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REAC
716

publisher: H.A. Neidig

organic editor: Joe Jeffers

Nitrating Acetanilide or Methyl Benzoate: Electrophilic Aromatic Substitution

prepared by **Carl T. Wigal**, Lebanon Valley College

PURPOSE OF THE EXPERIMENT

Demonstrate the regiochemistry of electrophilic aromatic substitution reactions for monosubstituted aromatic compounds.

EXPERIMENTAL OPTIONS

BACKGROUND REQUIRED

You should be familiar with vacuum filtration, melting point measurement, and recrystallization techniques.

BACKGROUND INFORMATION

Most substitution reactions at aliphatic carbon atoms are nucleophilic. However, aromatic substitution reactions are generally electrophilic, due to the high electron density of the benzene ring. The species reacting with the aromatic ring is usually a positive ion or the positive end of a dipole. This electron-deficient species, or **electrophile**, may be produced in various ways, but the reaction between the electrophile and the aromatic ring is essentially the same in all cases. The most common electrophilic aromatic substitution mechanism is the **arenium ion mechanism**, shown in Figure 1.

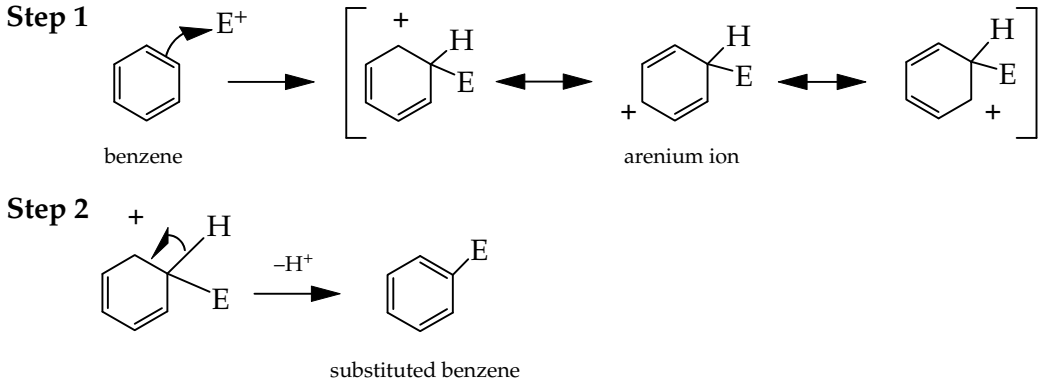


Figure 1 The arenium ion mechanism for electrophilic aromatic substitution

02 01 00 99 98 — 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

In the first step of the reaction, benzene donates an electron pair to the electrophilic species, designated E^+. A carbocation intermediate is formed, called an **arenium ion** or **sigma complex**. This arenium ion can be written in three resonance forms. Although the arenium ion is stabilized by these resonance forms, it is destabilized by the loss of aromatic stability (~ 36 kcal/mol). This aromatic stability is regained in the second step of the reaction, consisting of elimination of a proton from the arenium ion, forming a substituted benzene.

To accurately design an experiment involving an electrophilic substitution reaction performed on a monosubstituted benzene, several factors must be considered. One factor is the relative rate of the reaction. The substituent group already present on the ring may cause the substitution reaction to be slower or faster than the initial reaction with benzene.

Substituent groups that increase the reaction rate relative to the reaction rate with benzene are called **activators**. Activators donate electrons, increasing the electron density of the aromatic ring and thus stabilizing the arenium ion. Activators can donate electrons to the aromatic ring in either of two ways. Most activators donate electrons by resonance. Resonance donators have a lone pair of electrons on the atom directly connected to the ring. These electrons overlap with the pi cloud of the aromatic system. Examples of resonance donating groups are $–N(CH_3)_2$ and –OH.

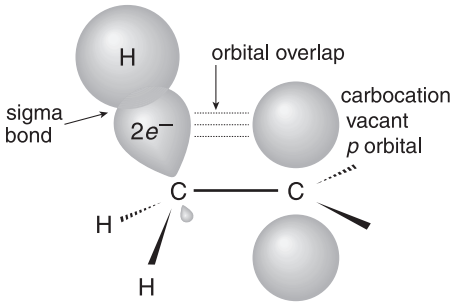


Figure 2 Hyperconjugation with a carbocation

Other activators stabilize the arenium ion through hyperconjugation. **Hyperconjugation** is the overlap of a neighboring sigma bond with the aromatic pi system. Figure 2 shows the overlap with an adjacent carbocation. Alkyl substituents are common examples of activators due to hyperconjugation.

Substituent groups that decrease the reaction rate relative to the reaction rate with benzene are called **deactivators**. Deactivators withdraw electrons and decrease the electron density of the aromatic ring, thus destabilizing the arenium ion. A substituent can withdraw electrons from the ring either by resonance or by induction.

Pi bonds that overlap a *p* orbital on the substituent with the pi system of the aromatic ring cause resonance electron-withdrawing effects. Most resonance withdrawing groups have a positive or partially positive atom directly connected to the ring. Examples of resonance withdrawing groups are $–NO_2$ and –CN.

Inductive effects result from electronegativity differences in bonding atoms. Electronegative atoms pull electrons away from the aromatic ring through connecting sigma bonds. Halogens are examples of deactivating groups that act through induction.

In addition to affecting the rate of substitution, the electronic nature of the substituent also directs the position of electrophilic substitution. There are three different **regioisomers** for disubstituted aromatic rings: ***ortho***, or 1,2; ***meta***, or 1,3; and ***para***, or 1,4.

The overall directing and rate effects of a substituent can be classified into three groups: *ortho-para*-directing activators; *ortho-para*-directing deactivators; and *meta*-directing deactivators. Any substituent that activates the aromatic ring is an *ortho-para*-director. Figure 3 shows the resonance forms of the arenium ion associated with a monosubstituted aromatic system. Electrophilic attack at either the *ortho*- or *para*-position places a positive charge on the carbon that bears the substituent X, indicated by resonance forms C and E, respectively. When X is an electron-

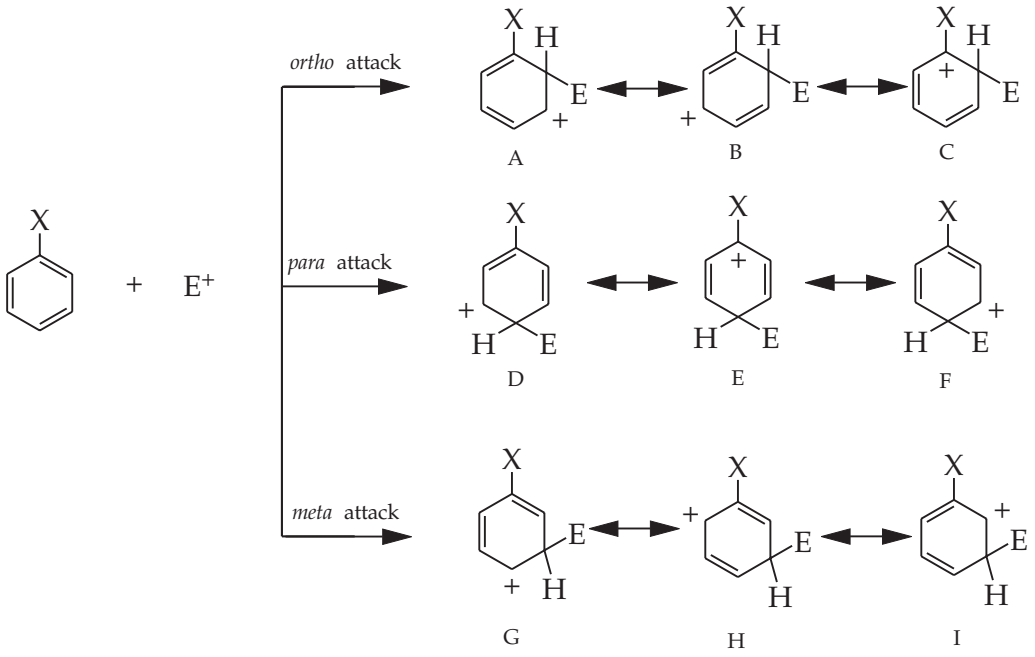


Figure 3 Resonance forms of a substituted arenium ion

donating substituent, stabilization of the positive charge results. This stabilization is not possible when attack occurs at the *meta*-position.

Electron-withdrawing substituents are usually *meta*-directors. *Ortho-para* attack on a deactivated ring would place a positive charge on the carbon that bears the substituent X. However, when X is an electron-withdrawing substituent, the electronic effects of the substituent destabilize the positive charge. Consequently, *meta* attack is favored because all resonance forms, G, H, and I, avoid this unfavorable electronic interaction.

The halogens are *ortho-para*-deactivators. Halogens possess both electron-withdrawing inductive effects and electron-donating resonance effects. Halogens deactivate the ring because of their high electronegativity, yet they can stabilize the arenium ion by sharing a lone electron pair. As a general rule, any atom that is directly connected to the aromatic ring and has a lone electron pair is an *ortho-para*-director. A summary of substituent directing effects is shown in Figure 4 on page 4.

Nitration is one of the most important examples of electrophilic aromatic substitution. Aromatic nitro compounds are used in products ranging from explosives to pharmaceutical synthetic intermediates. The electrophile in nitration is the **nitronium ion** (**NO_2^+**). The nitronium ion is generated from nitric acid by protonation and loss of water, using sulfuric acid as the dehydrating agent. The reaction is shown in Equation 1.

$$HNO_3 + 2\,H_2SO_4 \rightarrow NO_2^+ + H_3O^+ + 2\,HSO_4^- \qquad \text{(Eq. 1)}$$

In this experiment, you will nitrate either acetanilide or methyl benzoate as the substrate. You will use melting point data to determine which regioisomer is formed. The reactions, without showing regiochemistry, are shown in Equations 2 and 3 on page 4.

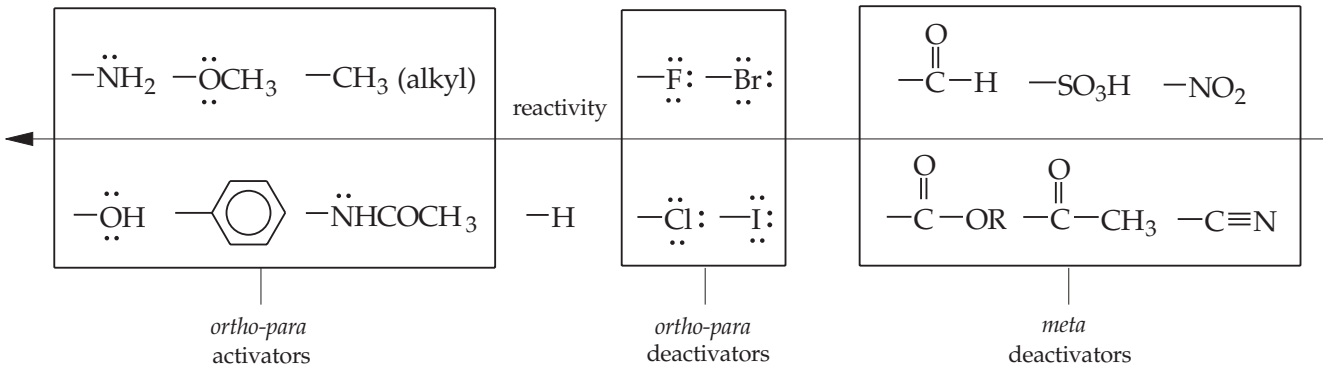
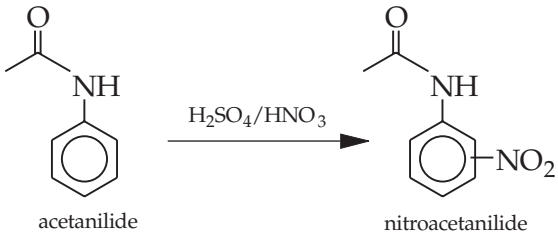
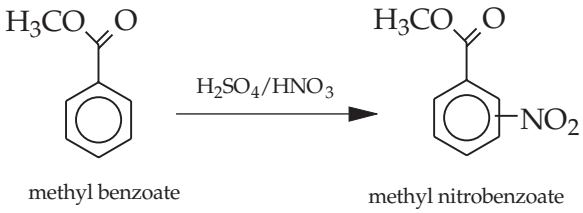


Figure 4 Classification of directing effects for substituents



(Eq. 2)



(Eq. 3)

Equipment

50-mL beaker	50-mL graduated cylinder
400-mL beaker*	marking pen
Büchner funnel,	microspatula
with filter paper and adapter	3 Pasteur pipets, with latex bulb
25-mL Erlenmeyer flask	3 pipets, 1-mL, with rubber bulb
125-mL Erlenmeyer flask	sand bath†
125-mL filter flask	support stand
glass stirring rod	2 test tubes, 15 × 125-mm
10-mL graduated cylinder	utility clamp

*for ice bath

†or hot plate, or electric heating well with heat controller

Reagents and Properties

substance	*quantity*	*molar mass (g/mol)*	*d (g/mL)*	*mp (°C)*	*bp (°C)*
acetanilide	0.5 g	135.17		113–115	
ethanol, 95%	5–10 mL	46.07			78
methyl benzoate	0.55 g	136.15	1.094	–12	198

methyl nitrobenzoate*	181.13	
nitroacetanilide*	180.16	
nitric acid conc.	0.5 mL	63.01
sulfuric acid conc.	1.6 mL	98.08

*product

Preview

- Prepare the ice bath
- Prepare the nitration solution
- Prepare the substrate solution
- Add the nitration solution to the substrate solution and react 30–45 min
- Quench the reaction with water
- Filter the product using vacuum filtration
- Wash the product with water and air dry
- Recrystallize the product from 95% ethanol
- Weigh the product
- Measure the melting point of the product

PROCEDURE

Chemical Alert

acetanilide—*toxic and irritant*
ethanol—*flammable and irritant*
methyl benzoate—*irritant*
nitroacetanilide—*irritant*
concentrated nitric acid—*toxic and oxidizer*
concentrated sulfuric acid—*toxic and oxidizer*

Caution: Wear departmentally approved safety goggles at all times while in the chemistry laboratory.

1. Preparing the Ice-Water Bath and Chilled Water

Place equal volumes of ice and tap water into a 400-mL beaker, so that the beaker is 75% full. Prepare chilled water for Parts 3 and 4 by pouring approximately 30 mL of distilled or deionized water into a 125-mL Erlenmeyer flask and placing the flask into the ice-water bath.

2. Preparing the Nitrating Solution

Caution: Nitric acid and sulfuric acid are toxic and oxidizing. They can cause severe burns. Prevent eye, skin, clothing, and combustible material contact. Avoid inhaling vapors and ingesting these compounds. Use a ***fume hood***.

Label two 15 × 125-mm test tubes "nitric acid" and "sulfuric acid", respectively. Transfer 0.5 mL of concentrated nitric acid into the "nitric acid" tube. Transfer 0.6 mL of concentrated sulfuric acid into the "sulfuric acid" tube. Chill both test tubes containing the acids in the ice-water bath for 15 min.

Caution: Mixing concentrated sulfuric and nitric acids is a highly exothermic reaction. Hot acid mixtures may bump and cause acid burns. Make certain the acids are *cold* before mixing.

Use a Pasteur pipet to *very slowly* add the *cold* sulfuric acid *dropwise* to the *cold* nitric acid. Swirl the reaction mixture after every 3 drops. After adding all the sulfuric acid, allow the nitrating solution to stand in the ice-water bath for 10 min.

3. Nitrating the Aromatic Compound [NOTE 1]

A. Nitrating Acetanilide

Caution: Acetanilide is toxic and irritating. Nitroacetanilide is irritating. Prevent eye, skin, and clothing contact. Avoid inhaling dust and ingesting these compounds.

NOTE 1: Your laboratory instructor may designate either procedure *A* or *B* for Part 3. If you do both procedures, you will need to do Part 2 for each procedure.

Place 0.5 g of acetanilide into a 25-mL Erlenmeyer flask. Add 1.0 mL of concentrated sulfuric acid. Heat the mixture *gently* to dissolve the acetanilide. Allow the mixture to cool to room temperature.

Clamp the flask containing the mixture to a support stand. Lower the flask into the ice-water bath for 5 min. Take care to prevent bath water from entering the reaction flask.

Use a Pasteur pipet to *slowly* add the nitrating solution in the test tube to the Erlenmeyer flask containing the acetanilide and sulfuric acid. [NOTE 2] After adding all the nitrating solution, allow the mixture to stand in the ice-water bath for 30–45 min, swirling the flask every 5 min.

NOTE 2: Rapid addition of the nitrating solution will cause the reaction mixture to heat up, turning the mixture dark brown. The dark product is difficult to recrystallize and has a lower melting point.

After 30–45 min, add 10 mL of chilled water to a 50-mL beaker. *Slowly and carefully* add the cold reaction mixture, with stirring, to the chilled water. Allow the chilled solution to stand 5–10 min to complete crystal formation.

B. Nitrating Methyl Benzoate

Caution: Methyl benzoate is irritating. Prevent eye, skin, and clothing contact. Avoid inhaling vapor and ingesting this compound.

Place 0.55 g (0.5 mL) of methyl benzoate into a 25-mL Erlenmeyer flask. Add 1.0 mL of concentrated sulfuric acid.

Clamp the flask containing the mixture to a support stand and lower the flask into the ice-water bath for 5 min. Take care to prevent bath water from entering the reaction flask.

Use a Pasteur pipet to *slowly* add the nitrating solution in the test tube to the Erlenmeyer flask containing the methyl benzoate and sulfuric acid. After adding all the nitrating solution, allow the mixture to stand in the ice-water bath for 30–45 min, swirling the flask every 5 min.

After 30–45 min, add 10 mL of chilled water to a 50-mL beaker. *Slowly and carefully* add the cold reaction mixture, with stirring, to the chilled water. Allow the chilled solution to stand 5–10 min to complete crystal formation.

4. Isolating, Purifying, and Characterizing the Product

Caution: Ethanol is flammable and irritating. Keep away from flames and other heat sources. Avoid inhaling vapors and ingesting this compound.

Filter the reaction mixture using vacuum filtration. Wash the crystals with 10 mL of chilled water to remove any residual acid. Allow your product to air dry in the filter funnel for 10 min.

Recrystallize your product from 95% ethanol. [NOTE 3] Filter the crystals using vacuum filtration. Allow your product to air dry in the filter funnel for 10 min.

NOTE 3: Approximate recrystallization volumes of 95% ethanol are 10 mL for nitroacetanilide and 5 mL for methyl nitrobenzoate.

Weigh your product and record its mass. Measure the melting point of your product.

5. Cleaning Up

Place your recovered materials in the appropriate labeled collection containers as directed by your laboratory instructor. Clean your glassware with soap or detergent.

Caution: Wash your hands thoroughly with soap or detergent before leaving the laboratory.

Post-Laboratory Questions

1. Based on your data, answer the following questions:
   (a) What is the percent yield of your product?
   (b) What is the melting point of your product?
   (c) Using the following data table, determine the regiochemistry of your product.

compound	*mol mass*	*ortho mp (°C)*	*meta mp (°C)*	*para mp (°C)*
nitroacetanilide	180.16	94	155	214–217
methyl nitrobenzoate	181.15	–13	78–80	94–96

   (d) Draw the structure of your product.
2. Draw the resonance forms for the arenium ion formed during your reaction.
3. 2,4,6-Trinitrotoluene (TNT) is synthesized by trinitrating toluene. The first nitration proceeds much faster than the second two. Briefly explain.

NAME SECTION DATE

REAC 716/Nitrating Acetanilide or Methyl Benzoate Electrophilic Aromatic Substitution

Pre-Laboratory Assignment

1. What precautions must be taken when using concentrated acids?

2. (a) At what position will electrophilic aromatic substitution occur for the following compounds?

bromobenzene	toluene
nitrobenzene	phenol
benzoic acid	benzaldehyde

   (b) In the list above, which compound is the most reactive? Briefly explain.

   (c) Which compound is the least reactive? Briefly explain.

3. Using the quantities given in the Procedure, calculate the theoretical yields for the mononitration of (a) acetanilide and (b) methyl benzoate. Record your results here and in your laboratory notebook.

ISBN: 0-87540-716-1