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Laboratory-Based Modules in an Organic Chemistry Classroom

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Abstract Student engaged learning has been at the forefront of chemical education for the past several decades. Improving student engagement leads to increased retention of information being presented in lecture and laboratory-based settings. With this goal in mind, three laboratory-based learning modules were developed to address difficult learning areas in organic chemistry (acid/base/extractions, substitution reactions, and aromaticity). These data-driven modules focus on students using critical thinking skills to analyze data and answer guided questions in these trouble areas. The implementation of modules and an evaluation of effectiveness are presented.

Keywords: *organic chemistry, lab-based learning modules, data analysis*

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1. Introduction

The use of learning modules for the improvement of student learning remains an important tool for science educators. Previously developed modules have emphasized an active learning approach as the primary vehicle to effectively engage students with the material of the course. Such methods that have been shown to promote positive student learning gains include process-oriented guided inquiry learning, peer-led team learning, problem-based or case-based learning, and the flipped classroom [1-18]. However, the use of activities that can assist students in developing scientific reasoning skills and emulate the true practice of science remain under-developed methods of student engagement. Indeed, this practice, which is commonly referred to as empirical research, is an integral investigative practice in the chemistry laboratory, but has not been widely applied in the chemistry classroom. Therefore, the development of laboratory-based learning experiences might provide an effective tactic for enriching the classroom-laboratory connection while simultaneously growing the empirical skills that educators hope to instill in students.

Our interest in the use of laboratory-based classroom exercises arose from several observations of student learning and behavior in our own curriculum at the U.S. Air Force Academy (USAFA). For example, the traditional organic chemistry lecture course is often characterized as a journey in which access to content occurs by way of rote memorization. Moreover, this default memorization mindset also promotes a learning environment dependent upon collecting facts and, therefore, likely minimizes the development of more desirable critical thinking and scientific reasoning skills. Indeed, recent literature has advocated the need for science courses to become less focused on content knowledge and instead should place more emphasis on developing scientific thinking [19]. Therefore, a distinct need exists for student learning activities that promote the development of scientific reasoning skills in addition to the traditional emphasis on acquisition of content knowledge. Ideally, these activities should present data and graphical information (tables, schemes, spectra, charts, etc.) that require students to draw inferences from the information in order to promote deeper understanding. The goal would be to have students evaluate data and arrive at their own conclusions, which might in turn lead to a more comprehensive student understanding of the material and deters from the rote memorization model of learning.

Often educators use question-driven exercises to facilitate this style of learning and, in a previous report, we observed the influential effect that question-driven exercises can have on student learning, especially when there is an emphasis on data interpretation [20]. Additionally, a repository of data-driven exercises that can be adopted by educators has been established via the Journal of Chemical Education Digital Library, but these examples are oriented toward physical chemistry courses [21]. Therefore, further development of teaching modules in which students can encounter laboratory-inspired learning in an organic chemistry context is important.

Second, we considered the non-traditional course sequence in organic chemistry at the US Air Force Academy, wherein students take only one laboratory course (during the spring term) and two semesters of organic chemistry lecture. The result is a course configuration that severely limits the scope of experimental techniques and

applications that we can effectively cover in only one term of organic chemistry laboratory. Therefore, we sought to employ a compensatory mechanism for the limited laboratory engagement in which specific exercises were developed to preview the key ideas needed to afford effective future learning. It should be noted these laboratory-based classroom exercises are different from the well-established virtual laboratory methods that have appeared elsewhere in the literature in the sense that the modules designed here are not intended to be video replacements for actual in-laboratory experiences [22-25]. Instead, the modules developed in this report are envisioned as preliminary engagements with the students that allow key content to be introduced prior to actual hands-on activity in the laboratory, serving as a means of foreshadowing the method to be experienced in the lab.

Finally, we have been continually discouraged by the high failure rate in organic chemistry. Indeed, several reports have suggested that there are several factors that contribute to low performance in organic chemistry [26-30]. Among these, we have been particularly interested in the complexity factor and the development of the knowledge space [29,30]. Indeed, this prompted a change in approach for the development of learning activities in which engagements might be streamlined, focused, and simplified in order to promote the development of appropriate thinking strategies that could improve student performance in the subject matter. With all these factors in mind, we envisioned a series of learning modules of limited scope that are integrally tied to genuine laboratory experiences and which might potentially improve student success in both the lecture and laboratory setting.

Therefore, we have developed two new data-driven instructional modules to specifically address key foundational trouble areas of learning in organic chemistry: (1) acid-base chemistry and (2) substitution reactions. We also have revised an (3) aromaticity module incorporating ChemDraw/3-D modeling. Historical low achievement in these three areas provides a strong argument for their selection for targeted learning and here we provide a concise proof-of-concept of their effectiveness. Finally, carefully designed modules may simultaneously promote assessment gains with respect to student learning as well as prepare students for laboratory investigation and data analysis. More importantly, the modules described here further benefit the learning by way of fortifying the empirical nature of scientific investigations calling on students to make inferences from data and describe the relevant principles that explain the claim.

2. Results and Discussion

The modular exercises described here were selected to advance student understanding in three critical developmental areas, which have traditionally presented challenges with respect to achieving desired learning objectives: acid-base chemistry, substitution reactions, and aromaticity. Moreover, the ability of the students to develop a molecular understanding of acid/base chemistry/extractions and substitution reactions before performing the experiment provides foundational knowledge that leads to an overall increased understanding of the material in both the classroom and laboratory setting. The process is catalyzed by carefully prepared guided/directed questioning based on the specific trouble areas in these topics. The learning objectives of the three learning modules are displayed in Table 1.

The extraction and Bronsted-Lowry acid/base module focuses on the student's ability to determine partitioning between aqueous and organic solvents, solubility predictions, and Bronsted-Lowry acid/base equilibrium. Specifically, the module focuses on the student's ability to predict acid/base reactions and solubility in the aqueous/organic phase through a complex reaction workup. The substitution module focuses on initially focuses on using reaction rate data to look at the individual components of substitution reactions (alkyl halide substitution, solvent, leaving group ability, and nucleophile). Once the basics of substitution reactions have been introduced, rate data are provided and the students determine the reaction pathway and then answer a variety of guided question regarding the specific reaction.

The 3rd module utilized ChemDraw/Chem 3D to build molecules and introduces conjugated vs. isolated dienes, planarity, and then finally asks the students to apply these concepts to aromaticity and acid/base chemistry of molecules.

Table 1. Learning goals of each laboratory-based instructional modules are

Module	Learning Goals:
Extraction and Bronsted-Lowry Acid/Base Chemistry	• Solubility of analytes in aqueous and organic solvents • Predicting organic vs aqueous layers in extractions • Predicting reactions and equilibrium in Bronsted-Lowry acid/base reactions
Determining the Mechanism of Substitution Reactions (S_N1/ S_N2)	• The roles of alkyl halide substitution, nucleophile, leaving group ability, and solvent in S_N1 & S_N2 reactions • Relationship of kinetics to S_N1 & S_N2 reactions • Predicting product(s) in S_N1 & S_N2 reactions • Determining stereochemical outcome • Writing reaction mechanisms for S_N1 & S_N2
Aromaticity	• Background of computational chemistry • Stability of isolated versus conjugated dienes • Molecular geometry of non- versus aromatic compounds • Role of heteroatoms in aromaticity • Acid-base properties in relationship to aromaticity

The students are assigned the laboratory-based instructional modules as a normal course graded event and complete them individually. The first two exercises (extraction & substitution reactions) take approximately 1-2 hours to complete, while the aromaticity can take longer due to inexperience using ChemDraw/Chem 3D. For these experiments, no additional materials are needed except for the aromaticity data set which requires a simple molecular modeling software. For the aromaticity data set, ChemDraw/Chem3D was utilized, but would be compatible with any computational software. The *supplemental data* is available here and contains: 1) Three laboratory-based learning modules focused on acid/base/extraction, nucleophilic substitution reactions, and aromaticity, and 2) answer keys for these data-driven exercises.

An anonymous questionnaire on the general efficacy of the extraction acid/base (1) and substitution reaction (2) laboratory-based modules were administered and the results displayed in Figure 1 and Figure 2. The questionnaire aimed to assess if the assignments better prepared the students for the extraction/acid base and substitution experiments they conducted for both the 2nd semester lab and in-class examinations. Figure 1 displays questions focused on the ability of the lab-based modules to better prepare students for both the 2nd semester organic laboratory and examinations. In Figure 1, 44% of the students strongly agreed/agreed that the in-class assignment helped with the extractions, 57% Bronsted-Lowry acid/base portion, and 61% substitution reactions. Although not necessarily impressive alone, we perceived these results to be quite favorable given the inherent challenge presented in these three content areas of organic chemistry. The results overall indicate that the students find value in the lab-based modules. However, some attention should be paid to the lower response value for the extractions portion of the modules. Although encouraging, we believe that further development is warranted in this particular module to enhance its fidelity and ultimate impact.

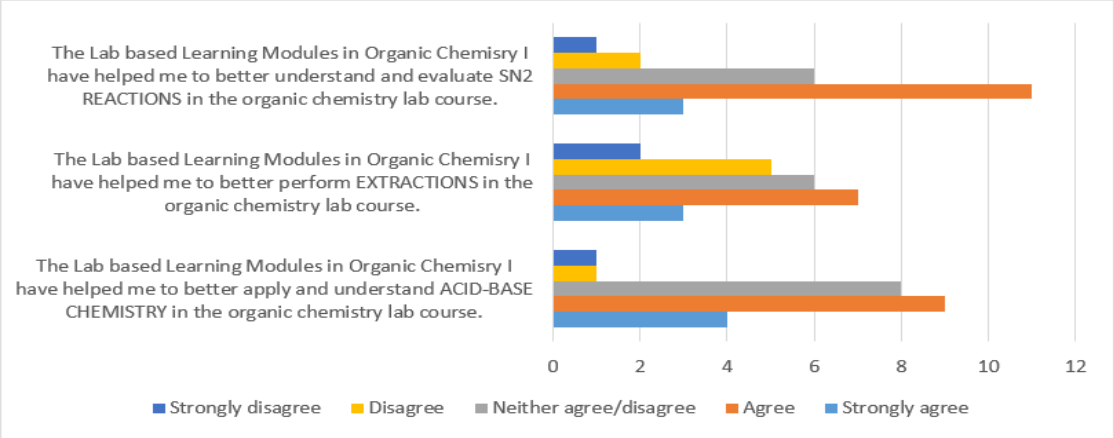

Figure 1. General efficacy of lab-based learning modules

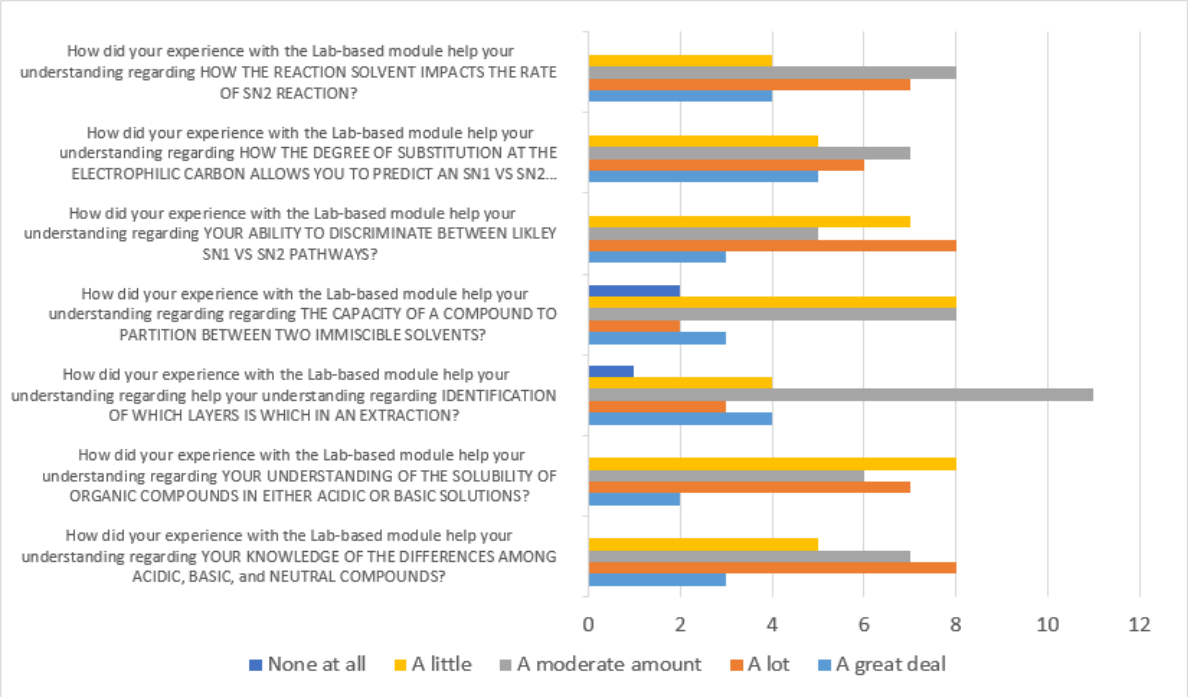

Figure 2. Student responses to key learning objectives

The 2nd portion of the questionnaire (Figure 2) focused on the discrete learning objectives for the individual laboratory-based learning modules. The data display a positive response for the key reaction components of S_N1 and S_N2 reactions including the role of both the solvent and alkyl halide. Most importantly and somewhat surprising to us, the questionnaire did not contain a single "none at all" for the substitution lab-based modules displaying the usefulness from the student's perspective. In contrast to the substitution module, the acid/base and extraction modules had mixed reviews. The lowest response was pertaining to the solvent-solvent extraction portion of the module, and is consistent with the moderate learning gains for this same module as shown in Figure 1. The two areas the students had the lowest response was determining if solvents were immiscible and the location of individual solvents in a separatory funnel. Although this result was discouraging, it is not surprising as this is difficult concept to master in a non-laboratory setting, but we look to further revise the module to promote enhanced learning gains.

3. Conclusion

We have developed three new learning modules to supplement learning in the classroom by introducing laboratory concepts. These modules foster student learning by focusing on data-driven critical thinking thus leading to better retention of the material. Anonymous feedback has shown that learning objectives are being met by the learning modules and the students see value in completing these tasks.

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Declaration

The authors have no competing interests.

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Microactivity #1: Extraction and Acid/Base Chemistry

Name:

The purification of organic reactions is both a difficult and expensive procedure. One of the easiest methods for purifying organic mixtures into individual components is using a method called extraction. Extraction purifies organic molecules based on solubility and reactivity. Below is an example of an extraction in which dichloromethane (CH_2Cl_2) and water form two distinct layers due to the differences in intermolecular forces (Figure #1). Water which is less dense (density=1.00 g/mL) than CH_2Cl_2 (density=1.34g/mL) appears as the top layer and the heavier dichloromethane on the bottom. Using solubility and Bronsted-Lowry acid/base chemistry you can separate and isolate pure compounds from a mixture. For example, how would you purify a mixture of (**1**) anthracene (**1**) and 1-Aminoanthracene (**2**)? Both of these molecules would be soluble in an organic solvent such as dichloromethane (CH_2Cl_2).

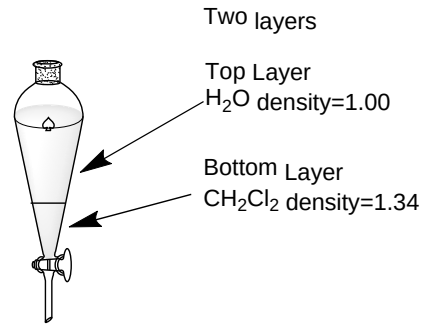
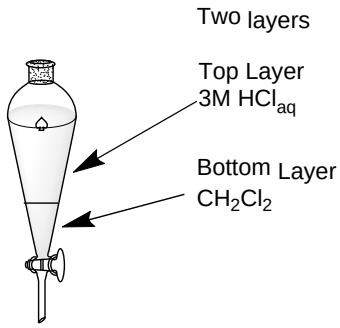


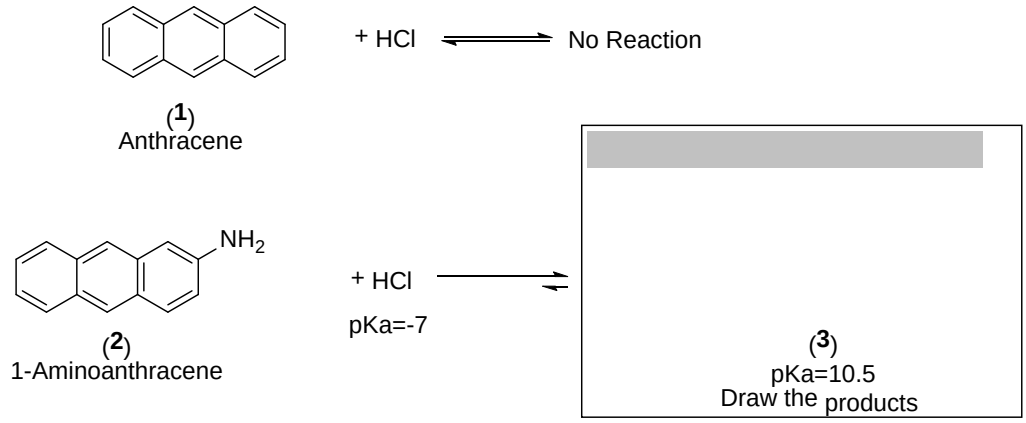
Figure #1. An example of an extraction using a separatory funnel

(**1**) Anthracene (**2**) 1-Aminoanthracene

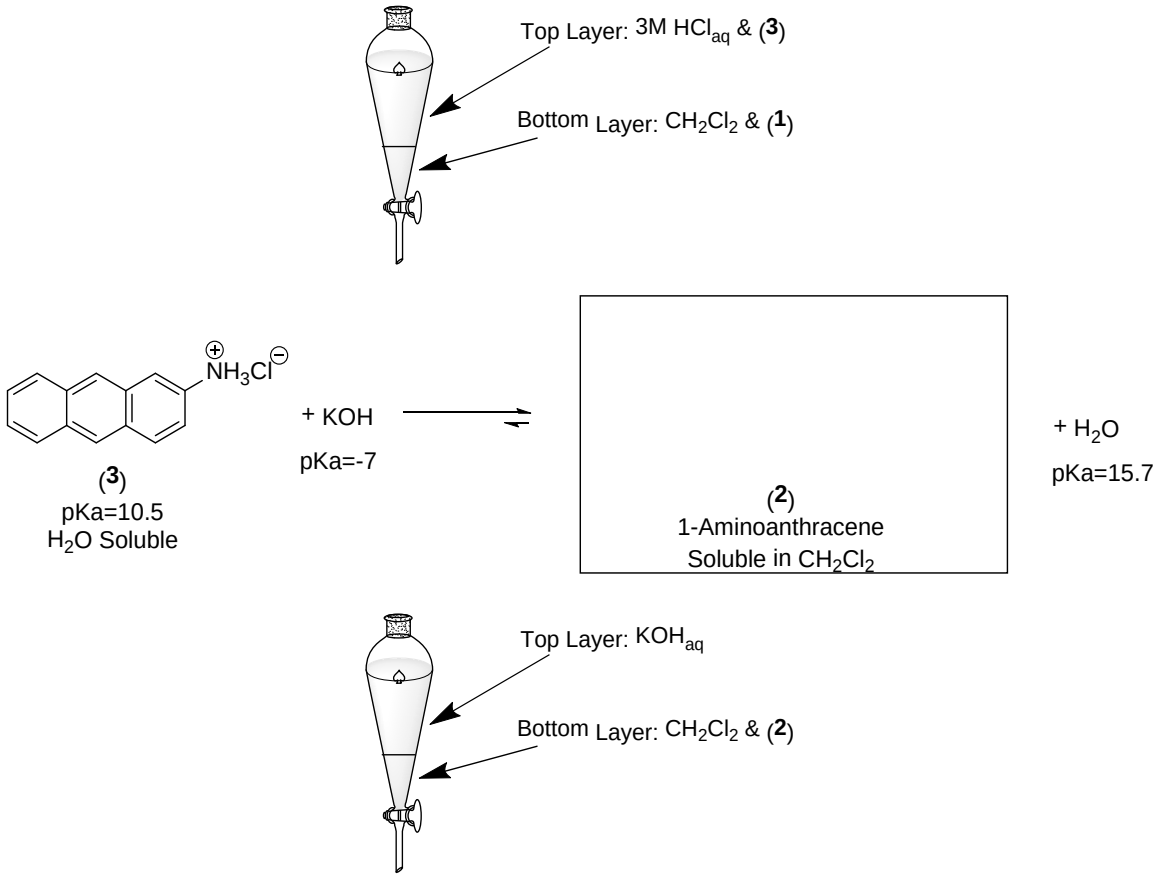
So the question is how will we be able to separate these if they are both soluble in CH_2Cl_2? Here we can use acid/base and intermolecular forces to our advantage. What happens if you add 3M $HCl_{(aq)}$ (remember $_{(aq)}$ means aqueous) to the mixture? First, we observe two layers because the aqueous 3M HCl and CH_2Cl_2 are not soluble in each other.



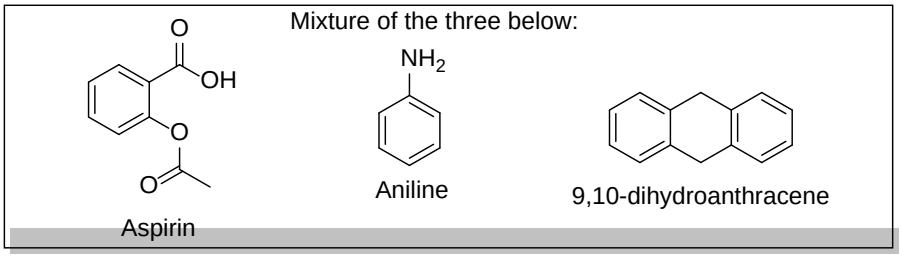
Now, what happens to the anthracene (**1**) and aminoanthracene (**2**)? To determine this, we need to think about Bronsted-Lowry acid/base equilibrium chemistry. Anthracene being composed of only C-H and C-C bonds does not contain any acidic/basic functional groups. However in the case of 1-aminoanthracene (**2**), the amine is basic, and when it is reacted with HCl the equilibrium strongly favors the formation of an ammonium chloride salt (3) (Scheme 1). Due to this favorable equilibrium molecule (3) now contains an ionic bond and will be extracted to the water layer due to the increased solubility. Separating the H_2O layer now produces the purified ammonium chloride salt of Aminoanthracene (**3**) from the two component mixture. However we are not done, as it is incredibly difficult to remove organic molecules from water. What we know is that the ammonium salt (**3**) is water soluble but 1-aminoanthracene (**2**) is not. How do we convert the ammonium salt back to 1-aminoanthracene? We can again use acid/ base chemistry and deprotonate the ammonium salt producing aniline which is insoluble in water but soluble in CH_2Cl_2.



Scheme 1.



For this assignment, you will have to devise a plan using extraction and Bronsted-Lowry acid/base properties to for the purification of the following mixture using the available materials below: Also, it may be useful to watch the following video for more background information: https://www.youtube.com/watch?v=DmvaOb1xb1o



Available Materials
CH_2Cl_2
H_2O

Available Reagents
1M $NaHCO_{3(aq)}$
3M $HCl_{(aq)}$
1M $NaOH_{(aq)}$

Step #1: Do you think these molecules will be soluble in dichloromethane (CH_2Cl_2)?

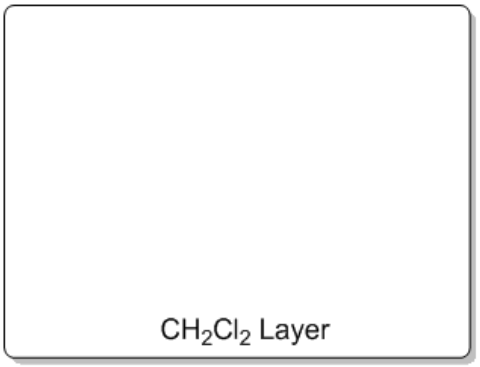
Why or why not? If unsure, a Google search on solubilities might be adequate.

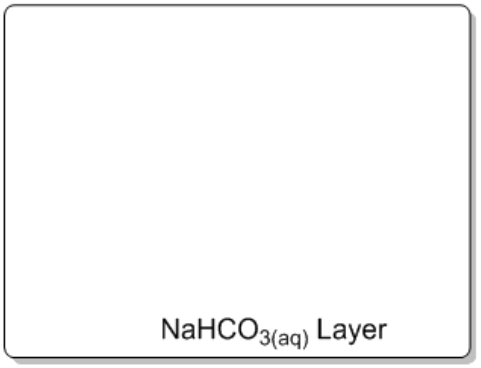
Step #2: Let's assume that all three are soluble in CH_2Cl_2. What happens if you add $NaHCO_3$ (aq) and place in a separatory funnel?

How many layers do you think would form?

Draw the reaction that will take place and predict equilibrium.

What molecules are in each layer (draw the structures below)?



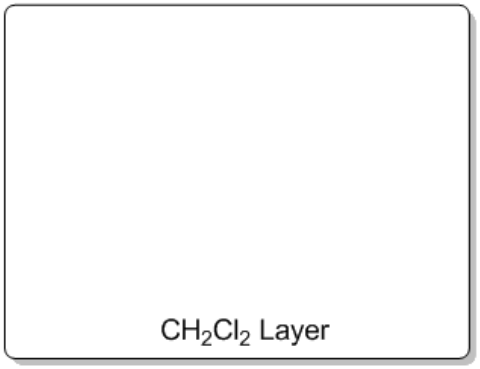


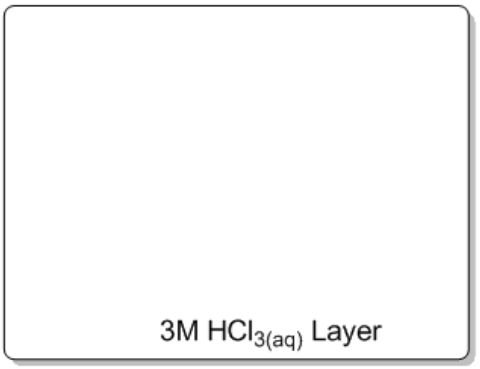
Step #3: If we remove the $NaHCO_{3\,(aq)}$ layer and add 1M HCl and adjust the pH to 2 what reaction will occur? Draw the reaction below.

Step #4: Return to the CH_2Cl_2 layer. If we know add 3M HCl (aq) and the CH_2Cl_2 to the separatory funnel how many layers will form?

Draw the reaction that will take place and predict equilibrium.

What molecules do the two layers contain? Draw the structures below:





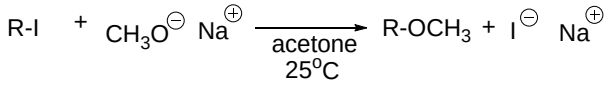
You have now successfully separated a three component organic mixture using intermolecular forces and Bronsted-Lowry acid/base chemistry.

Microactivity #2: Determining the Mechanism of Substitution Reactions (S_N1/ S_N2)

Name:

The nucleophilic substitution reaction is one of the most important transformations in organic chemistry. Nucleophilic substitution requires the reaction of a nucleophile (electron rich) with an electron deficient molecule (electrophile). This reaction can occur via two reaction pathways: a S_N1 or S_N2 reaction. In a S_N1 reaction, a stepwise mechanism in under operation and involves the formation of a carbocation intermediate. The formation of the carbocation intermediate is the rate determining step of the reaction, and therefore, the reaction follows 1st order reaction kinetics with the rate dependent upon the concentration of the alkyl halide. The 2nd pathway (S_N2) is a concerted mechanism (one step), and the rate of the reaction is directly related to both the concentration of the alkyl halide and the nucleophile. The two reaction pathways are under competition, but certain conditions favor one mechanism over the other. Please use the experimental data below to answer the following questions.

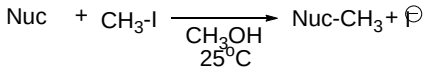
Experiment #1: Investigating the rate of sodium methoxide substitution with a variety of alkyl halides (R-I):



R=	Relative Rate
CH_3^-	2.9 x105
$CH_3CH_2^-$	2000
$(CH_3)_2CHCH_2^-$	72
$(CH_3)_2CH^-$	15.6
$(CH_3)_3C^-$	1

Question #1: Is this reaction most likely S_N1 or S_N2?
Question #2: Provide a detailed explanation for the difference in rates observed for the reactions.

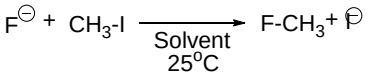
Experiment #2: Role of nucleophile (Nuc) in substitution reactions with methyl iodide:



Nuc	**Relative Rate ($M^{-1}s^{-1}$)**
$CH_3O^⊖$	5000
$PhO^⊖$	1580
$F^⊖$	1

Question #1: Is this reaction most likely S_N1 or S_N2?
Question #2: Provide a detailed explanation for the difference in rates observed for the reactions.

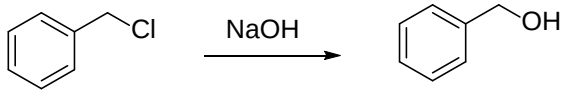
Experiment #3: Investigating the role of solvent in nucleophilic substitution reactions:



Solvent	**Relative Rate ($M^{-1}s^{-1}$)**
DMF	6.0×10^7 (RXN is extremely fast)
Methanol	1 (RXN is slow!)

Question #1: Is this reaction most likely S_N1 or S_N2?
Question #2: Provide a detailed explanation for the role of the solvent in the reaction and how this effects the rate.

Experiment #4: Using the two datasets answer the following:
a. Data set #1:

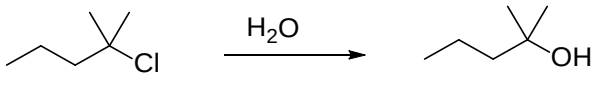


A

Trial Number	[$C_6H_5CH_2Cl$] [**A**]	[NaOH]	Rate M/s
1	0.10M	0.10M	$2.6x10^{-6}$
2	0.10M	0.20M	$5.1x10^{-6}$
3	0.20M	0.20M	$1.0x10^{-5}$

Problem #1: S_N1 or S_N2
Problem #2: Provide an explanation on how the reaction mechanism was determined?
Problem #3: Draw an arrow pushing mechanism for the predicted reaction pathway (S_N1 or S_N2).
Problem #4: Draw an energy diagram including transition state(s).

b. Data set #2:



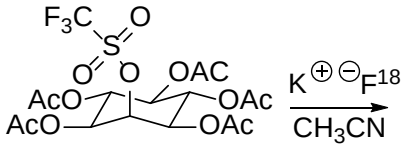
B

Trial Number	[RCl] [**B**]	[H_2O]	Rate M/s
1	0.10M	0.10M	$5.5x10^{-7}$
2	0.10M	0.05M	$5.5x10^{-7}$
3	0.20M	0.10M	$1.0x10^{-6}$

Problem #1: Is this reaction most likely S_N1 or S_N2
Problem #2: Provide explanation on how the reaction mechanism was determined?
Problem #3: Draw an arrow pushing mechanism for the predicted reaction pathway (S_N1 or S_N2).
Problem #4: Draw an energy diagram including transition state(s).

Supplemental problem:
PET (Positron emission tomography) imaging is commonly used for the detection of cancer in patients. In PET imaging, a glucose/mannose molecule containing an isotope that emits positrons is injected into a patient. Due to the rapid uptake of glucose in cancer cells (in comparison to normal), the carbohydrates are more concentrated in the infected cells. After the positron collides with an electron, two gamma rays are emitted ultimately as light (bright spot are cancer cells). In order for this to occur, glucose is derivatized with the positron emitting atom ^{18}F. The half-life of ^{18}F is 110 minutes! Therefore, approximately 110 minutes is the maximum time frame required to perform the following:
1. Produce and separate ^{18}F.
2. React ^{18}F with glucose/mannose.
3. Inject the isotopically labelled glucose into the patient.
4. Run the PET scan.

Answer the following questions:
Problem #1: Draw the product (including stereochemistry) and an arrow pushing mechanism for the conversion of acetylated (OAc groups) mannose to the fluorinated version.



Problem #2: I this reaction most likely S_N1 or S_N2?
Problem #3: Why do you think this reaction pathway is ideal to produce the ^{18}F-Labelled carbohydrate?

Relative rate of reactions data for experiments 1-3 was adapted and modified from:
Loudon, M. and Parise, J. *Organic Chemistry 6th ed.* W. H. Freeman: New York, 2016.

Microactivity #3: A 3-D exploration into Conjugated Dienes & Aromaticity

Individual Assignment-Can use Chemdraw, Chem3D, textbook and class notes.

Name:

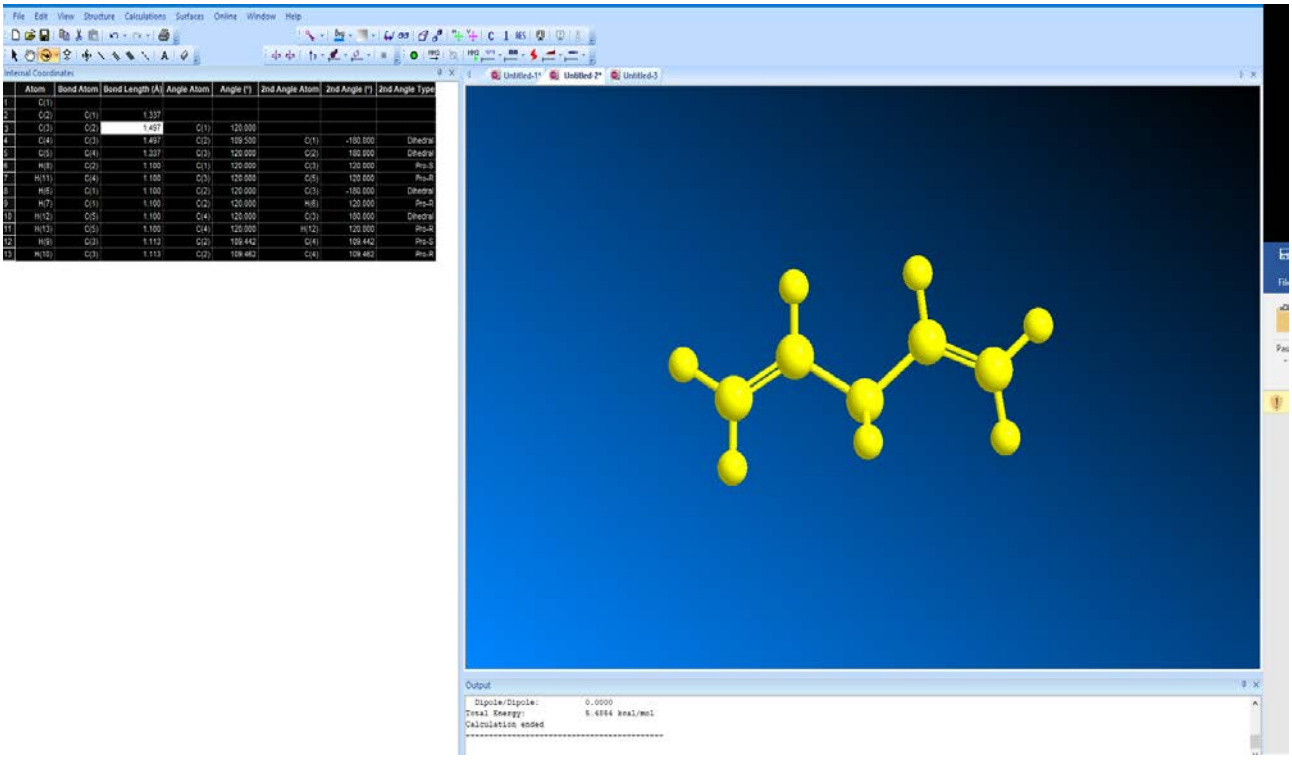
Objective: This assignment will help you further your ability to visualize organic molecules in three-dimension. This experiment will use Chemdraw and Chem3D to supplement our lessons on conjugation and aromaticity.

Exercise #1: Examining the effects of conjugation:

penta-1,4-diene **(1)**

(*E*)-penta-1,3-diene **(2)**

Build molecule **1** (penta-1,4-diene) in ChemDraw. Open up Chem 3D in a separate window and copy and paste **1** from Chemdraw to Chem3D. The 3-D structure should appear in your Chem3D window. Next open up the internal coordinates table under the view tab. Your Chem3D screen should look like the following:



The left window will be a table showing the atom, bond lengths, bond angles, and other information. You can also place your cursor on the bond to obtain the bond length as well. Now we want to calculate the molecular minimization energy for the molecule (MM2). Essentially, this will use computations (based on mathematics) to place the molecule in its lowest energy conformation. When you press the MM2 with reaction arrow in the tab bar (MM2 minimize), the molecule will begin to rotate and will be placed in its lowest energy geometry/conformation (this will take a few seconds). You will repeat this for a variety of molecules throughout this exercise. ***Make sure you open a new window in Chem 3D for each molecule!***

For Penta-1,4-diene **(1)** and answer the following questions?

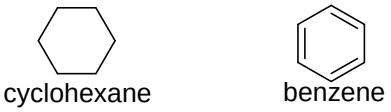
1. What is the bond-length between C(1) and C(2) in **(1)?** _____
2. What is the bond-length between C(2) and C(3) in **(1)?** _____
3. Are the bond lengths the same or different? Why?

Next, perform the same calculation for *E*-penta-1,3-diene **(2)** and answer the following questions?

4. What is the bond-length between C(1) and C(2) in **(2)?** _____
5. What is the bond-length between C(2) and C(3) in **(2)?** _____
6. Are the bond lengths the same or different? Why?
7. Now compare the bond lengths between **(1)** & **(2)**. Are they the same or different? Provide an explanation for your calculations.

Exercise #2: Aromaticity

Using Chemdraw and Chem3D as in the previous section, build and minimize cyclohexane **(3)** and benzene **(4)**.



For cyclohexane **(3)**:

1. What are the C-C bond lengths?_____
2. Is the molecule planar?_____
3. What is the hybridization of each carbon?_____

For benzene **(4):**
1. What are the C-C bond lengths?_____
2. Is the molecule planar?_____
3. What is the hybridization of each carbon?_____

Why are the bond lengths and hybridization of the carbons different for cyclohexane and benzene?

Using the Chemdraw and Chem3D as in the previous section, build and minimize tetrahydrofuran **(5)** and furan **(6)**.

tetrahydrofuran
(5)

furan
(6)

For tetrahydrofuran (THF) **(5)**:
1. In tetrahydrofuran planar?_____
2. What is the C-O bond length?_____
3. Is tetrahydrofuran conjugated?_____
4. What is the hybridization of oxygen in tetrahydrofuran?_____
5. Is tetrahydrofuran aromatic, non-aromatic, or antiaromatic?_____

For furan **(6)**:
1. In tetrahydrofuran flat?_____
2. What is the C-O bond length?_____
3. Is furan conjugated?_____
4. What is the hybridization of oxygen in furan?_____
5. Is tetrahydrofuran aromatic, non-aromatic, or antiaromatic?_____

Why is the hybridization of the oxygen in THF **(5)** and furan **(6)** different?

Exercise #3: Determining Aromaticity
Build the following molecules in Chem3D and fill in the chart below:

Molecule	**Cyclic (Yes or No)**	**Conjugated (Yes or No)**	**Planar (Yes or No)**	**Obeys Huckel's [4n + 2] rule for aromaticity (Yes or No)**	**Obeys [4n] rule for anti-aromaticity (Yes or No)**	**Aromatic non-aromatic, or anti-aromatic.**