REPORT

By collecting data from other students, you should be able to determine which product was obtained from the bromination of each of the three aromatic compounds. Using this information, arrange the three substituent groups (acetamido, amino, and methoxy) in order of decreasing ability to activate the benzene ring.

REFERENCE

Zaczek, N. M., and Tyszklewicz, R. B. "Relative Activating Ability of Various Ortho, Para-Directors." *Journal of Chemical Education, 63* (1986): 510.

QUESTIONS

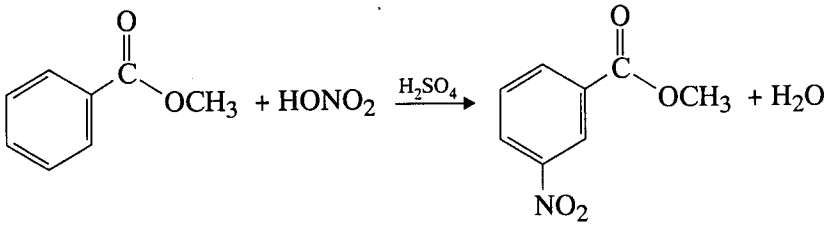
1. Using resonance structures, show why the amino group is activating. Consider an attack by the electrophile E^+ at the *para* position.
2. For the substituent in this experiment that was found to be least activating, explain why bromination took place at the position on the ring indicated by the experimental results.
3. What other experimental techniques (including spectroscopy) might be used to identify the products in this experiment?

Experiment 40

Nitration of Methyl Benzoate

Aromatic substitution
Crystallization

The nitration of methyl benzoate to prepare methyl *m*-nitrobenzoate is an example of an electrophilic aromatic substitution reaction, in which a proton of the aromatic ring is replaced by a nitro group:

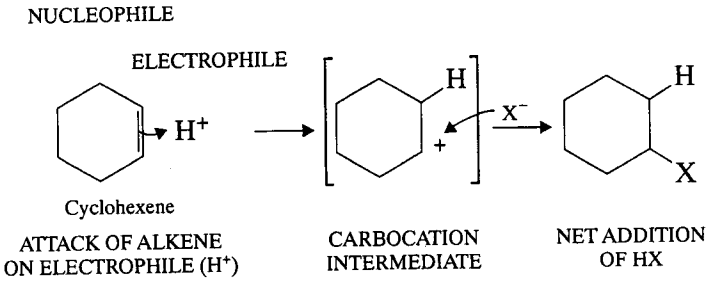


Methyl benzoate — Methyl *m*-nitrobenzoate

Many such aromatic substitution reactions are known to occur when an aromatic substrate is allowed to react with a suitable electrophilic reagent, and many other groups besides nitro may be introduced into the ring.

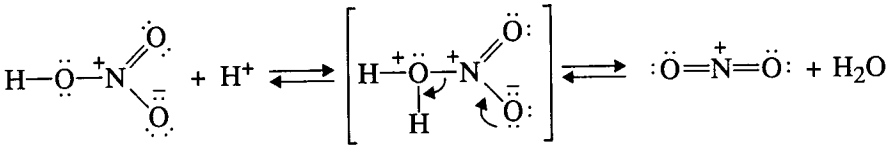
You may recall that alkenes (which are electron-rich due to an excess of electrons in the π system) can react with an electrophilic reagent. The intermediate formed is electron-

deficient. It reacts with the nucleophile to complete the reaction. The overall sequence is called **electrophilic addition.** Addition of HX to cyclohexene is an example.



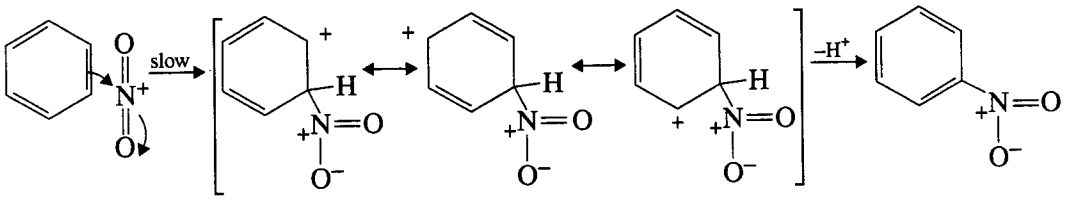
Aromatic compounds are not fundamentally different from cyclohexene. They can also react with electrophiles. However, because of resonance in the ring, the electrons of the π system are generally less available for addition reactions, because an addition would mean the loss of the stabilization that resonance provides. In practice, this means that aromatic compounds react only with **powerfully electrophilic reagents,** usually at somewhat elevated temperatures.

Benzene, for example, can be nitrated at 50°C with a mixture of concentrated nitric and sulfuric acids; the electrophile is NO_2^+ (nitronium ion), whose formation is promoted by action of the concentrated sulfuric acid on nitric acid:



Nitric acid — Nitronium ion

The nitronium ion thus formed is sufficiently electrophilic to add to the benzene ring, *temporarily* interrupting ring resonance:



The intermediate first formed is somewhat stabilized by resonance and does not rapidly undergo reaction with a nucleophile; in this behavior, it is different from the unstabilized carbocation formed from cyclohexene plus an electrophile. In fact, aromaticity can be restored to the ring if **elimination** occurs instead. (Recall that elimination is often a reaction of carbocations.) Removal of a proton, probably by HSO_4^-, from the sp^3-ring carbon **restores the aromatic system** and yields a net **substitution** wherein a hydrogen has been replaced by a nitro group. Many similar reactions are known, and they are called **electrophilic aromatic substitution reactions.**

The substitution of a nitro group for a ring hydrogen occurs with methyl benzoate in the same way it does with benzene. In principle, one might expect that any hydrogen on the ring could be replaced by a nitro group. However, for reasons beyond our scope here (see your lecture textbook), the carbomethoxy group directs the aromatic substitution preferentially to those positions that are *meta* to it. As a result, methyl *m*-nitrobenzoate is the

principal product formed. In addition, one might expect the nitration to occur more than once on the ring. However, both the carbomethoxy group and the nitro group that has just been attached to the ring *deactivate* the ring against further substitution. Consequently, the formation of a methyl dinitrobenzoate product is much less favorable than the formation of the mononitration product.

Although the products described previously are the principal ones formed in the reaction, it is possible to obtain as impurities in the reaction small amounts of the ortho and para isomers of methyl *m*-nitrobenzoate and of the dinitration products. These side products are removed when the desired product is washed with methanol and purified by crystallization.

Water has a retarding effect on the nitration because it interferes with the nitric acid–sulfuric acid equilibria that form the nitronium ions. The smaller the amount of water present, the more active the nitrating mixture. Also, the reactivity of the nitrating mixture can be controlled by varying the amount of sulfuric acid used. This acid must protonate nitric acid, which is a *weak* base, and the larger the amount of acid available, the more numerous the protonated species (and hence NO_2^+) in the solution. Water interferes because it is a stronger base than H_2SO_4 or HNO_3. Temperature is also a factor in determining the extent of nitration. The higher the temperature, the greater will be the amounts of dinitration products formed in the reaction.

REQUIRED READING

Review: Technique 5

SPECIAL INSTRUCTIONS

It is important that the temperature of the reaction mixture be maintained below 15°C. Nitric acid and sulfuric acid, especially when mixed, are very corrosive substances. Be careful not to get these acids on your skin. If you do get some of these acids on your skin, flush the affected area liberally with water.

WASTE DISPOSAL

The filtrate from the Hirsch funnel filtration should be placed in the designated container.

PROCEDURE

Add 0.210 mL of methyl benzoate to a tared 3-mL conical vial, and determine the actual weight of methyl benzoate. Add 0.45 mL of concentrated sulfuric acid to the methyl benzoate along with a magnetic spin vane. Attach an air condenser to the conical vial. The purpose of the air condenser is to make it easier to hold the conical vial in place. Prepare an ice bath in a 250-mL beaker using both ice and water. Clamp the air condenser so that the conical vial is immersed in the ice bath as shown in Figure 2.6, page 527. (Note that in Figure 2.6 a water bath is shown rather than an ice bath.) While stirring, *very slowly* add a cool mixture of 0.15 mL of concentrated sulfuric acid and 0.15 mL of concentrated nitric acid over a period of about 15 minutes. The acid mixture should be added with a 9-inch Pasteur pipet through the top of the air condenser. If the addition is too fast, the formation of by-product increases rapidly, reducing the yield of the desired product.

After you have added all the acid, warm the mixture to room temperature by replacing the ice water in the 250-mL beaker with water at room temperature. Let the reaction mixture stand for 15 more minutes without stirring. Then, using a Pasteur pipet, transfer the reaction mixture

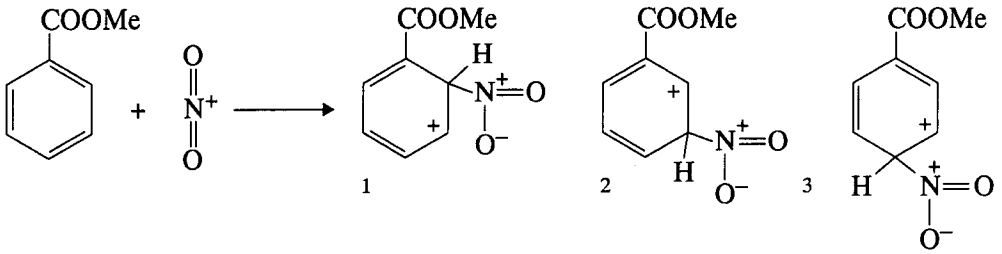
to a 20-mL beaker containing 2.0 g of crushed ice. After the ice has melted, isolate the product by vacuum filtration using a Hirsch funnel, and wash it with two 1.0-mL portions of cold water and then with two 0.3-mL portions of ice-cold methanol. Weigh the crude, dry product and recrystallize it from methanol using a Craig tube (see Technique 5, Section 5.4, p. 566).

Determine the melting point of the product. The melting point of the recrystallized product should be 78°C. Obtain the infrared spectrum as a KBr mull (Technique 19, Section 19.6.A, p. 753) or by the somewhat easier dry film method (Technique 19, Section 19.6.B, p. 753). Submit the product to your instructor in a labeled vial.

MOLECULAR MODELING (optional)

If you are working alone, complete Part One. If you have a partner, one of you should complete Part One and the other complete Part Two. If you work with a partner, you should combine results at the end of the experiment.

Part One: Nitration of Methyl Benzoate. In this exercise we will try to explain the observed outcome of the nitration of methyl benzoate. The major product of this reaction is methyl *m*-nitrobenzoate, where the nitro group has been added to the *meta* position of the ring. The rate-determining step of this reaction is the attack of the nitronium ion on the benzene ring. Three different benzenium ion intermediates *(ortho, meta,* and *para)* are possible:



We will calculate the heats of formation for these intermediates to determine which of the three has the lowest energy. Assume that the activation energies are similar to the energies of the intermediates themselves. This is an application of the Hammond Postulate, which states that the activation energy leading to an intermediate of higher energy will be higher than the activation energy leading to an intermediate of lower energy, and vice versa. Although there are prominent exceptions, this postulate is generally true.

Make models of each of the three benzenium ion intermediates (separately), and calculate their heats of formation using an AM1-level calculation with geometry optimization. Don't forget to specify a positive charge when you submit the calculation. What do you conclude?

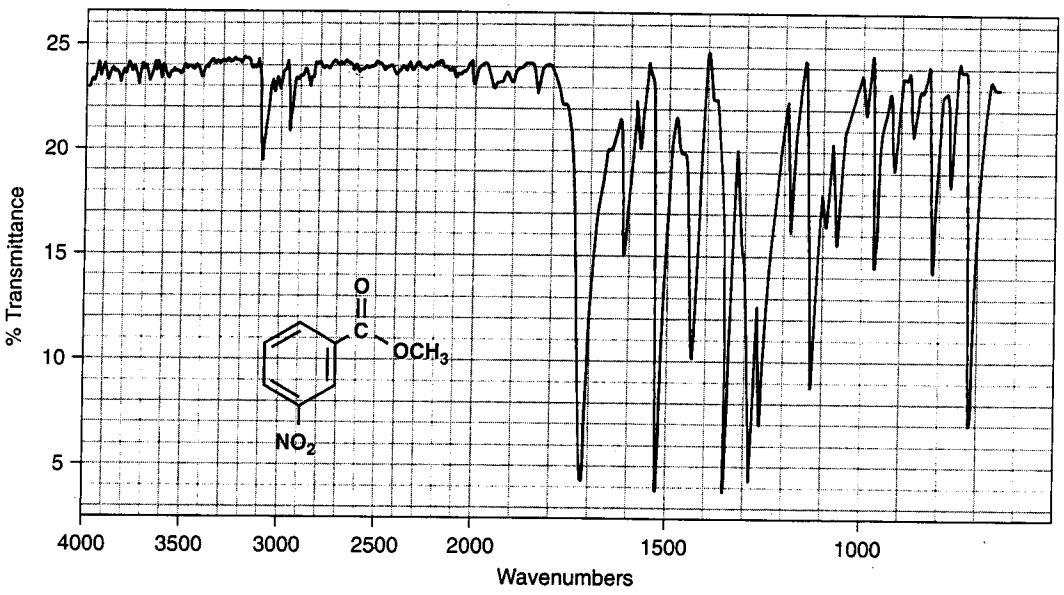
Now take a piece of paper and draw the resonance structures that are possible for each intermediate. Do not worry about structures involving the nitro group, only consider where the charge in the ring may be delocalized. Also note the polarity of the carbonyl group by placing a δ+ symbol on the carbon and a δ– symbol on the oxygen. What do you conclude from your resonance analysis?

Part Two: Nitration of Anisole. For this computation you will analyze the three benzenium ions formed from anisole (methoxybenzene) and the nitronium ion (see Part One). Calculate the heats of formation using AM1-level calculations with geometry optimization. Don't forget to specify a positive charge. What do you conclude for anisole? How do the results compare to those for methyl benzoate?

Now take a piece of paper, and draw the resonance structures that are possible for each intermediate. Do not worry about structures involving the nitro group, only consider where the charge in the ring may be delocalized. Do not forget that the electrons on the oxygen can participate in the resonance. What do you conclude from your resonance analysis?

QUESTIONS

1. Why is methyl *m*-nitrobenzoate formed in this reaction instead of the ortho or para isomers?
2. Why does the amount of the dinitration increase at high temperatures?
3. Why is it important to add the nitric acid–sulfuric acid mixture slowly over a 15-minute period?
4. Interpret the infrared spectrum of methyl *m*-nitrobenzoate.
5. Indicate the product formed on nitration of each of the following compounds: benzene, toluene, chlorobenzene, and benzoic acid.



Infrared spectrum of methyl *m*-nitrobenzoate, KBr

Essay

Local Anesthetics

Local anesthetics, or "painkillers," are a well-studied class of compounds with which chemists have shown their ability to study the essential features of a naturally occurring drug and to improve on them by substituting totally new, synthetic surrogates. Often such substitutes are superior in desired medical effects and in lack of unwanted side effects or hazards.

The coca shrub *(Erythroxylon coca)* grows wild in Peru, specifically in the Andes Mountains, at elevations of 1,500 to 6,000 ft above sea level. The natives of South America have longed chewed these leaves for their stimulant effects. Leaves of the coca shrub have even been found in pre-Inca Peruvian burial urns. Chewing the leaves brings about a

yield, and determine the microscale boiling point. Determine the infrared spectrum of the product using salt plates (Technique 19, Section 19.2, p. 743). Submit the remainder of your sample in a properly labeled vial, along with the infrared spectrum (see page 214), when you submit your report to the instructor.

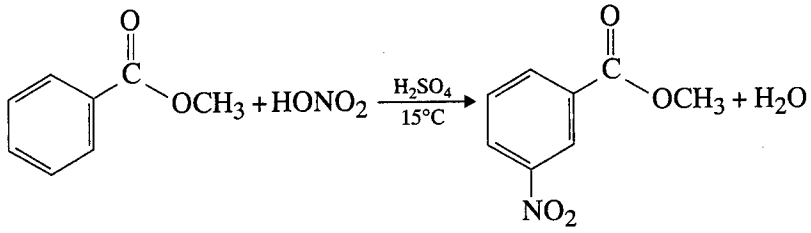
QUESTIONS

Answer the questions given in Experiment 21, p. 215.

Experiment 54

Nitration of Methyl Benzoate

Aromatic substitution
Macroscale technique
Crystallization



Methyl benzoate — Methyl *m*-nitrobenzoate

REQUIRED READING

Review: Introductory material in Experiment 40
Techniques 1, 2, and 3
Technique 19

New: Essay: How to Scale Up a Reaction: Macroscale Methods
Technique 5 Crystallization: Purification of Solids, Sections 5.3, 5.6, and 5.7

SPECIAL INSTRUCTIONS

It is important that the temperature of the reaction mixture be maintained at or below 15°C. Nitric acid and sulfuric acid, especially when mixed, are very corrosive substances. Be careful not to get these acids on your skin. If you do get some of these acids on your skin, flush the affected area liberally with water.

WASTE DISPOSAL

All aqueous solutions should be placed in the container designated for that purpose. Place the methanol used to recrystallize the methyl nitrobenzoate in the container designated for nonhalogenated organic waste.

PROCEDURE

In a 150-mL beaker, cool 12 mL of concentrated sulfuric acid to about 0°C and add 6.1 g of methyl benzoate. Using an ice-salt bath (see Technique 2, Section 2.5, p. 526), cool the mixture to 0°C or below and add, VERY SLOWLY, using a Pasteur pipet, a cool mixture of 4 mL of concentrated sulfuric acid and 4 mL of concentrated nitric acid. Avoid getting ice into the reaction mixture. During the addition of the acids, stir the mixture continuously and maintain the temperature of the reaction below 15°C. If the mixture rises above this temperature, the formation of by-product increases rapidly, reducing the yield of the desired product.

After you have added all the acid, warm the mixture to room temperature. After 15 minutes, pour the acid mixture over 50 g crushed ice in a 250-mL beaker. After the ice has melted, isolate the product by vacuum filtration through a Büchner funnel and wash it with two 25-mL portions of cold water and then with two 10-mL portions of ice-cold methanol. Weigh the product, and recrystallize it from an equal weight of methanol (Technique 5, Section 5.3, p. 561). Determine the melting point of the product. The melting point of the recrystallized product should be 78°C. Obtain the infrared spectrum as a KBr mull (Technique 19, Section 19.4, p. 746) or by the somewhat easier dry film method (Technique 19, Section 19.6B, p. 753.) Submit the product to your instructor in a labeled vial, along with your infrared spectrum. Compare the spectrum with the one found on page 346.

MOLECULAR MODELING (optional)

See the instructions outlined in Experiment 40, page 345. These instructions are directly applicable to this experiment as well as to Experiment 40.

QUESTIONS

Answer the questions given in Experiment 40, page 346.