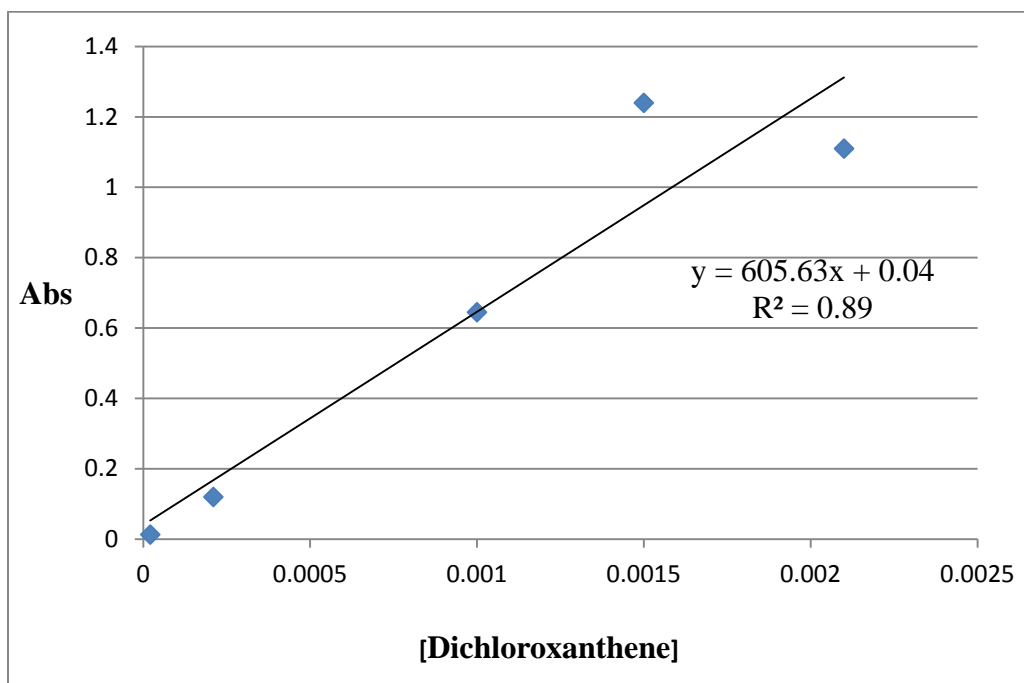


Figure 28. Beer-Lambert curve.

Chemical Kinetics

Measurements of the absorption or emission spectra as a function of time can give quantitative analysis for several compounds that are participating in the reaction.³⁰

Knowing how fast reactions are is a topic of central importance in industrial chemistry as well as in biological research.⁵⁴ The rate of a chemical reaction is expressed as a change in concentration of some species with time. Therefore, the dimensions of the rate must be those of concentration divided by time such as moles/L. s. The rate can be expressed in terms of the disappearance of **A** or the appearance of **B** for the given reaction 3.¹⁷



Kinetics also shed light on the reaction mechanism. Chemical kinetics studies can be used to support either S_N1 or S_N2 reaction mechanisms. Kinetic studies involve investigation of the factors that influence the reaction rates. To use kinetic evidence, first the rate determining step for a particular reaction should be examined. The rate determining step for the S_N1 reaction is the formation of carbocation from the substrate. In the S_N1 mechanism, the rate of reaction should be proportional only to the concentration of substrate (Equation 4). In this case, the reaction is first order for the substrate and zero order for the nucleophile, which means that the reaction rate is only dependent on the concentration of the substrate but not the nucleophile. On the other hand, the rate determining step for the S_N2 involves the attack by the nucleophile on the substrate. Therefore, the reaction rate is proportional to the concentration of the substrate and the nucleophile. The reaction is second order overall, yet still first order in the substrate.¹⁴

$$\text{Rate of reaction} = -d[\mathbf{A}]/dt = k [\mathbf{R-L}] \quad (4)$$

$$\text{Rate of reaction} = -d[A]/dt = k [R-L][Nu] \quad (5)$$

where [R-L] is the concentration of the alkyl group bearing the leaving group.

Smith and March¹⁵ wrote that there is kinetic evidence wherein the S_N2 reaction should be second order overall and satisfy the rate equation (see Equation 5). Another piece of evidence that the S_N2 mechanism has is the inversion of configuration when substitution occurs at a chiral carbon atom.¹⁵

First-Order Reactions

The rate of a first-order reaction is directly proportional to the logarithm of the concentration of one species and not dependent on the concentration of any other species present in the reaction vessel (see Figure 29).¹⁷

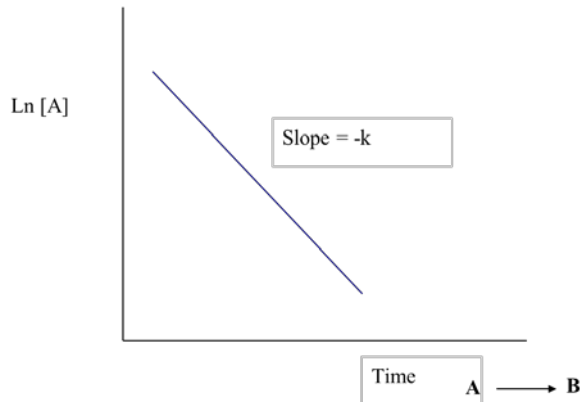


Figure 29. First-order reaction.

Second-Order Reactions

Second-order reactions are of two types: those that are second order in a single reactant and those that are first order in each of two reactants. The reaction studied in this work should behave as if it were first order in each of the two reactants and second-

order reaction overall. A plot of the reciprocal of the concentration versus time gives a straight line with slope of k for second-order reaction in a single reactant (see Figure 30).

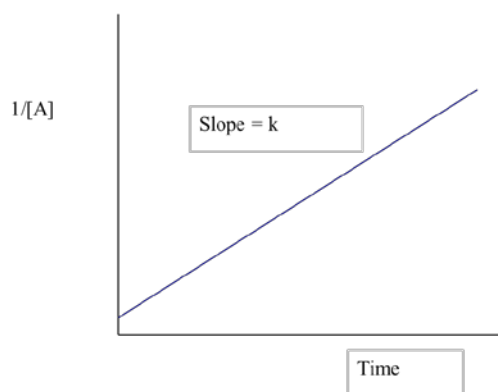


Figure 30. A plot of reciprocal of concentration versus time (second-order plot).

Zero-Order Reaction

A zero-order reaction is a reaction in which the rate is independent of the concentration of reacting substances.⁵⁵ For a zero-order reaction, a plot of concentration versus time gives a straight line with slope of $-k$. This plot is expressed in Figure 31.

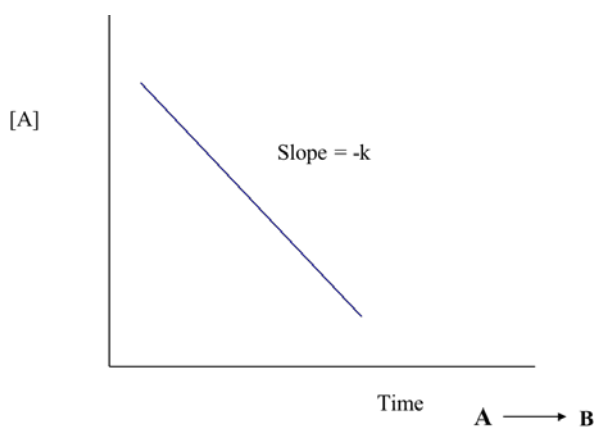


Figure 31. Concentration versus time (zero-order plot).

Dilution Effects

Using the UV-vis spectrometer, the absorbance of dichloroanthene at 412 nm was measured, and then toluene was added instead of the alcohol solution to examine the effect of dilution on the halogenation reaction using the same volumes. The relative percent drop in the absorbance as a function of time was then subtracted from each of the kinetic runs for the reaction of dichloroanthene and alcohol. The resulting kinetic data would then show the appropriate values of the reaction as they occurred without dilution. Those data were analyzed for this study.

The different absorbance values of dichloroanthene were converted to concentration values using Beer's law. Three graphs of [dichloroanthene], $1/[\text{dichloroanthene}]$, and $\ln [\text{dichloroanthene}]$ versus time were plotted. Each concentration of dichloroanthene and alcohol was repeated multiple times in an effort to ensure reproducibility of the data.

Data Analysis

Each kinetic run, after subtraction of the dilution effects and conversion to a plot of time versus concentration, was analyzed by creating the plots of concentration versus time (zero order plot), $1/\text{concentration}$ versus time (second-order plot) and $\ln(\text{concentration})$ versus time (first-order plot). Each plot was then analyzed for linearity and the plot that provided the straightest line was chosen as the indicator of the kinetics of that run. Each run was treated separately, the analysis was conducted separately, and then the results compared to provide the answer of reaction order.

Finally, the rate constant for each trial was calculated based on the consensus of the reaction order for all multiples of that trial. The rate constants were then averaged and the standard deviation determined.

CHAPTER IV

RESULTS AND DISCUSSION

Reaction of 9,9-Dichloroxanthene and Alcohols

9,9-Dichloroxanthene was prepared in the laboratory as needed. All other materials, including those used to make the dichloroxanthene, were obtained from Aldrich Chemical Company and used without purification.

Preparation of 9,9-Dichloroxanthene

A roundbottom flask fitted with a water cooled condenser was charged with 2.452 grams of xanthone and 6.00 mL thionyl chloride. A stir bar was added to let the reactants mix for an hour. The mixture was then heated and refluxed for an hour. Then the mixture was fitted with a simple distillation apparatus and distilled to remove the majority of the excess thionyl chloride. At the end of an hour, the reaction mixture was placed on a rotary evaporator and the liquids, including excess thionyl chloride, and any other byproduct of the reaction, were removed under vacuum. The remaining residue, solid 9,9-dichloroxanthene, was then transferred to a brown bottle and diluted to 50 mL volumetric flask with toluene to make a solution that was 0.21 *M* 9,9-dichloroxanthene in toluene. This final product was sensitive to the air and it will convert back to xanthone if it is exposed to moisture. This stock solution was stored in the refrigerator for up to 2 weeks. Aliquots were removed and diluted to the appropriate volume to make the solutions used in this study.

Preparation of Alcohol Solutions

A known volume of each of the pure three alcohols, 1-butanol, 2-butanol, and 2-methyl-2-propanol, was diluted with toluene to prepare a stock solution with a concentration of 0.00100 M. This stock solution was further diluted with toluene to give the solutions used in the study.

Solutions Used for Study

A dilute toluene solution of the 9,9-dichloroxanthene was mixed thoroughly with a dilute toluene solution of an alcohol at the appropriate concentrations and was prepared and studied by IR Spectroscopy and UV-visible spectroscopy. A set of dilutions of each reactant was prepared in attempts to reduce the reaction rate to a point that it could be measured by these spectroscopic techniques.

Infrared Spectra

IR spectroscopy of the product mixture, prepared by combining dilute toluene solutions of the 9,9-dichloroxanthene and alcohols, showed no peaks in the alcohol region ($3600\text{--}3200\text{ cm}^{-1}$) for a series of primary, secondary, and tertiary alcohols, which confirmed that all alcohol functional groups were converted into alkyl halides. The reaction appeared to be quantitative by analysis of the IR spectrum as well. Since the conversion of tertiary alcohols to alkyl halides followed the S_N1 reaction mechanism when using strong hydrohalic acids, the same type of mechanism in the dichloroxanthene case was envisioned. Although the secondary alcohols typically undergo both S_N1 and S_N2 mechanisms, there was some evidence that the replacement of leaving groups by the S_N2 mechanism occurred in this system. In addition, the primary alcohols proceeded by the S_N2 mechanism in the case of the conversion using hydrohalic acids.

Figure 32 shows the IR spectrum of the secondary alcohol, 2-butanol. This alcohol was used as the test case for the use of IR spectroscopy as a tool to measure the rate of the dichloroxanthene reaction. As shown later in this discussion, IR spectroscopy failed to be the suitable technique for determining the rate of reaction. Therefore, the primary and tertiary alcohols were not examined using IR spectroscopy.

An IR cell, with 0.1mm pathlength, was filled with the appropriate dilute solution of 2-butanol in toluene. Then, an appropriate dilute solution of the 9,9-dichloroxanthene was injected into the cell while the IR spectrometer recorded spectra. Figures 32, 33 and 34 show the IR spectra of the secondary alcohol, 2-butanol, during and after the addition, respectively. By comparing the IR spectrum of 2-butanol with its spectrum after the addition of the chlorinating reagent, 9,9-dichloroxanthene, it was obvious that the halogenation reagent was efficient. The 2-butanol was converted completely to 2-chlorobutane as confirmed by the disappearance of the signal in the alcohol region. Changes in the IR absorbance between the two spectra confirmed a structural change in the molecule. The alcohol functional group was no longer present in the reaction vessel and was converted to other functionality. The reaction was repeated multiple times at varying dilutions; but in each case, the reproducibility of the reaction was unable to be verified. Again, because the IR data were not reproducible, they were excluded from evaluation of the reaction mechanism and kinetics.

It appeared that the reaction was too fast to be measured by IR, i.e., the time lapse between the start of the reaction and the completion of the reaction was shorter than the IR data could measure. This was due to either problems of diffusion of dichloroxanthene through the alcohol solution in the solution cell (incomplete mixing) or the rapid kinetics

of the reaction with the relatively high concentrations used in the IR. Attempts were made to dilute the alcohol and dichloroxanthene in an effort to observe the reaction in the absence of diffusion but this did not result in any useful information. Therefore, the only utility of the IR analysis was to verify that the reaction had occurred and that the product, 2-chlorobutane, was the predominant product.

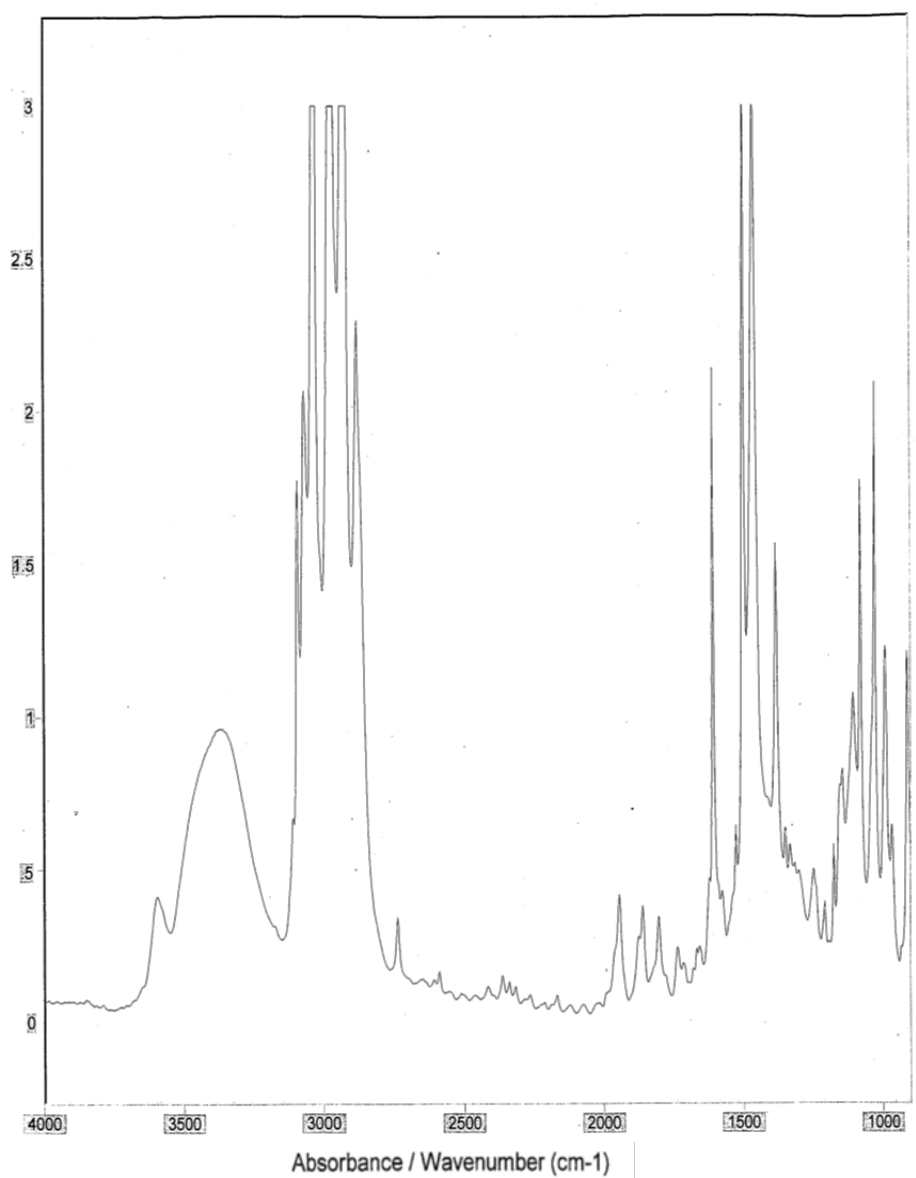


Figure 32. 2-Butanol infrared spectrum.

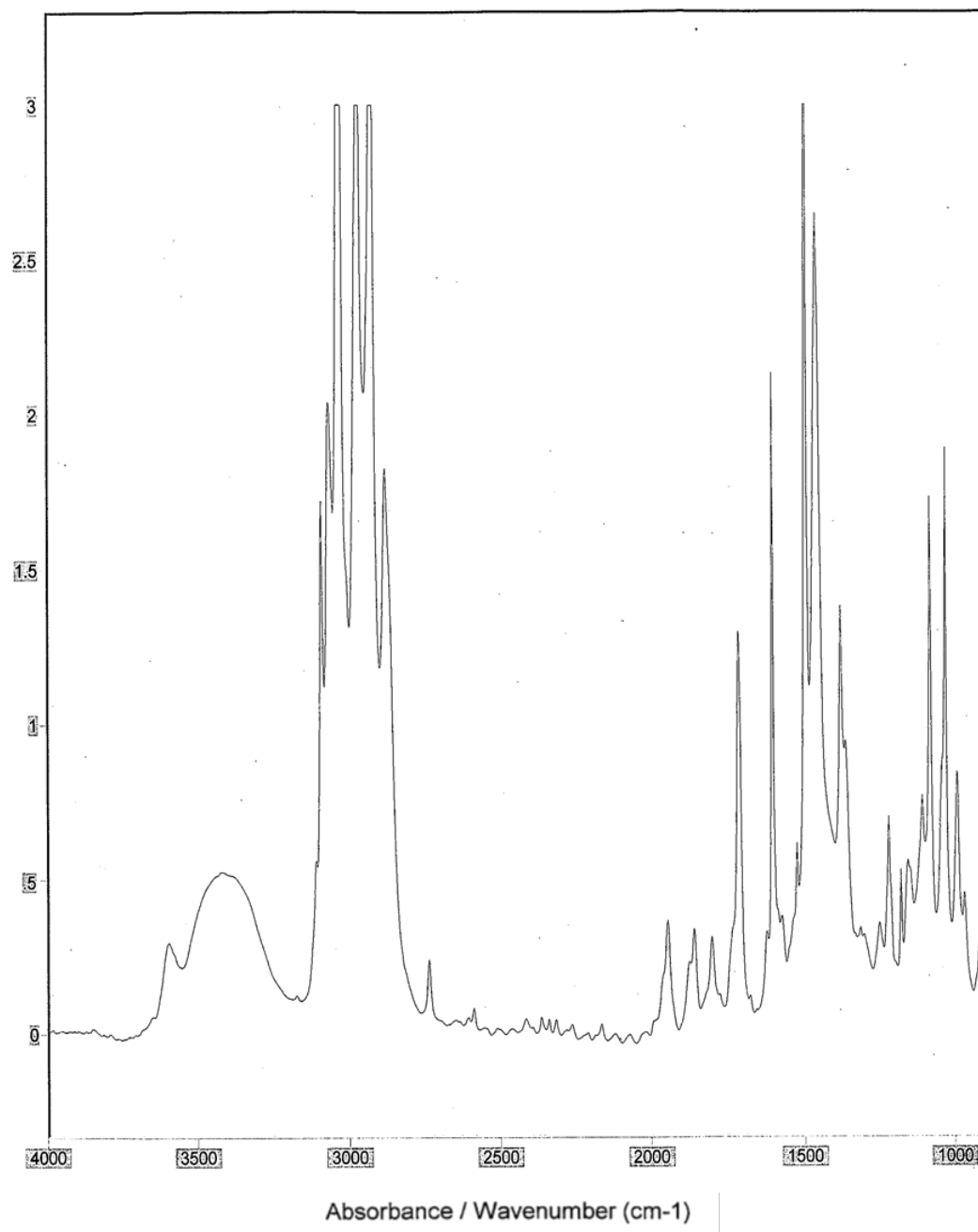


Figure 33. 2-Butanol infrared spectrum during the reaction.

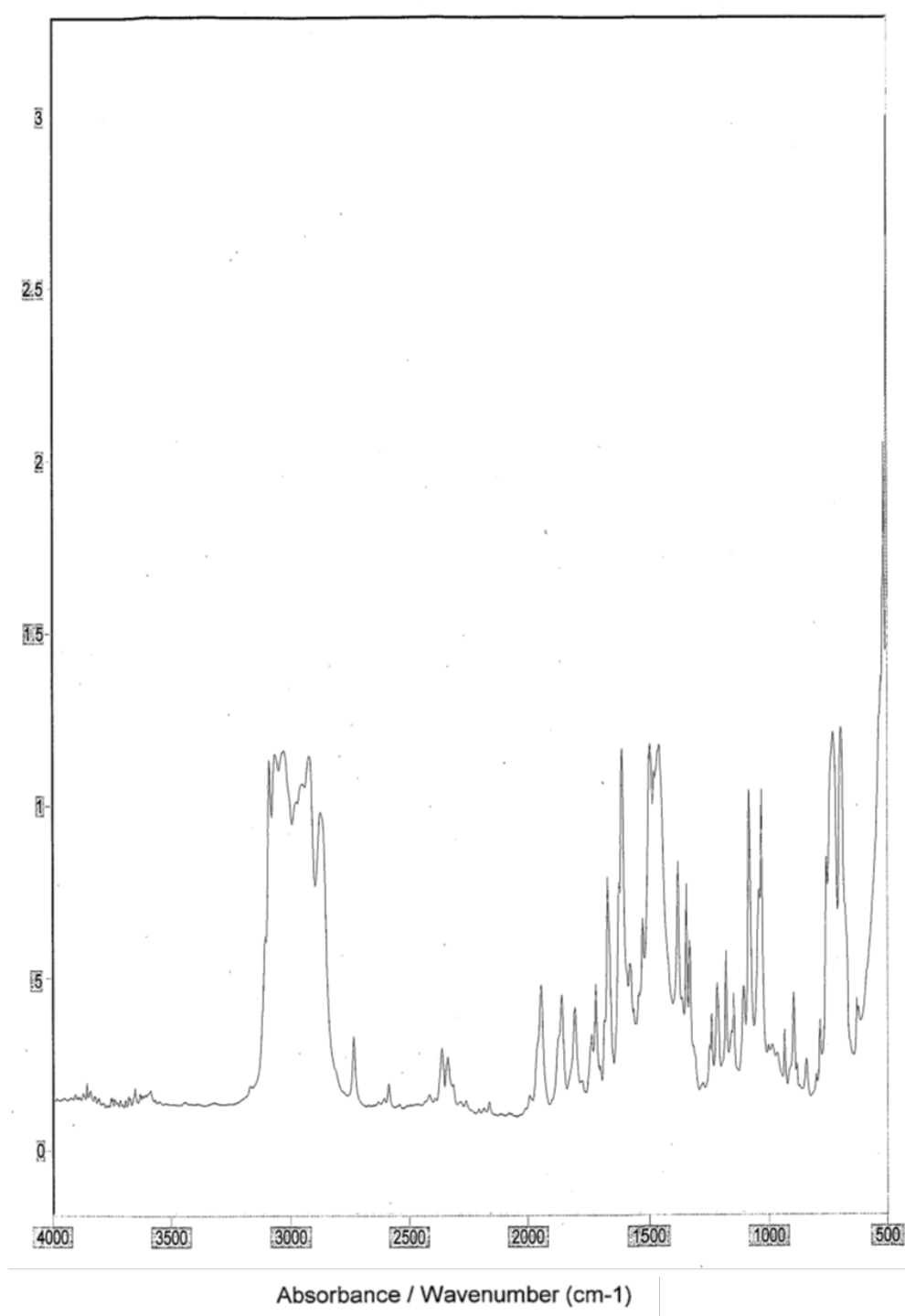


Figure 34. 2-Butanol infrared spectrum after the reaction.

Ultraviolet-Visual Spectra

An alternative choice to using IR spectroscopy for the analysis of the reaction was using UV-vis spectroscopy to monitor the halogenation reaction. UV-vis spectroscopy allowed using lower concentrations than IR because the molar absorptivity of the aryl ring system was greater in the UV-vis spectrum than OH in the IR spectrum.

A dilute solution of xanthone in toluene was made and the UV-vis absorbance of this solution was measured. The xanthone, the end-product of the 9,9-dichloroxanthene in the reaction, was chosen to compare the UV-vis spectrum with the starting 9,9-dichloroxanthene. By knowing the UV-vis spectra of the xanthone product, the reaction was monitored using UV-vis spectroscopy.

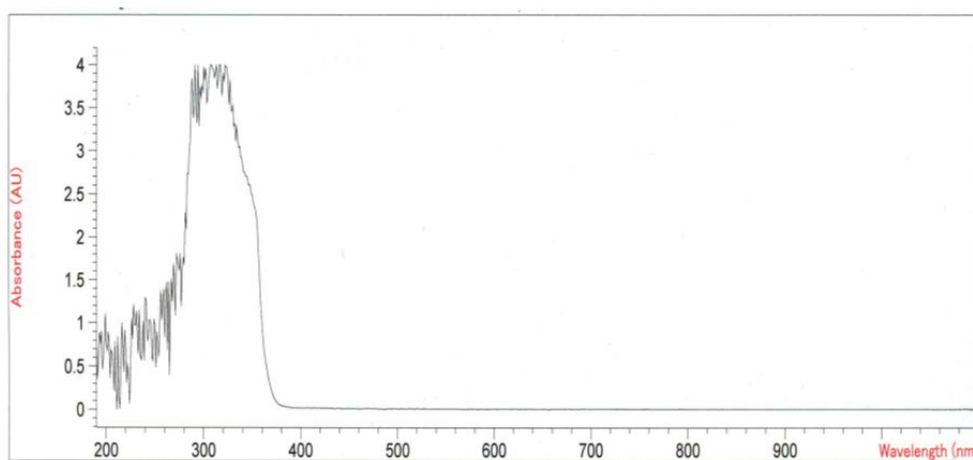


Figure 35. Xanthone ultraviolet visual spectra.

To perform the reaction, 2mL of the appropriate concentration of 9,9-dichloroxanthene in toluene was placed in a quartz cuvette and the spectrum obtained. Then, 1mL of the appropriate concentration of the alcohol was added to the cuvette while the spectrometer

recorded the absorbance at 412nm (see Figure 35). When alcohols were mixed with dichloroxanthene, disappearance of the absorbance at 412nm (due to the presences of dichloroxanthene) occurred, indicating that the dichloroxanthene had been converted to xanthone and alcohols were converted into chlorides. The signal at 412 nm never reached zero in any of the analyses but a significant, rapid decrease was always a feature for the reaction (see Figure 36).

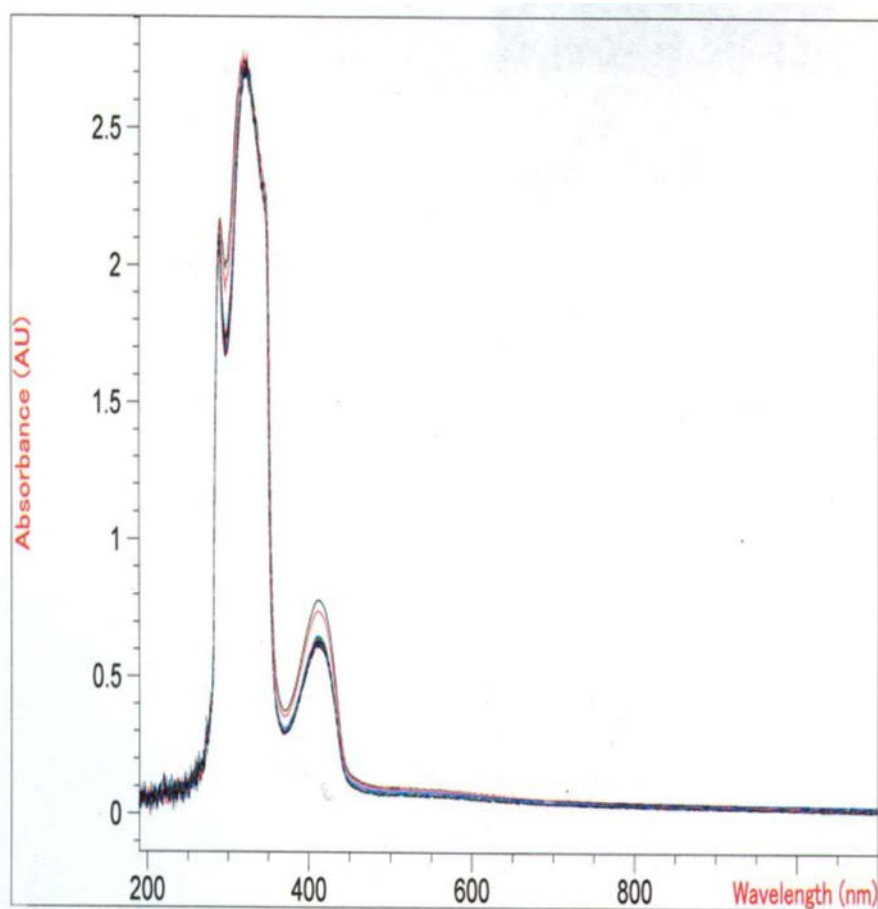


Figure 36. Dichloroxanthene/alcohol ultraviolet visual spectra.

Determining Dilution Effects

After mixing the reactants, not all changes in the absorbance values were due to the reaction between the alcohols and the dichloroxanthene. A portion of this change was due to the dilution of the original dichloroxanthene with a toluene solution of the alcohol. To evaluate the rate of the reaction, the effect of the dilution of the sample and the concomitant reduction in the absorbance of the solution must be removed from the data obtained. The dilution of the sample was evaluated multiple times. Table 1 and the graph in Figure 37 show the trial selected to eliminate the dilution effect.

Table 1: Dilution Effects

Time, s	Abs _(Xanthene)
0	0.87
0.5	0.87
1	0.87
1.5	0.87
2	0.87
2.5	0.87
3	0.85
3.5	0.76
4	0.70
4.5	0.68
5	0.65
5.5	0.62
6	0.61
6.5	0.62
7	0.62
7.5	0.62

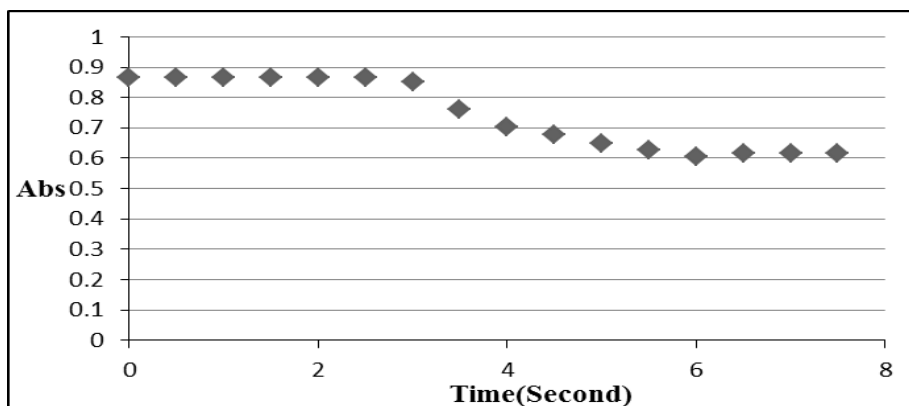


Figure 37. Determining dilution effects.

Verification of the Beer-Lambert Law

A series of 9,9-dichloroanthene solutions was prepared in toluene and the absorbance of each solution was measured using UV-vis spectroscopy. Figure 28 in Chapter III shows the plot of the absorbance at 412 nm of those solutions versus the concentration of dichloroanthene. The relationship of the data over the concentration range was found to be linear.

Determining Reaction Order for a Primary Alcohol, 1-Butanol

Primary alcohols were expected to follow S_N2 reaction mechanisms in this substitution reaction. Thus, the individual orders of reactants in the reaction, based on the standard S_N2 kinetics, should be first-order in each component. The order of the reaction with respect to the alcohol using that technique was prevented due to the inability to observe a change in alcohol concentration as a function of time by IR spectroscopy.

If the concentration of the dichloroanthene was kept large compared to the alcohol, the reaction kinetics would be reduced to a pseudo-first order reaction. To

determine if this was the kinetics observed in the dichloroanthene reaction, UV-vis spectroscopy was employed. Using UV-vis spectroscopy, the order of the reaction with respect to the dichloroanthene was determined. This reaction was monitored by observing a change in absorbance of the reaction mixture with time.

Graphical analysis of the reaction was made to determine the reaction rates. In the reaction of dichloroanthene with 1-butanol, the plot of $\ln[\text{dichloroanthene}]$ versus time was a straight line. Therefore, the reaction was a first-order reaction with respect to the dichloroanthene. The slope of this plot is equal to $-k$ (the rate constant). Figure 38 is a set of figures representing the reaction of dichloroanthene with 1-butanol concentration set at 0.00000100 M .

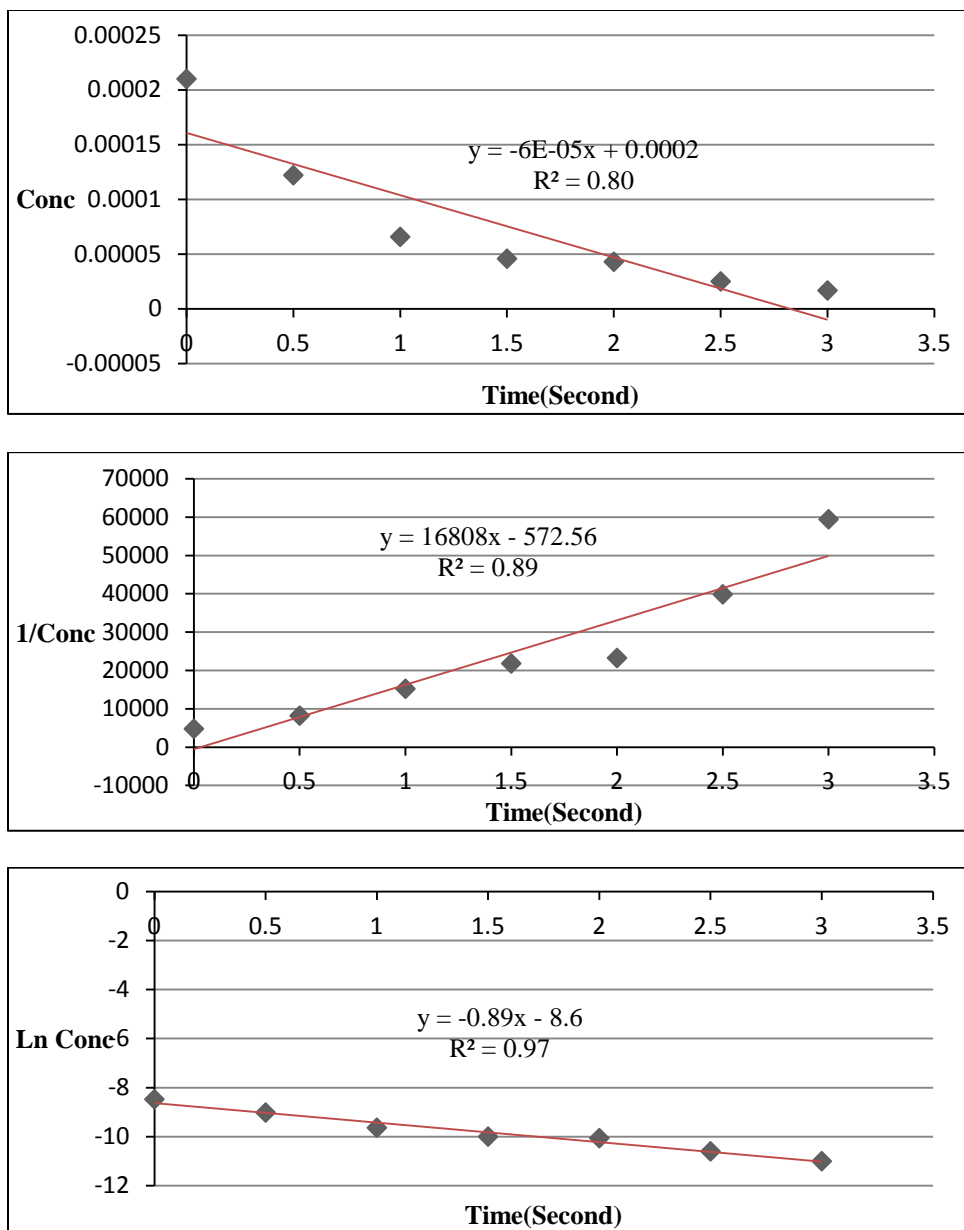


Figure 38. Primary alcohol ($1.00 \times 10^{-6} M$).

The first column in Table 2 is the time the data were collected in seconds. The second column in the table is the absorbance of the original solution. The absorbance at time = 0 seconds is equal to the start of the reaction, where the alcohol has been completely added to the reaction mixture. The third column represents the absorbance of

the dichloroxanthene that was subtracted from the lowest absorbance value, 0.67, in order to let the reaction end at zero absorbance for more accurate data. Column 4 represents the absorbance of the dichloroxanthene when diluted in toluene. Column 5 represents the absorbance values from column 4 but subtracted from the constant absorbance to make it end with zero absorbance values. Column 6 is the absorbance of the reaction after elimination the dilution effects. Then, these absorbance values were converted into concentrations in column 7 using Beer's Law. Columns 8 and 9 were calculated based on the concentrations from column 7.

Table 2: Example Primary Alcohol Reaction Data

Time	Abs		Xanthen	Xanthen-	Abs Dil	Conc	1/Conc	Ln Conc
		Abs-0.065		0.607				
0	0.0834	0.0184	0.851	0.244	0.017	0.00021	4761.49	-8.47
0.5	0.0756	0.011	0.762	0.155	0.010	0.00012	8194.32	-9.01
1	0.0706	0.006	0.703	0.096	0.005	6.58E-05	15204.12	-9.63
1.5	0.0688	0.0042	0.677	0.07	0.004	4.58E-05	21812.04	-9.99
2	0.0684	0.0038	0.648	0.041	0.004	4.30E-05	23241.43	-10.05
2.5	0.0668	0.0022	0.628	0.021	0.002	2.50E-05	39841.15	-10.59
3	0.0660	0.0014	0.608	0.001	0.001	1.68E-05	59422.1	-10.99

Determining Reaction Order for a Secondary Alcohol, 2-Butanol

Secondary alcohols also were also expected to follow S_N2 reaction mechanisms with substitution reactions. As in the reaction with primary alcohols, the order of the reaction should be first in each component in the secondary alcohol conversion. By keeping the concentration of 2-butanol small with respect to the dichloroxanthene, the

order of the reaction with respect to the dichloroxanthene could be determined using UV-vis spectroscopy. Graphical and tabular (see Table 3) analysis was made to determine reaction rates (see Figure 39). For the secondary alcohol, 2-butanol, a linear plot of $\ln[\text{dichloroxanthene}]$ versus time indicated a first order reaction with respect to the

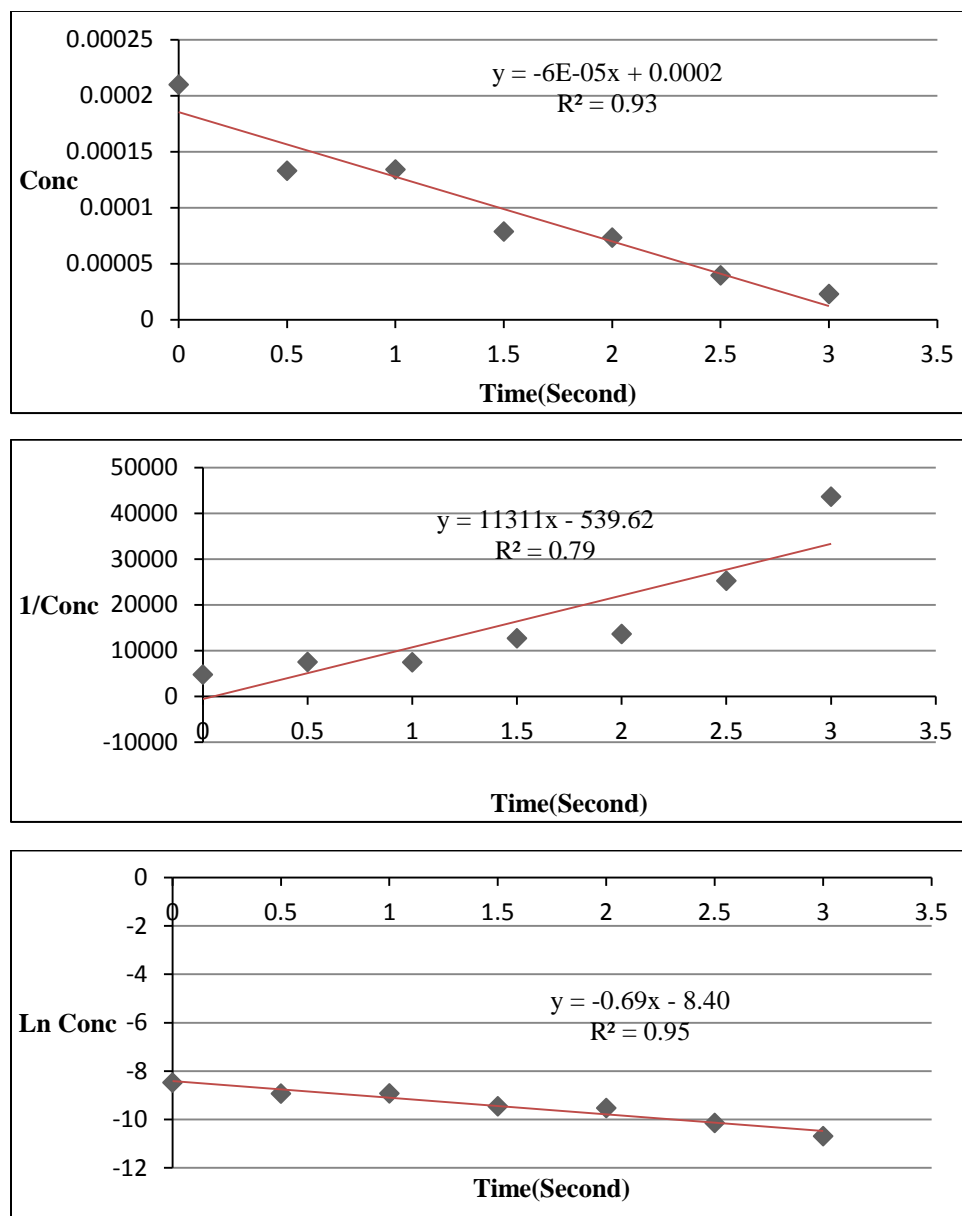


Figure 39. Secondary alcohol ($4.00 \times 10^{-6} \text{ M}$).

dichloroxanthene. The slope of this plot was equal to $-k$ (the rate constant). Therefore, k values were determined for 2-butanol.

The first column in Table 3 is the time the data were collected in seconds. The second column in the table is the absorbance of the original solution. The absorbance at time = 0 seconds is equal to the start of the reaction, where the alcohol has been completely added to the reaction. The third column represents the absorbance of the dichloroxanthene that was subtracted from the lowest absorbance value, 0.67, in order to let the reaction end at zero absorbance for more accurate data. Column 4 represents the absorbance of the dichloroxanthene when diluted in toluene. Column 5 represents the absorbance values from column 4 but subtracted from the constant absorbance to make it end with zero absorbance values. Column 6 is the absorbance of the reaction after subtracting the dilution effects. Then, these absorbance values were converted into concentrations in column 7 by Beer's Law. Columns 8 and 9 were calculated based on the concentrations from column 7.

Table 3: Example Secondary Alcohol Reaction Data

Time	Abs	Abs- 0.1062	Xanthen 0.607	Xanthen- 0.607	Abs Dil	Conc	1/Conc	Ln Conc
0	0.1376	0.0314	0.851	0.244	0.028	0.00021	4761.84	-8.47
0.5	0.1261	0.0199	0.762	0.155	0.018	0.00013	7515.59	-8.92
1	0.1255	0.0193	0.703	0.096	0.018	0.00013	7453.41	-8.92
1.5	0.1177	0.0115	0.677	0.07	0.011	7.87E-05	12700.44	-9.45
2	0.1166	0.0104	0.648	0.041	0.009	7.33E-05	13640.92	-9.52
2.5	0.1118	0.0056	0.628	0.021	0.005	3.95E-05	25268.15	-10.14
3	0.1093	0.0031	0.608	0.001	0.003	2.29E-05	43649.86	-10.68

Determining Reaction Order for a Tertiary Alcohol, 2-methylpropan-2-ol

Tertiary alcohols were expected to follow S_N1 reaction mechanisms in substitution reactions; the order of the reaction should be zero-order in the halogenating reagent and first-order with respect to the alcohol. The reaction of 9,9-dichloroxanthene with 2-methylpropan-2-ol was examined by UV-vis spectroscopy and the data analyzed

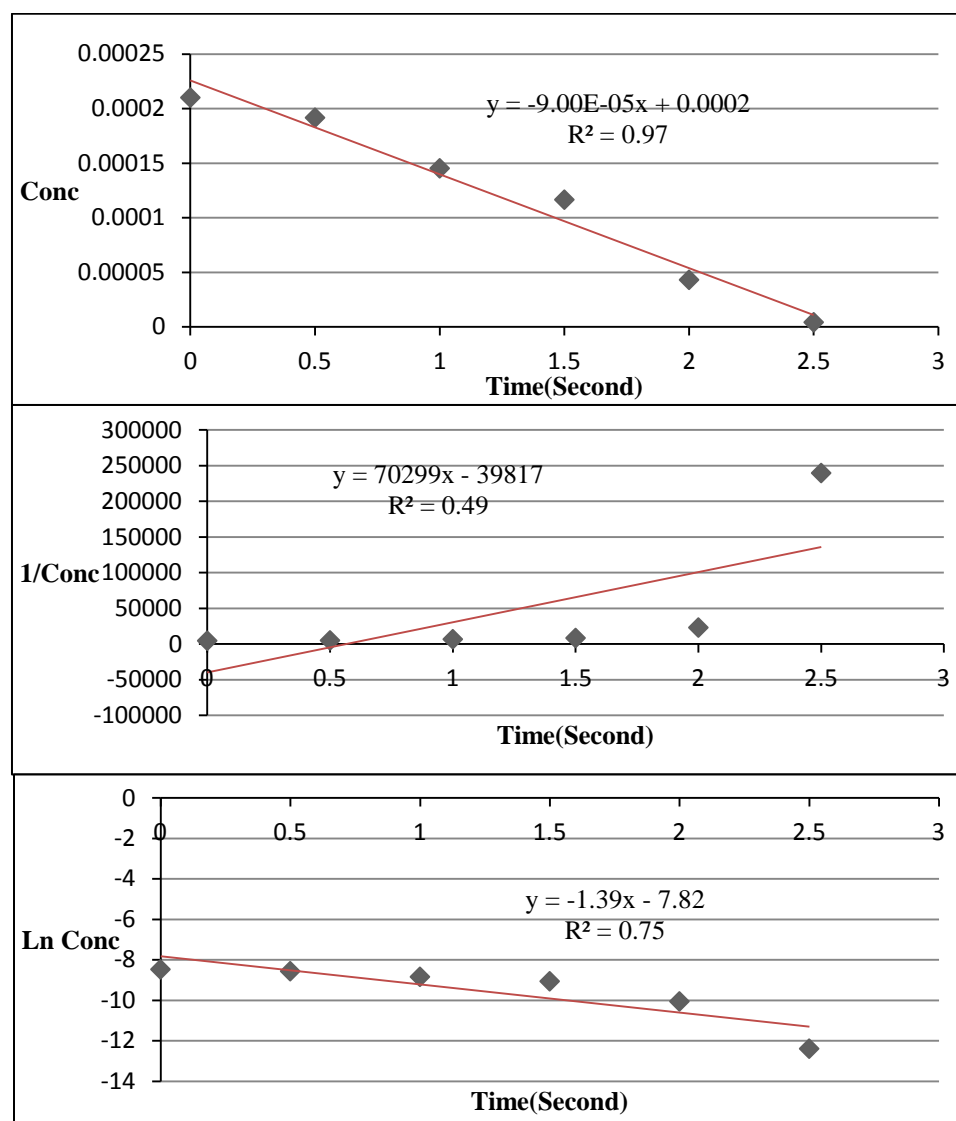


Figure 40. Tertiary alcohol (1.00×10^{-6} M).

to determine the order of the reaction (see Table 4). By examining the graphs in Figure 40, the order of the reaction with respect to the dichloroxanthene was determined. For the tertiary alcohol, 2-methylpropan-2-ol, a linear plot of dichloroxanthene concentration [dichloroxanthene] versus time indicated a zero order reaction with respect to the dichloroxanthene. The slope of this plot was equal to the negative value of k . Therefore, the rate constant of the reaction of dichloroxanthene and a tertiary alcohol was determined.

The first column in Table 4 is the time the data were collected in seconds. The second column in the table is the absorbance of the original solution. The absorbance at time = 0 seconds is equal to the start of the reaction, where the alcohol has been completely added to the reaction. The third column represents the absorbance of the dichloroxanthene that was subtracted from the lowest absorbance value, 0.67, in order to let the reaction end at zero absorbance for more accurate data. Column 4 represents the

Table 4: Example Tertiary Alcohol Reaction Data

Time	Abs	Abs- 0.0569	Xanthen 0.851	Xanthen- 0.607	Abs Dil	Conc	1/Conc	Ln Conc
0	0.0804	0.0235	0.851	0.244	0.023	0.00021	4761.74	-8.47
0.5	0.0782	0.0213	0.762	0.155	0.021	0.00019	5219.62	-8.56
1	0.073	0.0161	0.703	0.096	0.016	0.00015	6886.63	-8.84
1.5	0.0698	0.0129	0.677	0.070	0.013	0.00012	8585.39	-9.06
2	0.0617	0.0048	0.648	0.041	0.005	4.30E-05	23223.15	-10.05
2.5	0.0574	0.0005	0.628	0.021	0.0005	4.17E-06	239667.1	-12.39

absorbance of the dichloroxanthene when diluted in toluene. Column 5 represents the absorbance values from column 4 but subtracted from the constant absorbance to make it end with zero absorbance values. Column 6 is the absorbance of the reaction after subtracting the dilution effects. Then, these absorbance values were converted into concentrations in column 7 by Beer's Law. Columns 8 and 9 were calculated based on the concentrations from column 7.

Repetition of the Reaction

Each reaction was performed multiple times to ensure the reproducibility. Many concentrations of both the dichloroxanthene and the alcohols were prepared. Based on the Beer's Law plot, 0.00021 M of the dichloroxanthene was used. Concentrations higher than the chosen one would not obey Beer's Law. Alcohol concentrations were chosen to be appropriate for reactions with the dichloroxanthene. For example, alcohols were diluted to react with the dichloroxanthene at moderate rates in order for the reaction to be evaluated. The lowest possible concentrations were used to control the reaction rate.

Calculating k Values

For primary and secondary alcohols, k values were calculated from the slope of the $\ln[\text{dichloroxanthene}]$ versus time graph. These values are reported in Tables 5 and 6.

Table 5: Rate Constants for the Primary Alcohol

Primary Alcohol Concentration (M)	Rate Constant ($M^{-1} s^{-1}$)	Average
1.0×10^{-6}	0.89, 0.79, 0.80	0.82
1.0×10^{-5}	0.65, 0.67, 0.62	0.65
1.0×10^{-4}	0.73, 0.76, 0.77	0.75
		Average=0.74, Standard Deviation= 0.085

Table 6: Rate Constants for the Secondary Alcohol

Secondary Alcohol Concentration (M)	Rate Constant ($M^{-1} s^{-1}$)	Average
4.00×10^{-7}	1.57, 1.35, 1.62	1.51
4.0×10^{-6}	0.69, 0.66, 0.69	0.68
4.00×10^{-5}	1.01, 1.19, 1.00	1.06
		Average=1.08, Standard Deviation= 0.415

The tertiary alcohol, however, was found to have zero-order kinetics with respect to dichloroxanthene. Therefore, the slope of [dichloroxanthene] versus time represented the rate constant. The values of the rate constant (k) are reported in Table 7. Applying the Q-test allowed the elimination of the outlier in Table 7 (when $0.0000100 M$ tertiary butanol was used).

Table 7: Rate Constants for the Tertiary Alcohol

Tertiary Alcohol Concentration (M)	Rate Constant (s^{-1})	Average
1.0×10^{-6}	9.0×10^{-5} , 8.0×10^{-5} , 8.0×10^{-5}	8.3×10^{-5}
1.0×10^{-5}	1.0×10^{-3} , 2.0×10^{-3} , 1.0×10^{-3}	0.00043
1.0×10^{-4}	8.0×10^{-5} , 6.0×10^{-5} , 9.0×10^{-5}	7.7×10^{-5}
		Average = 8.0×10^{-5}

The average rate constants for the conversion of alcohols to alkyl halides using 9,9-dichloroxanthene in toluene are shown in Table 8. Due to the fact that the Q-test eliminated the runs for the determination of the rate constant for one of the tertiary alcohol experiments, the standard deviation was not determined for the tertiary alcohols.

Table 8: Rate Constants for the Butanols

Alcohol	Rate Constants
1-butanol	$0.74 \pm 0.17 \text{ } M^{-1} \text{ s}^{-1}$
2-butanol	$1.08 \pm 0.83 \text{ } M^{-1} \text{ s}^{-1}$
2-methylpropan-2-ol	$8.0 \times 10^{-5} \text{ s}^{-1}$

Discussion

Primary and Secondary Alcohols

Based on the graphical analysis, the dichloroxanthene in the primary alcohol case showed first-order kinetics with respect to the dichloroxanthene. Because the plot of $\ln[\text{dichloroxanthene}]$ versus time had the most linear relationship among the possible

kinetics graphs, the reaction could be assumed to be first-order with respect to the dichloroxanthene. This study depended on only observing the dichloroxanthene absorbance change. However, the order of the reaction with respect to the alcohols could be predicted. Knowing that primary alcohols typically undergo the S_N2 mechanisms, the order of the overall reaction could be extrapolated. Since the reaction was first-order with respect to the dichloroxanthene, it should be first-order also with respect to the alcohol. Therefore, the overall reaction order was suspected to be second order. It could never be zero-order overall since it was at least first order in dichloroxanthene.

Graphical analysis of the dichloroxanthene when it reacted with the secondary alcohol, 2-butanol, showed first-order kinetics with respect to the dichloroxanthene. Since secondary substrates tend to follow the S_N2 pathway, the reaction was predicted to be second-order overall. In the same manner, because the reaction already depended upon the dichloroxanthene concentration, the reaction could not be zero-order. In some cases, secondary substrates can also undergo S_N1 . Knowing the order of the reaction with respect to the nucleophile, dichloroxanthene, allows one to exclude that the reaction underwent the S_N1 pathway. By definition, S_N1 mechanisms could never be proportional to nor depend upon the nucleophile concentration. Therefore, since the reactions of the dichloroxanthene with primary and secondary alcohols depended on the dichloroxanthene concentration, it was believed to undergo the S_N2 mechanism. According to the data collected, it was impossible for the reaction to undergo either the S_N1 mechanism nor zero-order kinetics.

Tertiary Alcohols

Reactions of the tertiary alcohol with the dichloroxanthene showed a zero-order rate with respect to the dichloroxanthene. Substitution reactions are expected to undergo either second-order or first-order kinetics overall. Usually, tertiary substrates undergo first-order kinetics due to the stability of the carbocation formed as the intermediate of the reaction. This was one reason the zero-order reaction could be excluded. Since the dichloroxanthene when it reacted with the tertiary alcohol showed zero-order kinetics, the overall reaction could never be second-order. Therefore, the reaction with the tertiary alcohol was first-order overall and it could never undergo the S_N2 mechanism according to the collected data.

CHAPTER V

CONCLUSION AND RECOMMENDATIONS

Conclusion

Generally, alcohols have a limited range of reactivity toward substitution reactions without some type of activation. This activation can be as simple as adding an acid, forming alkoxides, or alternatively oxidizing the alcohols temporarily to carbonyl compounds. Aromatic cationic activation of alcohols, such as the reaction studied in this work, provides an efficient way to activate alcohols by converting them to highly activated aromatic intermediates.

A new chlorinating agent, 9,9-dichloroxanthene, for alcohols was prepared based on the *in situ* generation of aromatic cationic species. This chlorinating procedure was explored with primary, secondary, and tertiary alcohols. No acids, heating, or special conditions were involved in the transformation. Thus, the conditions of this reaction were considered relatively benign. IR and UV-vis spectroscopy were used to confirm the alcohols were converted to the alkyl halides.

IR spectroscopy was used to monitor the kinetics of the halogenation reaction. The reaction was performed and data were collected. However, the lack of reproducibility meant that none of the data collected with the IR were able to be used in the kinetic study. The lack of reproducibility might be due to the incomplete mixing of the diluted alcohol solutions in the narrow IR cell. Another factor that might have

contributed to the irreproducibility was the rapid kinetics of the reaction at the large concentrations needed to observe the appropriate IR absorbances. As a consequence, IR data in this research were used only to confirm the chlorination reaction of the alcohols and not the reaction kinetics.

For the alcohol/dichloroxanthene reaction, both of the reactants were studied to determine the overall kinetics. The reaction was studied by UV-vis spectroscopy but only by using large concentrations of dichloroxanthene with small concentrations of the alcohol. Thus, the order of the reaction with respect to dichloroxanthene was not determined. Instead, the order of the reaction with respect to the alcohol was determined using UV-vis spectroscopy.

Using UV-vis spectroscopy, the reaction was monitored by observing a change in the dichloroxanthene absorbance with time. Since the absorbance of xanthone, the product of the reaction, did not overlap with the dichloroxanthene absorbance at 412 nm, this compound could be monitored as an indicator of the progress of the reaction. The reduction of the absorbance was due to structural changes in the dichloroxanthene, indicating its conversion to xanthone. As a result, the alcohol was also converted to its chloride.

Using Beer's Law mentioned previously, all the absorbance values were converted to concentration values. To study the kinetics of the reaction, graphs of [dichloroxanthene] versus time, $1/[dichloroxanthene]$ versus time, and $\ln[dichloroxanthene]$ versus time were plotted. A linear relationship between the [dichloroxanthene] and time indicated a zero-order reaction while a linear plot of

$\ln[\text{dichloroxanthene}]$ versus time indicated a first-order reaction. Second-order kinetics, however, were determined from the linear plot of $1/[\text{dichloroxanthene}]$.

Based on the graphical analysis discussed above, the order of the reaction with respect to the dichloroxanthene was determined for primary, secondary, and tertiary butanols. Moreover, the rate constant, k , for the reaction was calculated based on the data. As mentioned previously, the main pathway to convert alcohols to their corresponding alkyl chlorides was via either the S_N1 or the S_N2 mechanisms. Zero-order kinetics probability was neither considered nor investigated. As expected, the primary and the secondary butanols underwent S_N2 mechanisms while the tertiary butanol underwent the S_N1 mechanism. 1-Butanol and 2-butanol have similar rate constant values. That might have contributed to the pathway they followed. Moreover, the values of the rate constants of the primary and the secondary butanols were bigger than the values of the rate constant of the tertiary butanol. That also could have contributed to the different reaction pathways. According to these values, the rate of the chlorination reactions of the primary and the secondary butanols was much higher than the rate of the tertiary butanol.

Recommendations/Proposals for Future Work

Fast reactions require specific techniques to determine the rate constants. Many factors directly affect the rate of the reaction. For instance, lowering temperatures is a factor with high influence on the reaction rate. Usually, a decrease in temperature is accompanied by a decrease in the reaction rate.⁵⁶ Decreasing temperatures means decreasing the kinetic energy of molecules that can decrease the chance for molecules to collide and interact effectively. Decreasing temperatures also increase the viscosity of

the solutions and hence the rates of the reaction. Future studies of this reaction at reduced temperatures could provide a more accurate determination of the rate constant and rate law of the reaction.

Using very dilute solutions has another impact on the chemical kinetics. The number of collisions per unit time can be decreased by reducing concentrations. This would lead to lowering the reaction rates (except for zero-order reactions) and allow a more accurate determination of the reaction kinetics. For example, alcohol substitution reactions follow either the S_N1 or the S_N2 mechanisms. For a first-order reaction, decreasing the concentration by a factor of two decreases the rate by a factor of two. However, for a second-order reaction, the rate is proportional to the squared concentration values for reactions that depend on the concentration of one species.³⁶

In this research, efforts have been made to dilute the reactants to very dilute solutions but not so dilute as to lose the absorbances of the compounds in the IR or UV-vis spectrum. To have valid data, changes in absorbance values should be observable. The use of more sensitive spectroscopic techniques might allow the concentrations to be reduced further, thus slowing the reaction.

In future studies, stopped-flow techniques at low temperatures should be considered to insure both the complete mixing and the more accurate kinetic study especially when using the FT-IR. Another way to improve the study would be to design a longer UV-vis cuvette instead of using the 1 cm path length cell. The concentrations could then be decreased dramatically and aid in the uncertainty of the data.

Another future plan would be to isolate the halide product in order to calculate the percentage yields to determine the efficiency of the chlorinating reagent. Because high

yield is important for industrial scales, such information would also be useful for this reaction. Moreover, the isolated product can be used to study the mechanism. Carroll⁵⁷ stated that chiral substrates react to give chiral products with inversion in configuration in case of the S_N2 mechanism while S_N1 mechanism involves the formation of racemic mixtures or at the very least a partial scrambling of the stereochemistry.⁵⁷

The stereochemistry of the reaction can be monitored by measuring the optical activity of the reaction as it is being performed. If the optical activity changes to the optical activity of the inverted halide, the reaction would be expected to follow an S_N2 mechanism. The rate of change of the optical activity from one to the other could be monitored to determine the rate constant of the reaction. If the optical activity of the reaction did not progress entirely to match the optical activity of the expected inverted product, then an S_N1 mechanism would be expected. Again, the rate of change of the optical activity could be monitored to determine the rate constant of the reaction. Unfortunately, the use of optical activity would not be possible with a primary alcohol as primary alcohols cannot, by definition, be optically active.

REFERENCES

- 1) Constable, D. J. C.; Wells, A.; Zaks, A.; Zhang, T. Y.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A. Key Green Chemistry Research Areas - A Perspective from Pharmaceutical Manufacturers. *Green Chem.* **2007**, 9(5), 411-420.
- 2) Klein, S. M.; Zhang, C.; Jiang, Y. L. Simple Synthesis of Fresh Alkyl Iodides using Alcohols and Hydriodic Acid. *Tetrahedron Lett.* **2008**, 49(16), 2638-2641.
- 3) Tajbakhsh, M.; Hosseinzadeh, R.; Lasemi, Z.; Rostami, A. Solvent-Free Conversion of Alcohols into Iodides with NaI Supported on KSF Clay. *Synth. Commun.* **2005**, 35(22), 2905-2911.
- 4) Dauben, W. G. Ed.; *Organic Reactions*; John Wiley & Sons: Flushing, NY, 1983 , Vol. 29; pp 1-28.
- 5) Landini, L.; Montanari, F.; Rolla, F. Conversion of Primary Alcohols to Alkyl Chlorides Using Aqueous Hydrochloric Acid in the Presence of Phase- Transfer Catalysts. *Synthesis*, **1974**, 37 (1), 37-38.
- 6) Jones, R.; Pattison, J. B. Reaction between Unsaturated Alcohols and Potassium Iodide in the Presence of Polyphosphoric Acid. *J. Chem. Soc.* **1969**, 7, 1046.
- 7) Senaratne, P. A.; Orihuela, F. M.; Malcolm, A. J.; Anderson, K. G. Recyclable Lucas Reagent in Converting Aliphatic Alcohols to Chlorides. *Org. Process Res. Dev.*, **2003**, 7(2), 185-186.

- 8) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part B: Reactions and Synthesis*, 5; Springer: New York, NY, 2007; pp 217-218.
- 9) Schaefer, J. P.; Weinberg, D. S. Bimolecular Displacement Reactions. I. Reaction of Endo-Norbornanol and 7-Norbornanol with Triphenylphosphine and Bromine. *J. Org. Chem.* **1965**, 30 (8), 2635–2639.
- 10) Bailey, P. D.; Cochrane, P. J.; Foerster, A. H.; Morgan, K. M.; Pearson, D. P. J. Synthesis of Polycyclic Indolic Structures. *Tetrahedron. Lett.* **1999**, 40 (24), 4597-4600.
- 11) Kelly, B.; Lambert, T. Aromatic Cation Activation of Alcohols: Conversion to Alkyl Chlorides Using Dichlorodiphenylcyclopropene. *J. Amer. Chem. Soc.* **2009**, 131 (39), 13930-13931.
- 12) Substitution reaction. In *McGraw-Hill Concise Encyclopedia of Science and Technology [Online]* **2006**. http://0-www.credoreference.com.source.unco.edu/entry/conscitech/substitution_reaction (accessed Oct 20, 2012).
- 13) Nucleophilic substitution. In *The Penguin Dictionary of Science [Online]* **2009**. http://0-www.credoreference.com.source.unco.edu/entry/penguinscience/nucleophilic_substitution (accessed Oct 20, 2012).
- 14) Gilbert, J. C.; Martin, S. F. *Experimental Organic Chemistry: A Miniscale and Microscale Approach*, 5; Brooks/ Cole Cengage Learning: Boston, MA, 2011; p 471.
- 15) Smith, M. B.; March, J. *March's Advanced Organic Chemistry Reactions, Mechanisms and Structure*, 6. Wiley-Interscience: Hoboken, NJ, 2007; p 427.
- 16) Uggerud, E. (2006). Reactivity Trends and Stereospecificity in Nucleophilic Substitution Reactions. *J. Phys.Org. Chem.* **2006**, 19(8-9), 461-466.

- 17) House, J. E. *Principles of Chemical Kinetics*, 2; Elsevier/Academic Press: Boston, MA, 2007; p 2.
- 18) Hage, D. S.; Carr, J. D. *Analytical Chemistry and Quantitative Analysis*; Boston: Prentice Hall, 2011; p 445.
- 19) Drake, G. W. F. (Ed.). *Atomic, Molecular, & Optical Physics Handbook*; AIP Press Woodbury, New York, 1996; p 467.
- 20) Hage, D. S.; Carr, J. D. *Analytical Chemistry and Quantitative Analysis*; Boston: Prentice Hall, 2011; p 446.
- 21) Hage, D. S.; Carr, J. D. *Analytical Chemistry and Quantitative Analysis*; Boston: Prentice Hall, 2011; p 448.
- 22) Introduction to Fourier Transform Infrared Spectroscopy. *Thermo Nicolet* [Online] 2001. <http://mmrc.caltech.edu/FTIR/FTIRintro.pdf> (accessed Oct 20, 2012).
- 23) Drake, G. W. F. (Ed.). *Atomic, Molecular, & Optical Physics Handbook*; AIP Press Woodbury, New York, 1996; p 468.
- 24) Michelson interferometer. In *McGraw-Hill Dictionary of Scientific and Technical Terms*[Online] **2003**. http://0-www.credoreference.com.source.unco.edu/entry/mhscience/michelson_interferometer (accessed Oct 20, 2012).
- 25) Michelson interferometer. In *Focal Dictionary of Telecommunications, Focal Press* [Online] **1999**. http://0-www.credoreference.com.source.unco.edu/entry/bhfidt/michelson_interferometer (accessed Oct 20, 2012).
- 26) Sternhell, S.; Kalman, J. R. *Organic Structures from Spectra*. Wiley: Chichester, New York, 1986; p 15.

- 27) Lambert, J. B.; Shurvell, H. F.; Lightner, D. A; Cooks, R. G. *Organic Structural Spectroscopy*; Prentice Hall: Upper Saddle River, NJ, 1998.
- 28) Hage, D. S.; Carr, J. D. *Analytical Chemistry and Quantitative Analysis*; Boston: Prentice Hall, 2011; p 435.
- 29) Drake, G. W. F. (Ed.). *Atomic, Molecular, & Optical Physics Handbook*; AIP Press Woodbury, New York, 1996; p 487.
- 30) Bauman, R. P. *Absorption Spectroscopy*; Wiley: New York, 1962; p 413.
- 31) Hage, D. S.; Carr, J. D. *Analytical Chemistry and Quantitative Analysis*; Boston: Prentice Hall, 2011; p 437.
- 32) Kellner, R.; Mermet, J. M.; Otto, M.; Widmer, H. M. Eds.; *Analytical Chemistry: The Approved text to the FECS Curriculum Analytical Chemistry*; Wiley-VCH: New York, 1998; p 527.
- 33) Laidler, K. J. *Reaction kinetics: Homogeneous gas Reactions*; Pergamon Press: New York, 1963; p 32.
- 34) Bleul, R.; Ritzi-Lehnert, M.; Höth, J.; Scharpfenecker, N; Frese, I; Düchs, D; Brunklaus, S.; Hansen-Hagge, T. E.; Meyer-Almes, F.; Drese, K. S. Compact, Cost-Efficient Microfluidics-Based Stopped-Flow Device. *Analyt. Bioanalyt. Chem.* **2011**, 399(3), 1117-1125.
- 35) Kellner, R.; Widmer, H. M. Eds.; *Analytical chemistry: A Modern Approach to Analytical Science*. Wiley-VCH: New York, 2004; p 452.
- 36) Wright, M. R. *An Introduction to Chemical Kinetics*. Wiley: Hoboken, NJ, 2004; 28-29.
- 37) Stopped-Flow Kinetics. *Boston Biomedical Research Institute* [Online] **2012**.
http://www.bbri.org/index.php/stopped_flow_kin.html (accessed May 10, 2012).

- 38) Ellwood, A. R.; Porter, M. J. Selective Conversion of Alcohols into Alkyl Iodides Using a Thioiminium Salt. *J. Org. Chem.* **2009**, 74(20), 7982–7985.
- 39) Dubey, A.; Upadhyay, A.; Kumar, P. Pivaloyl Chloride/DMF: A New Reagent for Conversion of Alcohols to Chlorides. *Tetrahedron Lett.* **2010**, 51(4), 744-746.
- 40) Smith, M. B.; March, J. *March's Advanced Organic Chemistry Reactions, Mechanisms and Structure* 5; Wiley: New York, 2001; p 518.
- 41) Kamal, A.; Ramesh, G.; Laxman, N. New Halogenation Reagent System for One-Pot Conversion of Alcohols into Iodides and Azides. *Synthetic Communications*, **2001**, 31(6), 827-833.
- 42) Ma, H.; Bao, Z.; Bai, L.; Cao, W. A New Facile Route to Chlorination of Alcohols via Lewis Acid AlCl₃. *Intern. J. Org. Chem.* **2012**, 2(1), 21-25.
- 43) van Kalker, H. A.; Leenders, S. H. A. M.; Hommersom, C. R. A.; Rutjes, F.P. J. T.; van Delft, F. L. In Situ Phosphine Oxide Reduction: A Catalytic Appel Reaction. *Chemistry (Weinheim an der Bergstrasse, Germany)*. **2011**. 17(40), 11290-11295.
- 44) But, T. Y. S.; Toy, P. H. The Mitsunobu Reaction: Origin, Mechanism, Improvements and Applications. *Chem. Asian J.* **2007**, 2 (11), 1340–1355.
- 45) Kiankarimi, M.; Lowe, R.; McCarthy, J. R.; Whitten, J. P. Diphenyl 2-Pyridylphosphine and Di-*tert*-butylazodicarboxylate: Convenient Reagents for the Mitsunobu Reaction. *Tetrahedron Lett.* **1999**, 40 (24), 4497–4500.
- 46) Toto, S. D.; Doi, J. T. A Functionalized Alkyldiphenylphosphine as an Efficient and Mild Reagent in CCl₄-Promoted Substitution Reactions: Kinetics and Mechanism of the Reaction in CHCl₃. *J. Org. Chem.* **1987**, 52, 4999-5003.

- 47) Firouzabadi, H.; Iranpoor, N.; Ebrahimzadeh, F. Facile Conversion of Alcohols into their Bromides and Iodides by N-bromo and N-iodosaccharins/ triphenylphosphine under Neutral Conditions. *Tetrahedron Lett.* **2006**, *47*, 1771–1775.
- 48) Pollastri, M. P.; Sagal, J. F.; Chang, G. The Conversion of Alcohols to Halides Using a Filterable Phosphine Source. *Tetrahedron Lett.* **2001**, *42* (13), 2459-2460.
- 49) Denton, R. M.; An, J.; Adeniran, B.; Blake, A. J.; Lewis, W.; Poulton, A. M. Catalytic Phosphorus (V) - Mediated Nucleophilic Substitution Reactions: Development of a Catalytic Appel Reaction. *J. Org. Chem.* **2011**, *76*, 6749–6767.
- 50) Behera, N.; Mishra, P. K.; Elias, A. J. The Chemistry of Cyclic Carbaphosphazenes: The First Observation of $(R_2PN)(ClCN)_2(R=Cl, Ph)$ as a Reagent for the Conversion of Alcohols to aldehydes, Ketones, and Alkyl Chlorides. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*(10), 2445-2452.
- 51) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. Borrowing Hydrogen in the Activation of Alcohols. *Adv. Synth. Cata.*, **2007**, *349* (10), 1555–1575.
- 52) Iranpoor, N.; Firouzabadi, H.; Jamalian, A.; Kasemi, F. Silicaphosphine (Silphos): A Filterable Reagent for the Conversion of Alcohols and Thiols to Alkyl Bromides and Iodides. *Tetrahedron Lett.*, **2005**, *61*, 5699-5704.
- 53) Khandpur, R. S. *Handbook of Analytical Instruments*. McGraw-Hill: New York, 2007; 40-41.
- 54) Berry, R. S.; Rice, S. A.; Ross, J. *Physical and Chemical Kinetics*, 2; Oxford University Press: New York, 2002; p 878.
- 55) Zero-order reaction. In *The Penguin Dictionary of Science* [Online] **2009**.
http://0-www.credoreference.com.source.unco.edu/entry/penguinscience/zero_order_reaction (accessed Oct 20, 2012).

- 56) Chemistry time: Factors affecting the rate of a chemical reaction. *J. Chem. Edu*, **1998**, 75(9), 1120A-1120B. <http://0-search.proquest.com.source.unco.edu/docview/211905085?accountid=12832> (accessed Nov 7, 2012).
- 57) Carroll, F. A. *Perspectives on Structure and Mechanism in Organic Chemistry*; Brooks/Cole Pub: Pacific Grove, CA, 1998; p 328.