

Lecture 4

Synthesis of Alkylbenzenes and Substituent Effects

Dr Andrea Vernall

andrea.vernall@otago.ac.nz

Reference textbook

- “Organic Chemistry” by Paula Yurkanis Bruice, 8th Edn.
- This lecture – Chapter 18, in particular 18.7, 18.8, 18.12,

Learning Objectives – Lecture 4

*Section 2– Substituted benzenes and electrophilic aromatic substitution,
Section 3 - FG interconversion and Section 6 – Synthesis problems*

Discuss and account for complications that may arise during alkylation of benzene derivatives, and propose alternative syntheses which overcome these problems.

Describe and account for the general effects of electron-donating and electron-withdrawing substituents on the rate of S_EAr .

Explain the difference between inductive and mesomeric effects of substituents on the stability of the intermediates of electrophilic aromatic substitution reactions, and classify the effects of a range of substituents as '+I', '-I', '+M' or '-M'

Explain why it is an acceptable approximation to relate the effect of substituents on the reactive intermediate of electrophilic aromatic substitution to the rate of reaction

Predict and account for the effects of common substituents on the chemical shifts of aromatic protons in 1H NMR spectra of substituted benzene derivatives

Recall the reagents..... reduction of carbonyl groups to methylene groups (Clemmensen and Wolff-Kishner reductions)

Lecture Outline: L4

1. Alkylation of benzene

- a. Problems with Friedel Crafts alkylation
- b. Acylation, then reduction

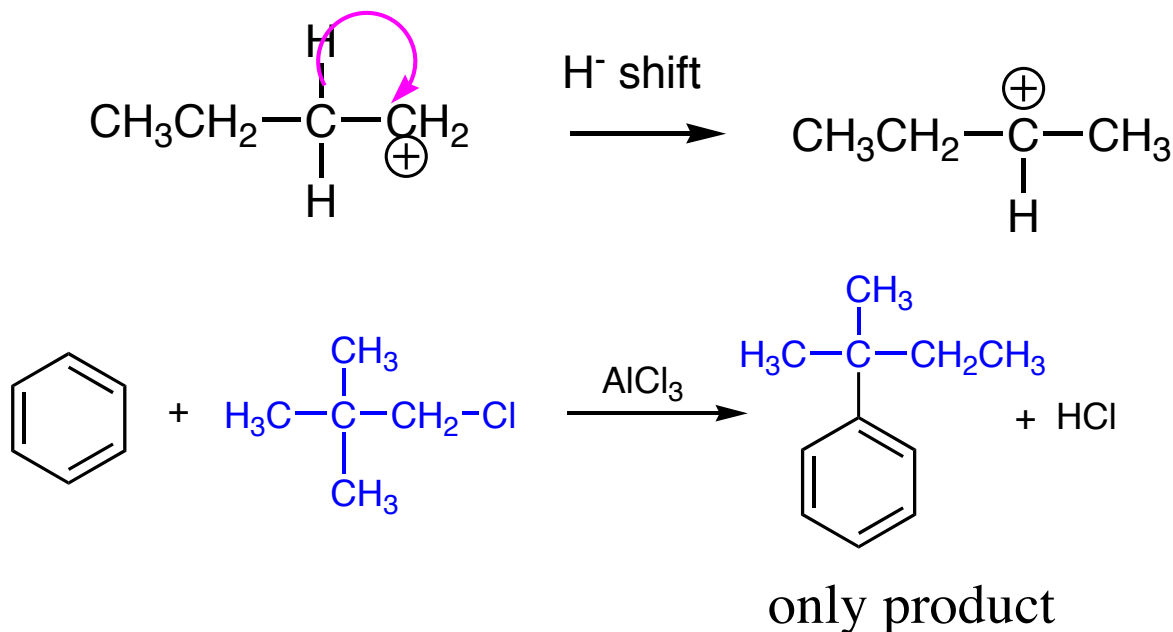
2. Substituent Effects

- a. Overview
- b. Inductive effects
- c. Resonance (mesomeric) effects
- d. Examples in context of S_EAr

1. Alkylation of benzene

a. Problems with FC alkylation

- 1). In S_EAr , the electrophile is a **carbocation**, but a carbocation will rearrange to form a more stable carbocation via a hydride or alkyl group migration, e.g. -



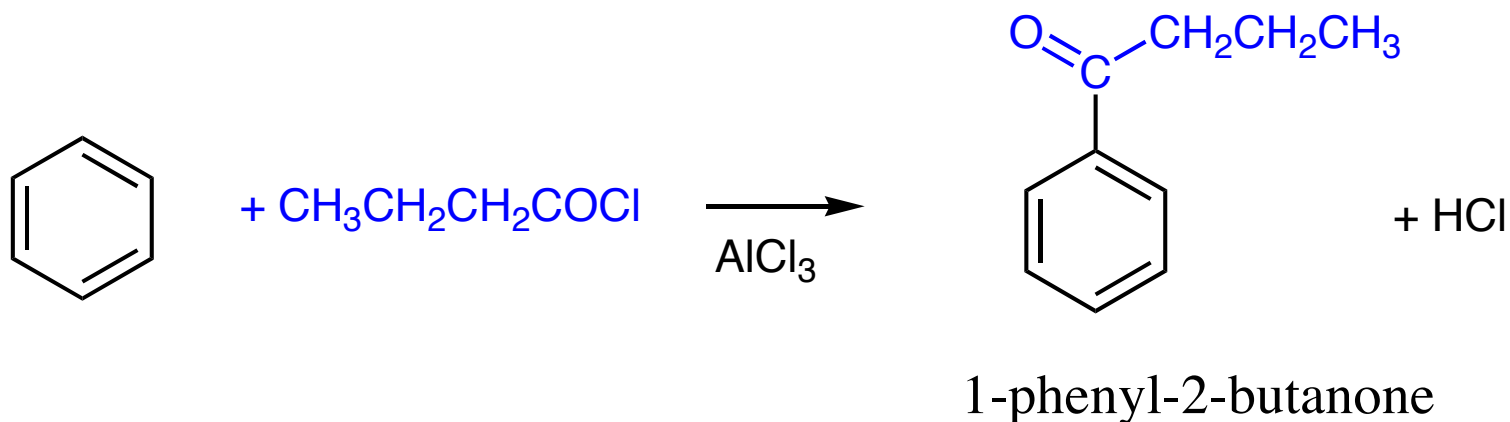
- 2). Another 'problem' with FC alkylation is often the product is **more reactive towards the electrophile**, and a large excess of starting material must be used

So how could we make aromatic systems with unbranched side-chains?

1. Alkylation of benzene

b. Acylation, then reduction

The problem of electrophile rearrangement does NOT occur in FC acylation



The **acylium** ion is **stable**, rearrangement does not occur

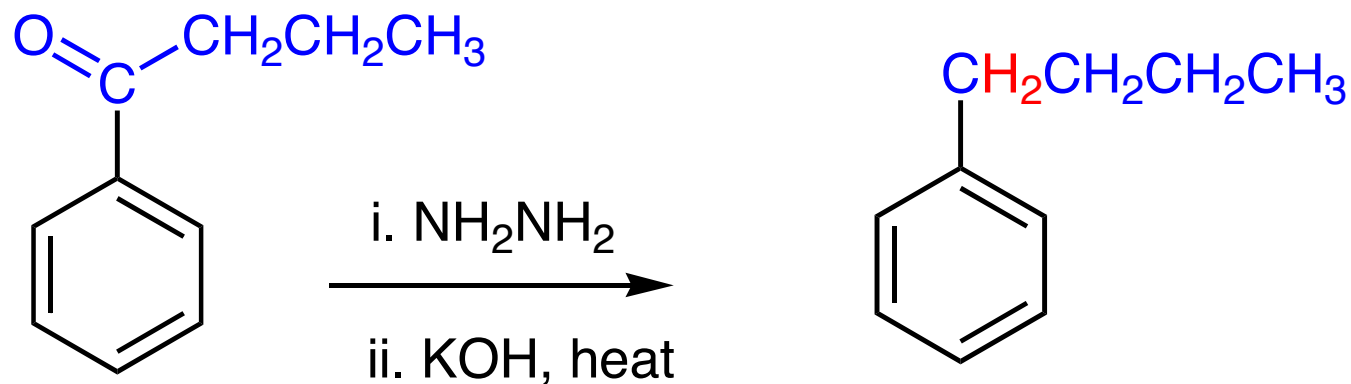
Also, the product is usually **LESS reactive towards the electrophile** (c.f. alkylation)

Now we just need to reduce the carbonyl group

1. Alkylation of benzene

b. Acylation, then reduction

- Now reduce the carbonyl group
- There are many ways this can be done, a method often used is the **Wolff-Kishner reduction**

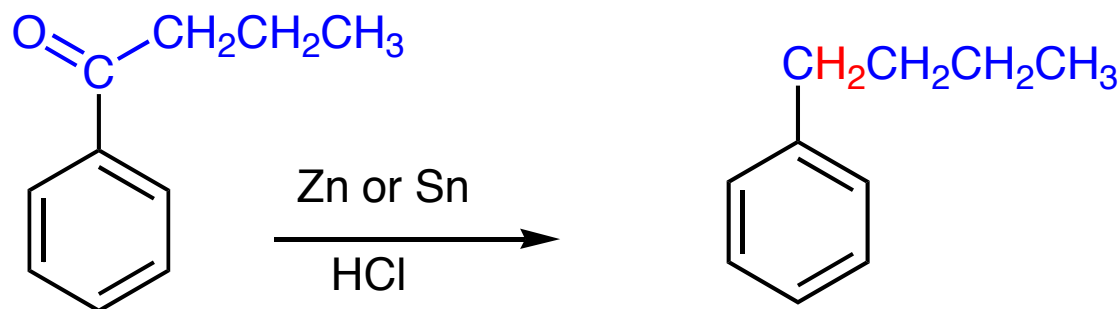


1. Alkylation of benzene

b. Acylation, then reduction

- Now reduce the carbonyl group
- Another commonly used way is a **dissolving metal reduction (Clemmensen)**

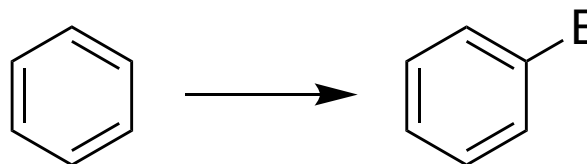
**Dissolving metal
reduction
(Clemmensen)**



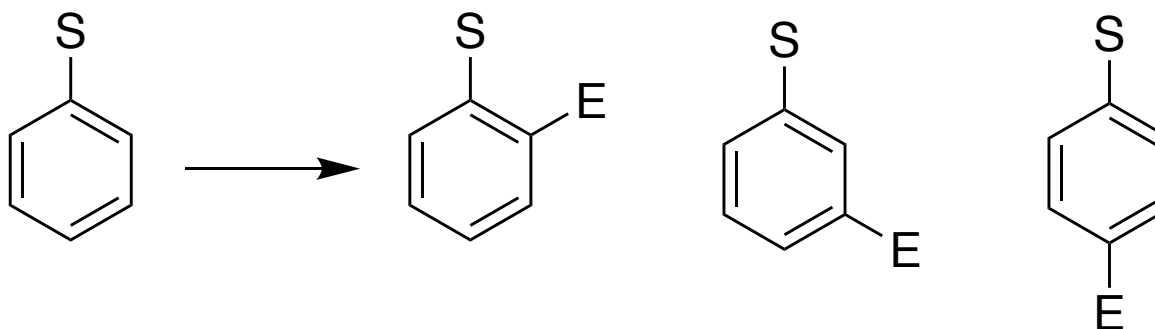
2. Substituent Effects

a. Overview

- So far we have discussed this



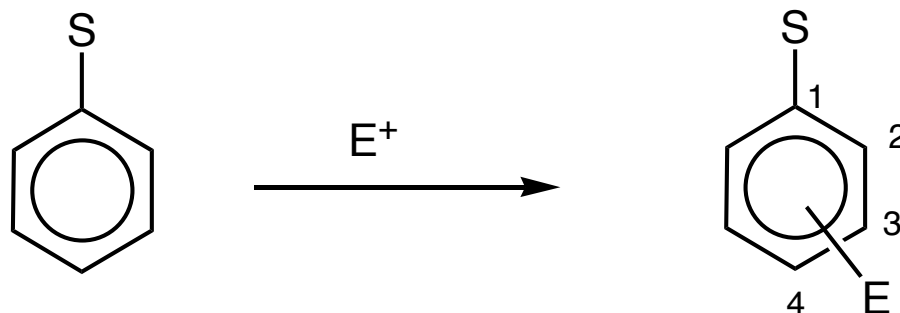
- But what if benzene has a substituent (S), how will this change the reaction with an electrophile (E)?



- First we will discuss how **S increases or decreases the reactivity** of the ring towards **electrophilic aromatic substitution (RATE)**
- Next lecture we will discuss how S **directs E (POSITION)**

2. Substituent Effects

a. Overview – the nature of 'S' in the context of S_EAr



If S is **electron-donating**:

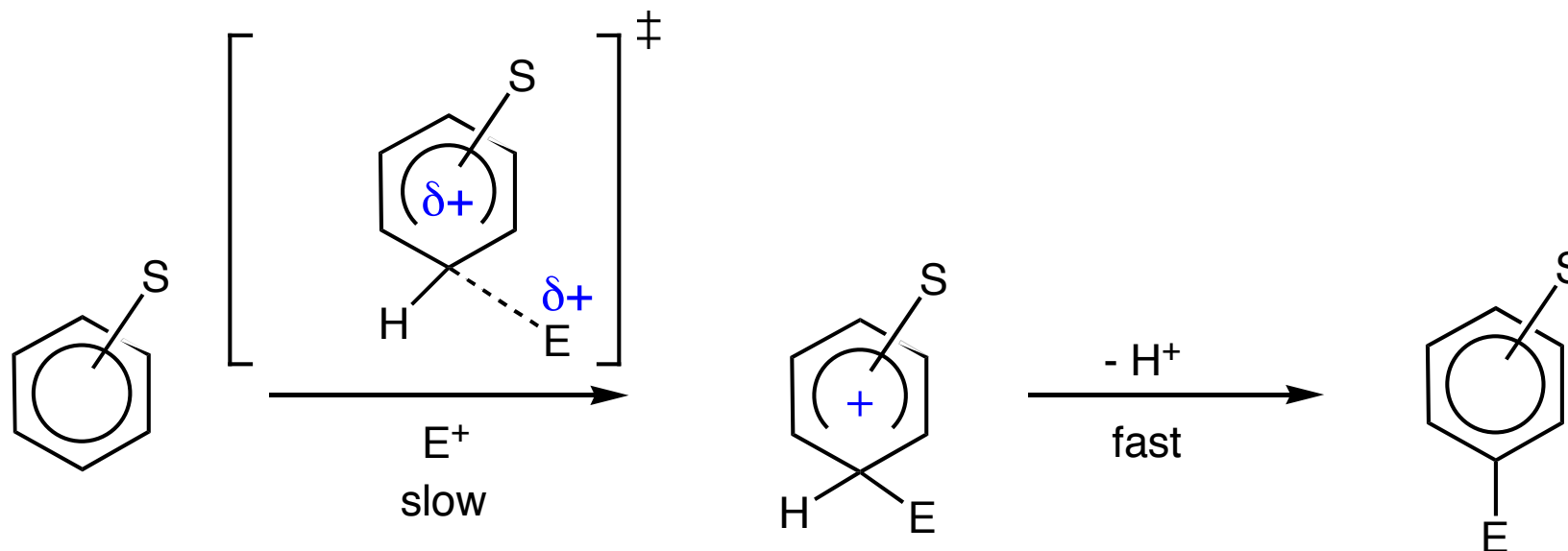
- Ring is **more nucleophilic**
- Positive charge in the TS is more stabilised
- ΔE_a is lower, **reaction rate faster**
- S is an **ACTIVATING** group

If S is **electron-withdrawing**:

- Ring is **less nucleophilic**
- Positive charge in the TS is much less stable
- ΔE_a is higher, **reaction rate slower**
- S is a **DEACTIVATING** group

2. Substituent Effects

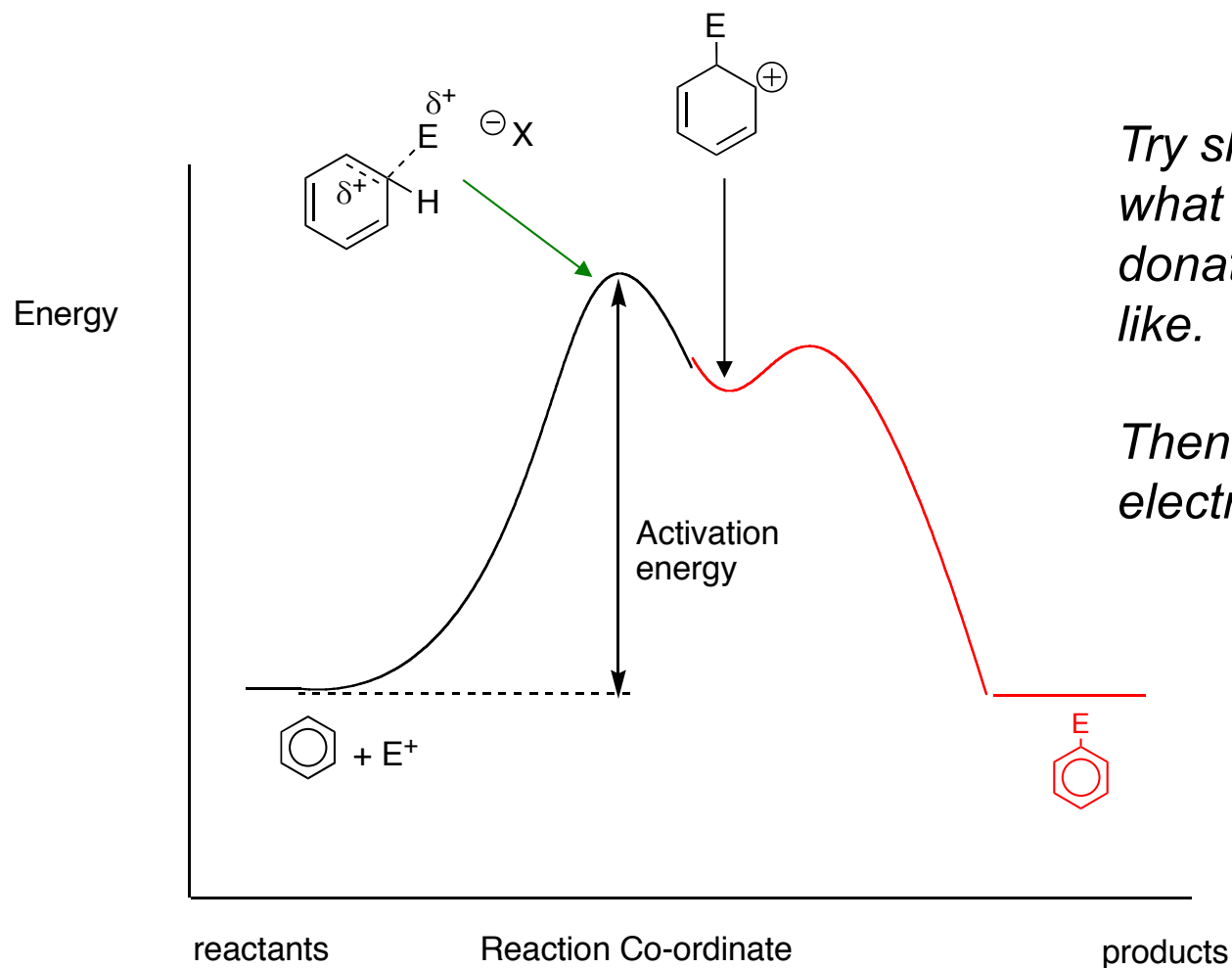
a. Overview – the nature of 'S' in the context of S_EAr , the Transition State (TS)



- The more electron donating S, the more delocalised the charge in the transition state, the lower ΔE_a , the greater the rate of reaction.
- The more electron withdrawing S, the less stabilised the TS, the higher ΔE_a , the lower the rate of reaction.

2. Substituent Effects

a. Overview – the nature of ‘S’ in the context of S_EAr , the Transition State



Try sketching onto the graph what an S_EAr with an electron donating substituent would look like.

Then do this again but with an electron withdrawing substituent

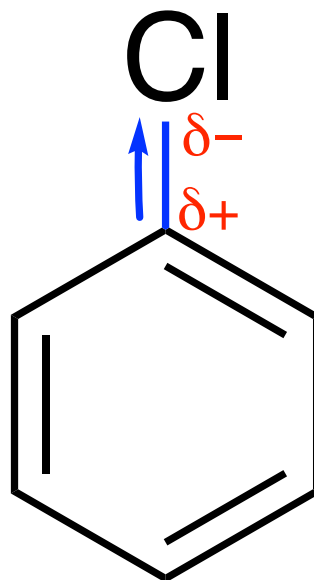
BREAK

2. Substituent Effects

How do **S_EAr** 'activating' and 'deactivating' substituents actually activate or deactivate the ring towards **S_EAr**? Each can be via one or both of Inductive or Mesomeric effects....

b. Inductive Effects (I)

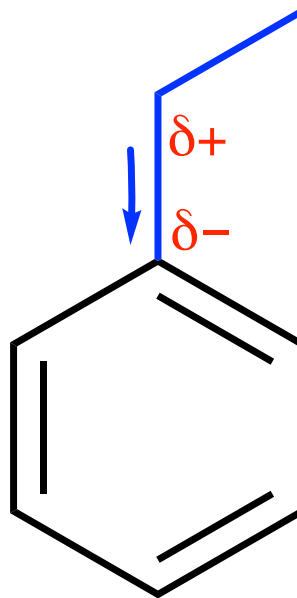
- This arises when 'S' has an electrostatic (polarisation) effect on the **σ bond**.
- i.e. a polarised **σ bond**, this is a **short range effect**
- Atoms more electronegative than e.g. carbon are **inductively electron withdrawing (-I)**



2. Substituent Effects

b. Inductive Effects (I)

- If the polarisation effect on the σ bond is more electrons towards the Ar, then the substituent (S) is **inductively electron donating (+I)**
- Again, this is a **short range** effect



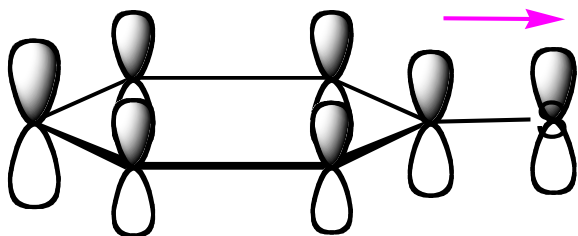
All alkyl groups; CH_3 , CH_3CH_2 , *t*-Bu, etc.....

i.e. the same groups which stabilise carbocations (CHEM 191)

2. Substituent Effects

c. Resonance or Mesomeric Effects (M)

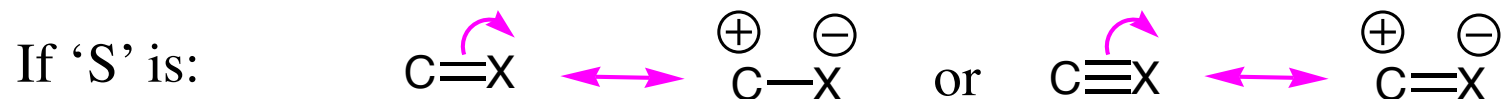
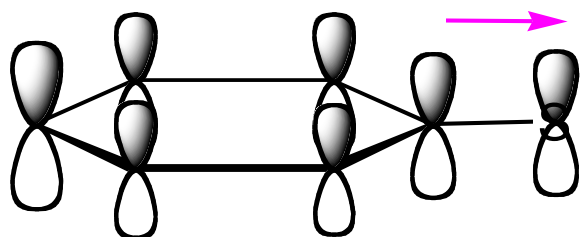
- This arises when 'S' has an orbital (vacant or filled) that can overlap with the π system of the aromatic ring.
- This is via resonance (recall earlier lecture), usually longer range than 'I' effects.
- **Can be mesomerically electron withdrawing ($-M$)**



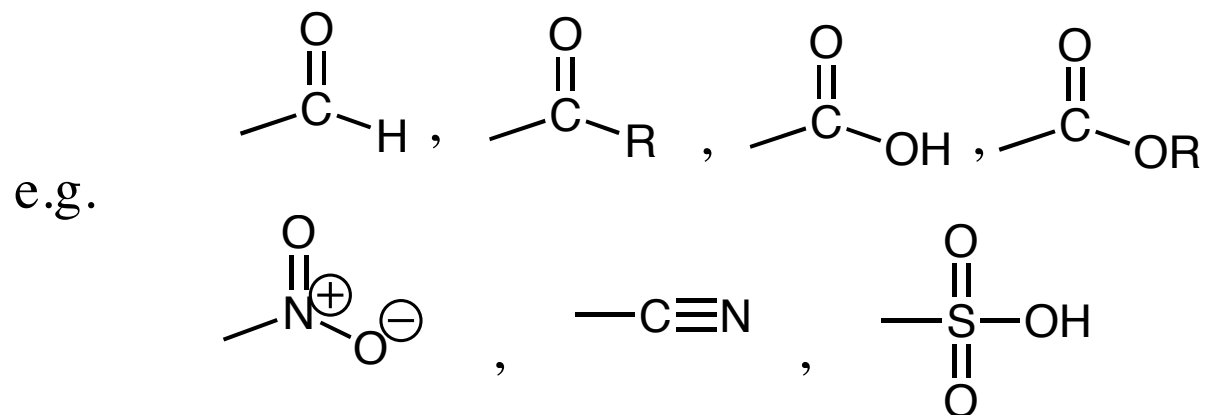
2. Substituent Effects

c. Resonance or Mesomeric Effects (M)

- Examples of electron withdrawing (–M)



it is a –M group

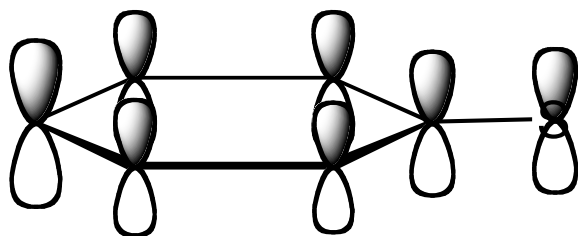


2. Substituent Effects

c. Resonance or Mesomeric Effects (M)

- Examples of **mesomerically electron donating (+M)**

'S' has a pair of non-bonded π electrons it increases the π electron density of the ring



2. Substituent Effects

Most substituents have I and M effects.

d. **Examples**, (refer to Table 18.1 page 923)

Strongly Activating towards S_EAr

$-\text{NH}_2$	Ortho/Para	$+M \gg -I$
$-\text{NHR}$	Ortho/Para	$+M \gg -I$
$-\text{NR}_2$	Ortho/Para	$+M \gg -I$
$-\text{OH}$	Ortho/Para	$+M \gg -I$
$-\text{OR}$	Ortho/Para	$+M \gg -I$

Activating towards S_EAr

$-\text{NHCOR}$ (amide)	Ortho/Para	$+M > -I$
$-\text{OCOR}$ (ester)	Ortho/Para	$+M > -I$
$-\text{Alkyl}$	Ortho/Para	$+I$

2. Substituent Effects

Most substituents have I and M effects.

d. Examples, (refer to Table 18.1 page 923)

Weakly Deactivating towards S_EAr

—F, —Cl, —Br, —I	Ortho/Para	—I > +M
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Deactivating towards S_EAr

—COH (aldehyde)	Meta	—I, —M
—COR (ketone)	Meta	—I, —M
—COOR (ester)	Meta	—I, —M
—COOH (acid)	Meta	—I, —M
—COCl (acid chloride)	Meta	—I, —M

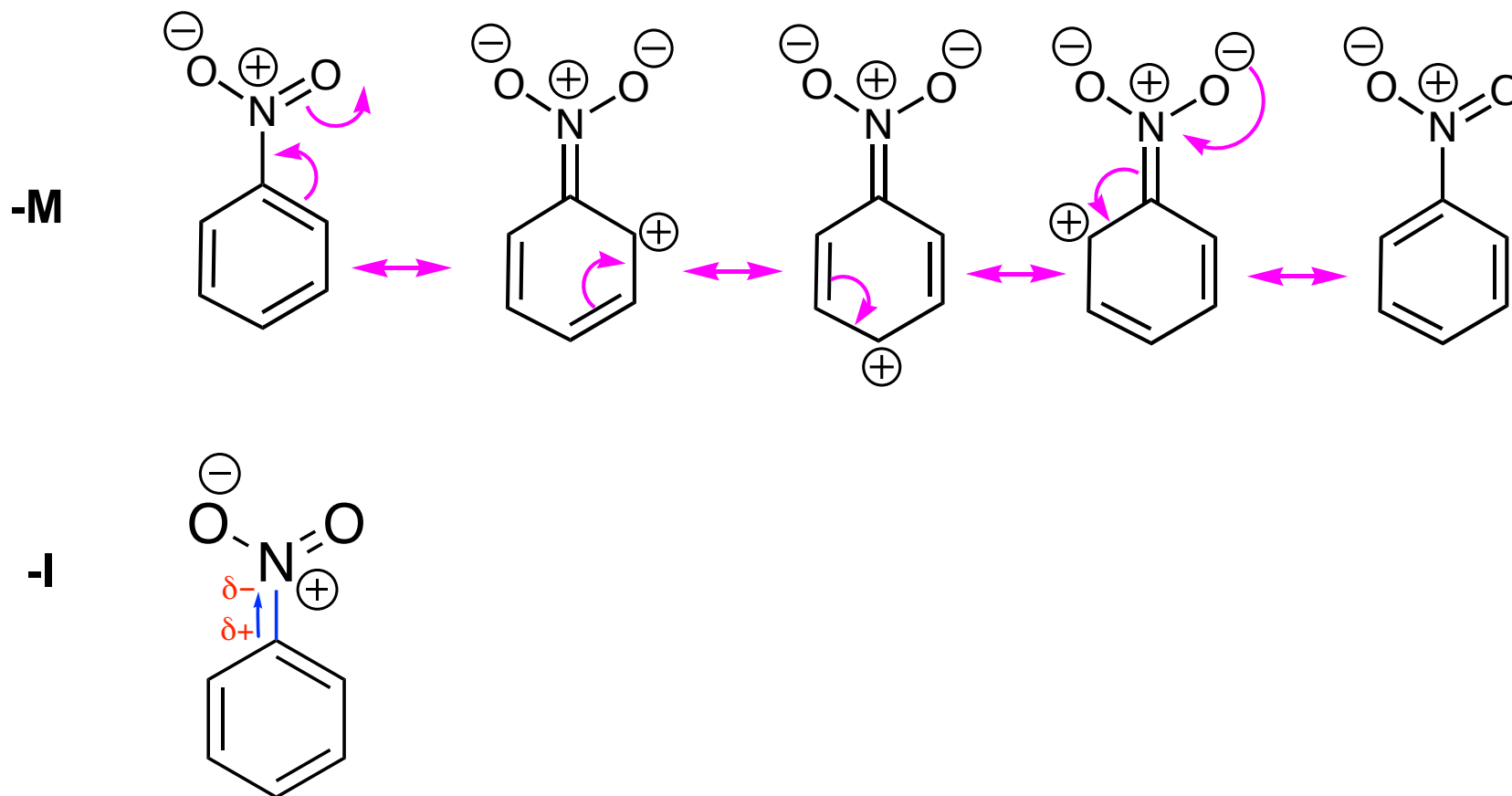
Strongly Deactivating towards S_EAr

—NO ₂	Meta	—I, —M
—CN	Meta	—I, —M
—SO ₃ H	Meta	—I, —M
—NH ₃ ⁺	Meta	strong —I
—NR ₃ ⁺	Meta	strong —I

2. Substituent Effects

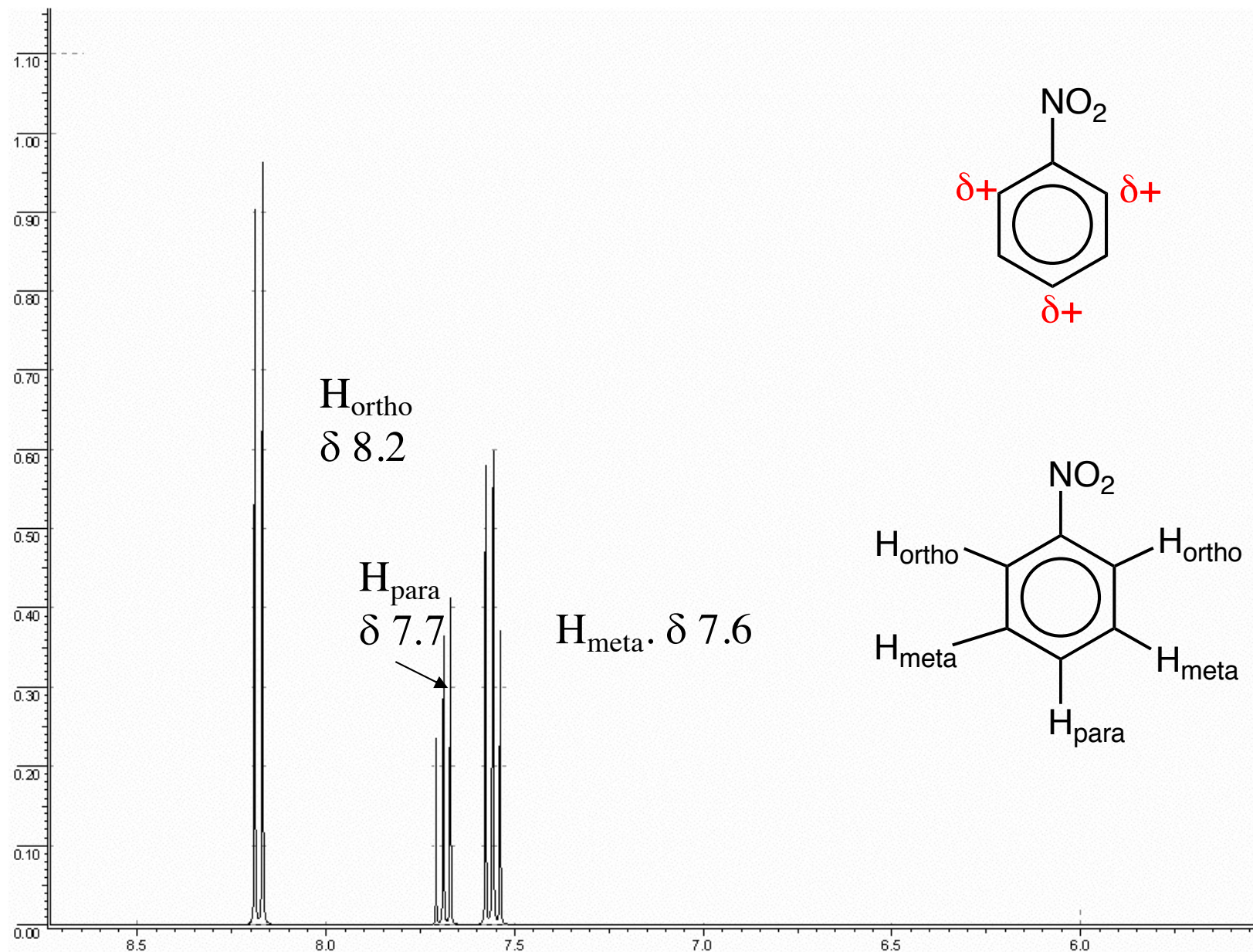
d. Examples

e.g. nitrobenzene is strongly deactivating towards S_EAr , **-M** and **-I**



2. Substituent Effects

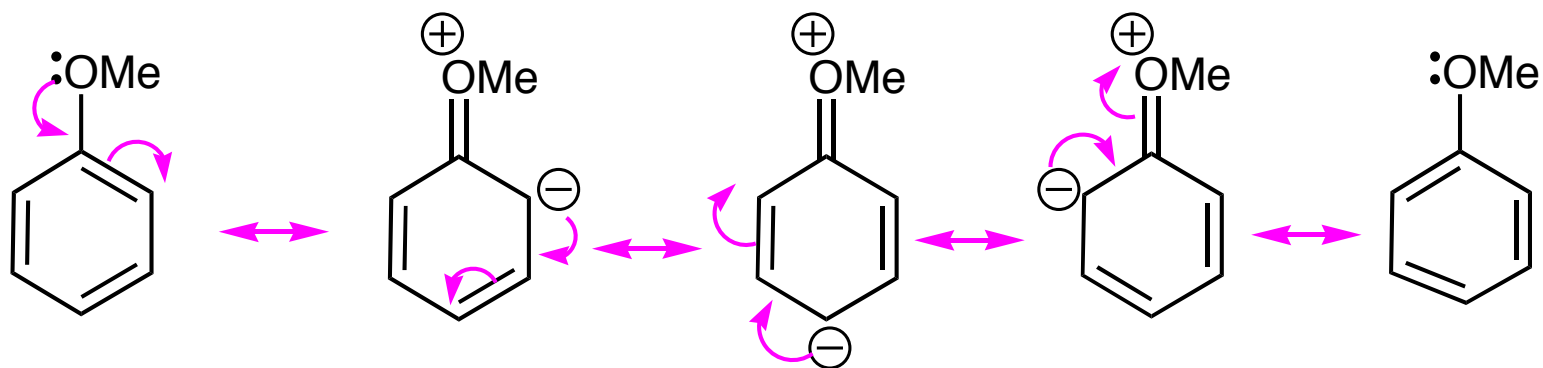
d. Examples e.g. nitrobenzene is **-M** and **-I**, ^1H NMR spectrum



2. Substituent Effects

d. Examples

e.g. methoxy is strongly activating towards S_EAr , $+M \gg -I$



Real structure:

