14: Substituent Effects

- *Substituents and Their Effects*
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- *Electrophilic Aromatic Substitution Reactions*

14.1 Substituents and Their Effects

This chapter describes how variations in one part of a molecule can predictably affect the chemistry and properties of another part of the same molecule.

Substituent Effects (14.1A)

When the part of the molecule that we vary is a discrete atom or molecular fragment, we call it a **substituent**. **Substituent effects** are the changes on a reaction or property in the unchanged part of the molecule resulting from *substituent variation*.

Some Reactions or Properties. We have already seen examples of *substituent effects*. They include the effect of alkyl groups on the stability of carbocations, or the effect of conjugation on chemical reactivity. In this chapter, we will illustrate more *substituent effects* on (1) *acidity of carboxylic acids*, (2) *rates of S_N1 reactions*, and (3) *rates and product distributions of electrophilic aromatic substitution reactions*.

Transmission of Substituent Effects. Effects of substituents on known reactions or properties of molecules tell us about the steric and electronic characteristics of *substituents*. We can then use these substituents to influence chemical reactions and properties in predictable ways. Alternatively, we can use substituent effects to understand chemical reactions with unknown mechanisms or features.

We will divide the electronic influence of substituents into **inductive effects** and **resonance effects**. *Inductive effects* involve electrostatic effects transmitted through σ *bonds* or through *space*. *Resonance effects* involve transmission of electron density through the π system of molecules.

Substituents (14.1B)

Here are some specific examples of *substituents* and *reactions* or *properties* they affect:

(1) Cl-CH_2-CO_2H is a stronger acid than H-CH_2-CO_2H. The substituent is Cl and the property is the acidity of the CO_2H group (Figure 14.01).

Figure 14.01

(2) Methoxybenzene is nitrated more rapidly than benzene. The substituent is CH_3O and the reaction is electrophilic aromatic nitration on the benzene ring (Figure 14.02).

Figure 14.02

(3) CH_3-CH^+-CH_3 is a more stable carbocation than CH_3-CH_2^+ . The substituent is CH_3 and the property is carbocation stability (Figure 14.03).

Figure 14.03

(4) The bascity of Ph-NH_2 is less than that of CH_3-NH_2. The substituents are Ph and CH_3 and the property is the basicity of the NH_2 group (Figure 14.04).

Figure 14.04

A List of Substituents. Substituents in Table 14.01 are examples of the large number of substituents that influence chemical reactions or chemical properties of molecules.

Table 14.01. Some Possible Substituents (S)

S	Name	S	Name
X	halo	R(C=O)	acyl
R O	alkoxy or hydroxy	R	alkyl
R_2N	amino	H	hydrogen
HSO_3	sulfonic acid	R_2C=CR	alkenyl
N≡C	cyano	RC≡C	alkynyl
O_2N	nitro	Ar	aryl

Structure-Reactivity Correlations. We will see that these substituents almost always influence reactions and properties in consistent and predictable ways no matter what type of reaction or property we consider. We refer to these

effects of substituent variation (structural variation) on chemical reactivity or chemical properties as **structure-reactivity correlations**.

14.2 Carboxylic Acid Acidity

The acidity of carboxylic acids (R-CO_2H) depends on the structure of the R group.

Substituent Effects on Acidity Constants (14.2A)

Organic chemists have examined how substitutents affect the acidity of carboxylic acids (R-CO_2H) by varying the group S in carboxylic acids with the general structure S-CH_2-CO_2H.

Magnitude of the Effect. We summarize the acidity constants K_a of the carboxylic acids S-CH_2-CO_2H for various S groups in order of increasing acidity in Table 14.02.

Table 14.02. Approximate Acidity Constants for Some Carboxylic Acids with the Structure S-CH_2-CO_2H.

S	K_a	pK_a	
CO_2^-	2.0×10^{-6}	5.7	(least acidic)
CH_3	1.3×10^{-5}	4.9	
H	$\mathbf{1.7 \times 10^{-5}}$	**4.8**	
I	7.6×10^{-4}	3.1	
Br	1.4×10^{-3}	2.9	
Cl	1.4×10^{-3}	2.9	
F	2.2×10^{-3}	2.7	
NO_2	2.1×10^{-2}	1.7	(most acidic)

The subsituents I, Br, Cl, F, and NO_2, increase the acidity of the CO_2H group over that of the unsubstituted compound (S = H). In contrast, the substituents CH_3 or CO_2^- decrease the acidity of the CO_2H group compared to the unsubstituted compound.

Acidity Constants. K_a values of acids directly reflect the acidity of acids. The larger the K_a value, the stronger the acid and *vice-versa*. pK_a values also describe acidity. Since $K_a = 10^{-pKa}$, pK_a values decrease as K_a values increase.

Origin of the Substituent Effect. While substituent effects can be transmitted by *resonance* or by *inductive effects,* S affects CO_2H acidity in these carboxylic acids only by *inductive effects*. *Resonance effects* are not possible because the S group and the CO_2H group are not conjugated (Figure 14.05).

Figure 14.05

The CH_2 group intervening between S and CO_2H has a tetrahedral carbon, with no π orbitals, that prevents conjugation between S and CO_2H.

When the Substituent is F. *Inductive effects* often result from σ bond polarization that is the result of electronegativity differences between bonded atoms as we illustrate for C-F bonds (Figure 14.06).

Figure 14.06

F is much more electronegative than H, so C-F bonds are highly polarized (Chapter 3) as we show for fluoroacetic acid (fluoroethanoic acid). The *inductive effect* of F on the acidity of the CO_2H group is a result of the positively polarized CH_2 carbon to which the CO_2H group is attached.

How C-F Polarity Affects Acidity. Fluoroacetic acid is an acid because it donates a proton to water or other bases (Figure 14.07).

Figures 14.07 and 14.08

Its acid strength is measured by the acidity constant (K_a) for its reaction with water (Figure 14.08). The K_a value reflects the relative amounts of FCH_2CO_2H and $FCH_2CO_2^-$ that are present at equilibrium.

The relative amounts of each of these species depend on their relative free energy values (Figure 14.09).

Figure 14.09 and 14.10

Fluoroacetic acid ($F\text{-}CH_2CO_2H$) is a stronger acid than acetic acid ($H\text{-}CH_2CO_2H$) because the free energy difference between $F\text{-}CH_2CO_2H$ and $F\text{-}CH_2CO_2^-$ is less than the free energy difference between $H\text{-}CH_2CO_2H$ and $H\text{-}CH_2CO_2^-$ (Figure 14.10).

We explain this by arguing that F lowers the free energy of (stabilizes) the

F-$CH_2CO_2^-$ anion. The negatively charged CO_2^- group in F-$CH_2CO_2^-$ is stabilized by the positively charged CH_2 group to which it is attached (Figure 14.11).

Figure 14.11

The lower free energy of F-$CH_2CO_2^-$ compared to H-$CH_2CO_2^-$ (Figure 14.10) makes it "easier" for the CO_2H group to ionize in F-CH_2-CO_2H than in H-CH_2-CO_2H. We arbitrarily put the absolute energy levels of F-CH_2CO_2H and H-CH_2CO_2H at the same value in Figure 14.10 in order to clearly show that the effect of substitution of F for H mainly influences the energy level of F-$CH_2CO_2^-$ compared to H-$CH_2CO_2^-$.

> **Through Space or Through Bond**. We will see later in this section that the inductive effect of F on CO_2^- groups can also occur *via* a "through-space" electrostatic interaction between dipoles. These through-space effects are referred to as **field effects**.

Inductive Effects for Other S Groups (14.2B)

Substituent groups can be *electron withdrawing* or *electron donating.*

Electron Withdrawing Groups. Because F pulls electrons toward itself, and positively polarizes the C to which it is bonded, it is called an inductive **electron withdrawing group** (**EWG**). The other halogen atoms, as well as the NO_2 group (Table 14.02), are also inductive *EWGs.* Each of these groups polarizes the S-CH_2 σ bond so that the attached carbon is more positive than when S = H as we show in Figure 14.12.

Figure 14.12

The magnitudes of the effects of the other halogens on carboxylic acid acidity (Table 14.02) are less than that of F. This is consistent with their lower electronegativities as described in Chapter 3. However, the effect of the nitro group (NO_2) is greater than that of F. This is a result of the combined effect of the three relatively electronegative atoms in NO_2 and the high electron deficiency on nitrogen in this group as we see in the structures shown in Figure 14.13.

Figure 14.13

Although we use resonance structures for the NO_2 group to illustrate its polar character, the NO_2 group does not influence the acidity of S-CH_2CO_2H by

resonance. As we mentioned earlier, the intervening CH_2 group prevents a resonance interaction between NO_2 and CO_2H.

Electron Donating Groups. A few substituents act as if they donate electron density, by inductive effects, toward the carbon to which they are attached so we call them inductive **electron donating groups** (**EDG**). There are only a few *EDGs* and typically they are negatively charged groups or alkyl groups.

Negatively charged S groups, such as CO_2^- (Figure 14.14), inhibit the formation of the negatively charged CO_2^- group from CO_2H by electrostatic repulsion.

Figure 14.14

The result is that S = CO_2^- lowers the acidity of S-CH_2-CO_2H (Table 14.02) because such S-CH_2-CO_2^- species would contain two negatively charged groups.

Alkyl groups sometimes act as if they donate electron density to groups to which they are attached (Figure 14.14). We expect such electron donation to destabilize the formation of the carboxylate ion by raising its energy. You can see that the CH_3 group decreases the acidity of S-CH_2CO_2H compared to S = H (Table 14.02), however the effect is very small. We will also see later in this chapter that CH_3 groups sometimes act as weak *EWGs* as well as *EDGs.*

+I and -I Groups. We simmarize inductive EWGs and EDGs in Table 14.03.

Table 14.03. Inductive Effects of Substituent Groups (S).

Inductive EWG Groups (-I Groups)

NR_3^+, NO_2, C≡N, X (F, Cl, Br, I), R(C=O), OR, NR_2, $CR{=}CR_2$, C≡CR, Ar

Inductive EDG Groups (+I Groups)

O^-, CO_2^{--}, CR_3

In this table, we designate the inductive *EDGs* as **+I** groups. The I stands for "inductive" and the (+) sign indicates that the group donates (or adds) electrons to the rest of the molecule. Similarly, the inductive EWGs are designated as **-I** groups where the (-) sign indicates that the group withdraws (subtracts) electrons from the rest of the molecule.

Location of S Groups (14.2C)

The magnitude of *inductive effects* depends on both the number of substituents and their location in a molecule relative to the site of their reacting group.

Distance Attenuation. *Inductive effects* decrease in intensity as the separation between the substituent and the reaction site in the molecule increases. We see this by comparing the acidity constants for the carboxylic acids in Table 14.04.

Table 14.04. Location of Cl Substitution and Approximate Acidity Constants for Carboxylic Acids.

Carboxylic Acid	pK_a	K_a	$K_{a(Cl)}/K_{a(H)}$
(1) $CH_3CH_2CH_2CO_2H$	4.9	1.3×10^{-5}	1
(2) $CH_3CH_2CH(Cl)CO_2H$	2.8	1.4×10^{-3}	108
(3) $CH_3CH(Cl)CH_2CO_2H$	4.1	8.7×10^{-5}	7
(4) $CH_2(Cl)CH_2CH_2CO_2H$	4.6	3.0×10^{-5}	2

Substitution of a Cl on the α-C of butyric acid (*1*), to give α-chlorobutyric acid (*2*), causes a 100-fold increase in K_a. In contrast, when Cl is on the β-C (β-chlorobutyric acid (*3*)), K_a increases by only a factor of 7. Finally, a γ-C-Cl, as in γ-chlorobutyric acid (*4*), increases K_a by only a factor of 2 (see structures in Figure 14.15).

Figure 14.15

These differences in the effects of an α, or β, or γ-Cl indicate that the influence of the electronegative Cl on CO_2^- decreases as distance between Cl and CO_2^- increases even though the polarization of the Cl-C bond is about the same in each case (Figure 14.15).

Field Effects. We have focused on the effect of Cl transmitted through σ bonds, but the influence of the Cl-C dipole on the CO_2^- group also operates through space. The effect of an α-Cl is primarily transmitted through the C-C bond connecting Cl-C and the CO_2H or CO_2^- group in α-chlorobutyric acid. However, the effect of that Cl in β or γ-chlorobutyric acid may operate to a significant extent by an electrostatic interaction through space called a **field effect** as we illustrate for γ-chlorobutyric acid (Figure 14.16).

Figure 14.16

It is often difficult to separately measure the "through-bond" or "through-space" effect of a substituent on a reactive site. As a result, through-space *field effects* and through-bond *inductive effects* are usually treated together. Some organic chemists refer to this combination as *field effects*, while others refer to the combination as *inductive effects* as we do in this text.

Additivity of Inductive Effects. Individual inductive effects of substituents combine when more than one H of a molecule is substituted with an S group. We illustrate this using data for unsubstituted, and mono, di, and trichloro substituted acetic acids in Table 14.05.

Table 14.05. Effect of Cl Substitution on Acidity of Acetic Acid.

Acid	pK_a	K_a	$K_{a(Cl)}/K_{a(H)}$
CH_3CO_2H	4.8	1.7×10^{-5}	1
$ClCH_2CO_2H$	2.9	1.4×10^{-3}	80
Cl_2CHCO_2H	1.3	5.1×10^{-2}	3,000
CCl_3CO_2H	0.7	2.2×10^{-1}	12,940

Substitution of one C-H in acetic acid by Cl leads to an 80 fold increase in K_a, substitution with two Cl's gives a 3000 fold increase in the acidity constant, while substitution with three Cl's causes K_a to increase by a factor of almost 13,000.

Inductive Effects are General. The inductive effects that we have just described are generally observed for substituents in all types of chemical systems. The +I or -I characteristics of each substituent that we described in Table 14.03 generally remain the same for any system. For example, the NO_2 group or the F atom each withdraw electron density (-I) from any carbon atom to which they are attached while alkyl groups usually act as if they are electron donating (+I).

How that electron withdrawal or donation affects a chemical reaction or chemical property of a molecule depends on the particular reaction or property that is being examined. The predictability of the inductive effect of a substituent as +I

or -I provides a powerful tool to an organic chemist. It permits us to control chemical reactivity or molecular properties of a system by using the appropriate substituent.

Similarly, both distance attenuation and the additivity of substituent effects are general. Inductive effects generally diminish in intensity as the distance between the substituent and the reaction site increases, while their effect is directly proportional to the number of substituents on the molecule.

14.3 S_N1 Reactions

S_N1 solvolysis reactions are also sensitive to substituent effects.

Origin of the Substituent Effect (14.3A)

We learned in Chapter 7 that S_N1 solvolysis of a substrate (S-R-Y) has a two-step mechanism (Figure 14.17).

Figure 14.17

Carbocation formation in the first slow step is followed by reaction of that carbocation with the nucleophilic solvent (Nu:) in the second fast step. Since the rate of formation of the carbocation S-R+ depends on its stability, substituent groups (S) influence this rate if they affect the ability of R (in S-R+) to stabilize a (+) charge.

Some Substrates S-R-Y (14.3B)

We illustrate the effects of substituents on S_N1 reactions using the two types of substrates (S-R-Y) that we show in Figure 14.18.

Figure 14.18

Their specific names depend on each substituent group S so we refer to them generally as **cumyl chlorides** and **adamantyl tosylates**. The terms *cumyl* and *adamantyl* are common names for their specific hydrocarbon structures (R).

Solvolysis of Adamantyl Tosylates. We show relative solvolysis rates for several *adamantyl tosylates* (Figure 14.18) with different S groups in Table 14.06 [next page]. We calculate the rate constant ratios k_S/k_H by dividing each rate constant (k_s) for a substituted adamantyl tosylate by the rate constant (k_H) for the unsubstituted molecule where S = H.

Table 14.06. Relative Rates of Solvolysis of Substituted Adamantyl Tosylates (70°C, 80% EtOH/H_2O)

S	Inductive Effect	k_S/k_H
CO_2^-	+I	2.1
$(CH_3)_2CH$	+I	1.8
H		(1)
CH_3	(+I)	0.78
CH_3O	-I	0.16
Cl	-I	5.6×10^{-4}
C≡N	-I	1.7×10^{-4}
NO_2	-I	3.5×10^{-5}

With the exception of S = CH_3, S groups that are inductively *EDGs* (+I) slightly increase the solvolysis reaction rate. In contrast, the -I (inductively *EWG*) substituents decrease the solvolysis rate. Since we expect +I substituents to stabilize a carbocation, and -I substituents to destabilize a carbocation (Figure 14.19), these trends are generally consistent with those expectations.

Figure 14.19

We mentioned earlier that while CH_3 usually acts as a +I group, it sometimes acts as a -I group as it does here. You can see that it retards the rate compared to S = H, but the effect is very small. There are several σ bonds separating each S group from the C+ center in these adamantyl systems. As a result it is likely that the effect of S is a *field effect* operating through-space as we described earlier.

Solvolysis of Cumyl Chlorides. We see similar effects of S on solvolysis rates of *meta*-substituted *cumyl chloride* (*2-chloro-2-phenylpropane*) systems (Table 14.07 [next page] and Figure 14.18). Once again, we calculate values for k_S/k_H by dividing the individual rate constants k_S for the substituted cumyl chlorides by the rate constant k_H for the unsubstituted compound where S = H.

Table 14.07. Relative Rates of Solvolysis of *meta*-Substituted Cumyl Chlorides (25°C, EtOH)

S	Inductive Effect	k_S/k_H
CH_3	+I	2.0
$(CH_3)_3C$	+I	1.9
H		(1)
CH_3O	-I	0.61
F	-I	0.025
Cl	-I	0.015
Br	-I	0.015
I	-I	0.023

Like the adamantyl systems, the +I substituent groups (in this case including CH_3) slightly increase the reaction rate, while -I substituents lower the reaction rate compared to S = H. These results agree with our predictions for inductive effects of substituents on a carbocation intermediate.

Resonance. In contrast with the *adamantyl* systems where the carbocation centers are localized, the (+) charge on *cumyl* carbocations is delocalized into the benzene ring (Figure 14.20).

Figure 14.20

However, these resonance structures show that the (+) charge is never on the C-S carbon so S cannot interact with this (+) charge by resonance. As a result, the influence of S on the carbocation intermediate in these systems is the result of its inductive effect in spite of resonance delocalization of the (+) charge.

Resonance Effects (14.3B)

So far we have rationalized all of the substitutent effects we have seen as *Inductive Effects*. In this section, we give examples of S_N1 solvolysis reactions where we must consider *Resonance Effects*.

p-Substituted Cumyl Chlorides. The effects of substituents substituted on the *para* position of cumyl chlorides (Figure 14.21) are much different than those for *meta* substituents (Table 14.08) [next page].

Figure 14.21

Table 14.08. Approximate Relative Rates of Solvolysis of *meta* and *para* Substituted Cumyl Chlorides (25°C, EtOH)

S	$k_{S\text{-}meta}/k_H$	$k_{S\text{-}para}/k_H$
CH_3	2	26
$(CH_3)_3C$	2	15
H	(1)	(1)
CH_3O	0.6	3,400
F	0.03	2
Cl	0.02	0.30
Br	0.02	0.21
I	0.02	0.24

In this table, we compare how S groups affect cumyl chloride solvolysis rates when substituted in the *para* position ($k_{S\text{-}para}/k_H$) and *meta* positions ($k_{S\text{-}meta}/k_H$ [*meta* data taken from Table 14.07]). You can see in several cases that the S groups have much bigger effects in *para* positions, and that the CH_3O and F groups reverse their behavior when moved from *m* to *p* positions.

The Substituents F and CH_3O. While F in a *meta* position lowers the solvolysis rate ($k_{S\text{-}meta}/k_H = 0.03$), it causes a small rate increase in the *para* position ($k_{S\text{-}para}/k_H = 2$). Similarly, CH_3O slightly lowers the solvolysis rate when it is *meta* ($k_{S\text{-}meta}/k_H = 0.6$), but dramatically raises it when it is *para* ($k_{S\text{-}para}/k_H = 3{,}400$). Both of these substituents act as *electron withdrawing groups* (*EWG's*) when they are in the *meta* position, however they act like *electron donating substituents* (*EDG's*) when they are in the *para* position!

These different effects in *m* and *p* positions for F and CH_3O are not due to any change in their *inductive effects* when they are moved from *m* to *p* positions. Both F and CH_3O are *inductively electron withdrawing* (-I) whether in the *meta* or *para* position. Rather, this positional variation in their effect on the reaction rate is because they interact with the carbocationic center not just *inductively*, but also by *resonance* when substituted in the *para* position. We will see below that the *resonance effects* of these two substituents are opposite to their *inductive effects*.

The Origin of the Resonance Effect. We illustrate the *resonance* behavior of *p*-CH_3O groups in Figure 14.22 [next page].

Figure 14.22

You can see that the (+) charge is fully delocalized into the aromatic ring when CH_3O is either *meta* or *para*. However, when CH_3O is *para*, one of the unshared electron pairs on O can interact with the positive charge giving the extra resonance structure that we see in Figure 14.22. This is not possible with *m*-CH_3O.

While the CH_3O substituent is *inductively electron withdrawing* because O is more electronegative than C, it is *resonance electron donating* when given the opportunity. The same is true for F as we show in Figure 14.23.

Figure 14.23

R Effects of Substituents. When a substituent such as CH_3O or F donates electron density by *resonance* we say it is a +R substituent. The (+) sign signifies electron *donation*, while R stands for *resonance*. We designate substituents that *withdraw* electron density by resonance as -R substituents. Table 14.09 shows common substituents grouped into these +R and -R categories.

Table 14.09. Resonance Effects of Substituent Groups (S).

Resonance EDG Groups (+R Groups)
NR_2, OR, X (F, Cl, Br, I), CR_3, Ar

Resonance EWG Groups (-R Groups)
NO_2, R(C=O), C≡N, CO_2H

+R Groups. With the exception of alkyl groups (CR_3) , and aryl groups (Ar, *e.g.* phenyl), the +R groups have an unshared electron pair that can delocalize into a π system by resonance as we show in the general example in Figure 14.24.

Figure 14.24

Among the halogens, this type of resonance donation is particularly favorable for F because, like O and N, its unshared electrons are in 2p orbitals. These 2p orbitals are geometrically suitable for overlap with π systems on the substrate (*e.g.* the cumyl ring system) that are also derived from overlap of 2p orbitals.

In contrast, the unshared electron pairs of the other halogens are in 3p (Cl), 4p (Br), or 5p (I) orbitals that overlap less efficiently with a π system on C atoms. As a result, moving a halogen from the *m* to *p* position has a much greater effect if it is F than when it is Cl, Br, or I. You can see that Cl, Br, and I continue to reduce the solvolysis rate in the *p* position, but their +R property causes those rate retardations to be less then when they are *meta*.

We rationalize the +R character of alkyl groups by hyperconjugation as we visualize in Figure 14.25.

Figure 14.25

Remember that the C-R bond does not actually break. The 2nd resonance structure indicates that the C-R electron pair overlaps with the C=C π system as we showed in Chapter 8.

Aryl groups such as phenyl rings can also donate electron density by resonance to a π system as we show in Figure 14.26.

Figure 14.26

We include all aryl (Ar) groups in the +R category (Table 14.09), but occasionally they act as -R groups.

-R Groups. All -R substituents that we show in Table 14.09 can accept electron donation by resonance from a π system. We show this in the general example in Figure 14.27 where we represent S by Y=Z.

Figure 14.27

For example, the general group Y=Z is an O=N bond in NO_2, the O=C bond in R(C=O) and CO_2H, the N≡C bond of the CN group, and a C=C bond in aryl groups. We show specific resonance structures for these substituents in section 14.4 that deals with Electrophilic Aromatic Substitution reactions.

Correspondence between I and R Properties. All -R substituents are also -I substituents. However, a similar analogy does not hold for +R substituents. With the exception of CR_3 groups (alkyl groups), all +R substituents in Table 13.9 are actually -I substituents.

The atom in S that is directly bonded to the substrate is usually more electronegative than H causing the S group to be -I. At the same time, that atom

generally has an unshared pair of electrons that it donates to a π system making it +R. We use CH_3O to illustrate this dual nature of substituents that are +R and -I (Figure 14.28).

Figure 14.28

+M and -M. Some advanced textbooks use the designations +M and -M, instead of +R and -R, to refer to resonance effects. Resonance effects were first referred to as "*Mesomeric (M) effects*" by Sir Christopher K. Ingold, a professor of chemistry in the United Kingdom, who was a pioneering contributor to this field. Although +R and -R are now more commonly used, the use of +M and -M might be preferable in order to avoid the possibility for confusion of +R and -R with the unrelated use of *R* to designate absolute configurations of chiral centers.

14.4 Electrophilic Aromatic Substitution Reactions

Our final example of substituent effects on reactions is *electrophilic aromatic substitution* that we described in Chapter 12 (Figure 14.29).

Figure 14.29

Reactions on Substituted Benzenes (14.4A)

The mechanism we show above is for unsubstituted benzene, but the same two-step mechanism occurs in reactions of electrophiles with substituted benzenes.

Rates and Products Depend on S. Both the rates and products of electrophilic aromatic substitution reactions depend on the substituent S. Substituted benzenes generally give a mixture of *ortho*, *meta*, and *para* products (Figure 14.30), but their relative amounts vary widely and depend on the nature of the substituent S.

Figure 14.30

The overall rates of formation of these products also depend on S. Some substituents lead to faster rates than those observed for unsubstituted benzene (S = H) while other substituents cause rates to be slower. We will see that *product distributions*, and *relative rates*, are both correlated with the *inductive* and *resonance* effects of the substituents that we have already described for *carboxylic acid acidity* and for *S_N1 solvolysis reactions*.

meta versus ortho/para Directors. All the substituents in Table 14.09 that are -R give electrophilic aromatic substitution product mixtures that have relatively high yields of *meta* product, and low combined yields of the *ortho* and *para* products. In contrast, substituents in Table 14.09 that are +R give product mixtures that have relatively high combined yields of *ortho* and *para* products, and low yields of the *meta* product.

We refer to substituents that give primarily *meta* products as ***meta*-directors**, and those that give primarily *para* and *ortho* product mixtures as ***ortho,para*-directors**. We show a number of these substituents (S) in Table 14.10 along with the product distributions from electrophilic aromatic nitration reactions ($E^+ = NO_2^+$) on benzene rings substituted with these S groups.

Table 14.10. Product Distributions for Nitration of Substituted Benzenes.

S	%-*ortho*	%-*para*	%-*o* + %-*p*	%-*meta*
***m*-directors**				
NO_2	6	2	8	92
NMe_3^+	trace	11	11	89
C≡N	17	2	19	81
CO_2H	9	1	10	80
$C(=O)CH_3$	26	trace	26	72
***o,p*-directors**				
CH_3	61	37	98	2
CH_3CH_2	46	51	97	3
$(CH_3)_2CH$	28	68	96	4
$(CH_3)_3C$	10	83	93	7
CH_2Cl	34	52	86	14
F	13	86	99	1
Cl	35	64	99	1
Br	43	56	99	1
I	45	54	99	1
OCH_3	40 to 60	60 to 40	100	0

Although specific product yields depend on the specific electrophile (E^+), the electrophile does not determine whether a substituent S generally behaves as an *o,p-director* or a *m-director*. You can see this in the product distributions for reactions of different electrophiles (E^+) with toluene ($S = CH_3$) in Table 14.11 [***next page***]. The exact yields vary, but the CH_3 substituent consistently gives

low yields of *meta* product and high combined yields of *ortho* and *para* products for a variety of electrophiles.

Table 14.11. Product Distributions for Electrophilic Substitution of Toluene (S = CH_3) with Different Electrophiles.

E^+	%-*ortho*	%-*para*	%-*o* + %-*p*	%-*meta*
NO_2^+	61	37	98	2
Br^+	33	67	>99	<1
Cl^+	60	40	>99	<1
CH_3^+	56	35	91	9
$CH_3CH_2^+$	38	41	79	21
$(CH_3)_2CH^+$	28	46	74	26

Similarly, electrophilic substitution on benzonitrile, with the deactivating substituent S = C≡N, gives high yields of *meta* product, and low combined yields of *o* and *p* products with two completely different electrophiles (Table 14.12).

Table 14.12. Product Distributions for Electrophilic Substitution of Benzonitrile (S = C≡N) with Different Electrophiles.

E^+	%-*ortho*	%-*para*	%-*o* + %-*p*	%-*meta*
NO_2^+	6	2	8	92
Cl^+	23	3	26	74

E *versus* S. Students sometimes get confused when they study reactions of electrophiles $\mathbf{E^+}$ with benzenes substituted by **S** groups. It is important to understand that there is no necessary connection between the **E's** and the **S's**.

We described a set of electrophiles ($\mathbf{E^+}$) in Chapter 12, and we use the same set of electrophiles here. In contrast, the **S** substituents are a separate group of chemical entities whose electronic properties we are probing with electrophilic substitution reactions. We can put some of those substituents **S** on benzene rings using chemically identical $\mathbf{E^+}$ electrophiles (e.g CH_3, Br, or NO_2). But we must use completely different reactions to put others (e.g. C≡N, CO_2H, or NMe_3^+) on benzene since they are not chemicaly identical to any of the E^+ species at our disposal.

In order to probe how **S** substituents affect electrophilic substitution reactions, we can in principle use any $\mathbf{E^+}$ with our set of substituted benzenes and obtain the same general results. For example, the substituent S = CH_3 is *activating* and *o,p*-

directing whether the electrophile is NO_2^+, or CH_3^+. Similarly, the substituent NO_2, is *deactivating* and *meta-directing* whether the electrophile happens to be NO_2^+ or CH_3^+.

Directive Effects of Substituents (14.4B)

When a benzene ring has a single substituent S, the electrophile E+ can react with any of the remaining five carbon atoms (Figure 14.31).

Figure 14.31

However we have just seen that the 3 possible products do not form in equal amounts. A comparison of the sets of resonance structures for the carbocation intermediates provides the basis for explaining the differences in product distribution for different substituents.

Resonance Structures for o, m, and p Reactions. We show in Figure 14.32 the sets of resonance structures for the different carbocations formed by reaction of E^+ at an *ortho*, or *meta*, or *para* position.

Figure 14.32

We only show resonance structures for *ortho* attack at one of the two *ortho* positions because those from attack at the other *ortho* position are completely equivalent. The same is true for for reaction at the two *meta* positions.

In each of these three sets of resonance structures, the positive charge "moves around the ring" in exactly the same way with respect to the carbon that has been attacked by the electrophile. In each set, the (+) charge is *ortho* to the C-E carbon in two structures, while it is *para* to the C-E carbon in a third structure. Finally, the (+) charge is never found on the C that is *meta* to the C-E carbon.

However, while these three sets of structures in Figure 14.32 share these similarities, there is a significant difference between them. Those sets arising from *ortho* or *para* attack of E^+ each have one resonance structure (enclosed in a "box") where the (+) charge is on the C-S carbon. In contrast, the (+) charge is never on the C-S carbon in the set from *meta* attack. We will see below that this difference explains the +R and -R directive effects of different substituents S.

+R Groups. When a substituent S can stabilize a (+) charge on its bonded C (S-C+), the electrophile E^+ prefers to attack ring C's that are *o* or *p* to the C-S

carbon. This is because these reactions give an intermediate resonance structure where the (+) charge is on the C-S carbon. Substituents that stabilize the intermediate cation are the +R substituents that we showed previously in Table 14.09.

We give examples in Figure 14.33 that show some of these +R substituents resonance-stabilizing the S-C+ cation that results from *o* or *p* attack.

Figure 14.33

The S group donates an electron pair to the C+ center causing the S group to become (+) charged. We cannot write such structures when E^+ reacts at a position *meta* to these +R substituents because the resulting (+) charge is never on the C-S carbon.

-R Groups. In contrast, a (+) charge on a C-S carbon when S is a -R group is very unfavorable. We show some examples in Figure 14.34 of the unfavorable situations that arise from attack of E^+ *ortho* or *para* to -R groups.

Figure 14.34

Not only is it impossible for the -R substituent to stabilize the adjacent (+) charge, but the -R substituent actually withdraws electron density from its attached C causing that C to be highly electron deficient even before attack by E+.

These unfavorable resonance structures do not form when E^+ attacks *meta* positions of substituted benzenes. In these cases the (+) charge is never on the C-S carbon in any of the resulting resonance structures (see Figure 14.32). After *meta* attack, the (+) charge is always separated from S by at least two ring C's as we show in Figure 14.35 for reaction of E^+ with nitrobenzene.

Figure 14.35

As a result, *meta* attack occurs because it is a better alternative than *ortho* or *para* attack on a benzene substituted with a -R substituent.

Reactivity of Substituted Benzenes (14.4C)

We explain in this section how substituents affect the reactivity of substituted benzenes in electrophilic aromatic substitution.

-R Substituents. Intermediate carbocations cannot be stabilized by -R substituents, so -R substituents dramatically lower rates of electrophilic substitution reactions. You can see examples of this in the data in Table 14.13 for CN and NO_2 that are -R substituents.

Table 14.13. Relative Rates of Nitration of Substituted Benzenes where S is a -R Group.

S	Relative Rate
H	(1)
C≡N	1×10^{-5}
NO_2	1×10^{-8}

Since all -R substituents **deactivate** the benzene ring to electrophilic substitution reactions, we say they are *deactivating substituents.*

Nitration of benzene shows both the *deactivating* and *m-directing* effects of -R groups. A single nitro group readily adds to unsubstituted benzene (Figure 14.36), but subsequent nitration of the product nitrobenzene is much slower (Table 14.13).

Figure 14.36

The resulting product is >90% 1,3-dinitrobenzene (Table 14.10) because the first nitro group is a -R substituent that is *m-directing* and *deactivating.*

Since 1,3-dinitrobenzene contains two -R groups, it is even less reactive than nitrobenzene. Addition of a third nitro group requires very vigorous reaction conditions (Figure 14.36) and the final product is exclusively 1,3,5-trinitro-benzene because both NO_2 groups direct the electrophile to the single remaining position that is *meta* to both of the NO_2 groups. We will describe electrophilic substitution reactions on disubstituted benzene rings in more detail later in this chapter.

+R Substituents. While all -R groups *deactivate* benzene rings, not all +R groups *activate* benzene rings. For example, while the NR_2, OR, Ar, and alkyl groups shown in Table 14.09 are +R and *activating groups*, all of the halogens (I, Br, Cl, and F) are also +R but *deactivating.*

The data in Table 14.14 for bromination ($E^+ = Br^+$) show that OCH_3 and CH_3 both *activate* benzene, while the more extensive data available for nitration ($E^+ = NO_2^+$) confirm that CH_3 is *activating* , but that the halogens are all *deactivating*.

Table 14.14. Bromination and Nitration of Benzenes Substituted with +R groups.

	Relative Rates	
S	**Bromination**	**Nitration**
OCH_3	19,000,000	
CH_3	610	27
(H)	(1)	(1)
I		0.13
F		0.11
Br		0.06
Cl		0.02

I and R Effects Can Compete. We explain this contradictory behavior of +R groups by the relative importance of their R and I effects. We have seen that -R groups (Table 14.09) are also -I groups (Table 14.03). But with the exception of alkyl groups that are both +R and +I, the other +R groups in Table 14.09 are -I groups (Table 14.03)! They act as electron donors by resonance (+R), but as electron withdrawing groups by inductive effects (-I). They stabilize carbocation intermediates by resonance (+R), but destabilize carbocations by inductive effects (-I).

For example, the data in Table 14.14 for CH_3O show that this group dramatically accelerates electrophilic substitution. Its +R effect appears to be much greater than its -I effect and this also agrees with its effect on S_N1 reactions of *p*-substituted cumyl chlorides that we described earlier in this chapter.

In contrast, the rate retardations that we see in nitration of halobenzenes (Table 14.14) are consistent with their -I effect dominating over their +R character in determining reaction rates. They destabilize the positively polarized transition

states for electrophilic aromatic substitution by inductive electron withdrawal whether these transition states are the result of *ortho*, *meta*, or *para* attack.

Halogens have Contradictory Rate and Product Effects. Although halogen substituents decrease substitution rates because of their -I effects, we saw earlier that they are *o,p* directors consistent with their +R character. We explain this contradictory behavior by proposing that the destabilization of transition states by halogen substitutents is less for *ortho* or *para* attack than for *meta* attack.

Using this rationale we expect more *o,p*-substitution compared to *m*-substitution in spite of overall rate retardation. We argue that in transition states resulting from *ortho* or *para* attack, the +R resonance electron donating ability of the halogen atoms to the C+ center partially compensates for their -I inductive electron withdrawal.

This is very different than with substituents such as Ar, OR, and NR_2 that also have -I but +R properties. We argue that their -I inductive effects are much less than those of the halogens. This permits their +R resonance electron donation to predominate resulting in both overall activation and *o,p* direction of an aromatic ring. Alkyl groups usually act as +R and +I groups, so the fact that they are both activating and o,p-directing is completely consistent with their resonance and inductive electron donating properties.

NR_2 versus NHR_2^+. NR_2 groups are strong activators and *o,p*-directors, however they are easily protonated under electrophilic substitution reaction conditions. The resulting NHR_2^+ groups are powerful deactivators, but you may be surprised to learn that the reaction products are often primarily *o,p*.

This occurs because there is a trace amount of unprotonated NR_2 group that always exists in equilibrium with the NHR_2^+ group. Unprotonated NR_2 groups are so strongly activating that the products primarily arise from the trace amount of aromatic compound with the unprotonated NR_2 group.

A Summary of Substituent Effects. We summarize the reactivity and directive effects of a variety of substituents in Table 14.15 [next page].

Table 14.15. Approximate Relative Reactivity and Directive Effects of Various Substituents (S)

S *(Reactivity Order)*	Reactivity	Directive Effect
O^- (most reactive)	Activator	*o,p*
NR_2	A	*o,p*
O R	A	*o,p*
NH(C=O)R*	A	*o,p*
OC(=O)R*	A	*o,p*
CR_3	A	*o,p*
Ar	A	*o,p*
(H)	-	-
F, I	Deactivator	*o,p*
Br, Cl	D	*o,p*
CCl_3	D	*m*
$C(=O)NH_2$*	D	*m*
C(=O)OR*	D	*m*
C(=O)R	D	*m*
SO_3H	D	*m*
C≡N	D	*m*
CF_3	D	*m*
NO_2	D	*m*
NR_3^+ (least reactive)	D	*m*

Their order reflects the relativity reactivity of the substituents. Those that provide the greatest reactivity are at the top while those that decrease rates the most are at the bottom. We identify substituents that we have not yet specifically discussed with an (*) and will describe those in Chapter 15.

Figure 14.37 is a graphical summary of the reactivity and directive effects of substituents shown in Table 14.15.

Figure 14.37

In order to make it less complicated, we have gathered substituents together into general groups. For example, NR_2 also includes NH(C=O)R, OR includes OC(=O)R, C(=O)Y includes $C(=O)NH_2$, C(=O)OR, and C(=O)R, while F, Cl, Br, and I are designated X.

CH_2-Y Groups. We see a delicate balance between I and R effects on reactivity and product distribution in rate and product data for electrophilic substitution on benzene rings with various S = CH_2Y (Table 14.16).

Table 14.16. Electrophilic Substitution on Some Substituted Benzenes where S = CH_2-Y.

CH_2-Y	k_S/k_H	%-*o*	%-*p*	%-*o* + %-*p*	%-*m*
CH_2-H	25	56	41	97	3
CH_2-OCH_3	6	51	42	93	7
CH_2-Cl	0.7	34	52	86	14
CH_2-C≡N	0.3	24	56	80	20
CH_2-NO_2	0.1	22	23	45	55

The first entry in this table is for toluene (S = CH_3, Y = H). Each subsequent entry is for an S = CH_2-Y where Y = H in toluene is replaced with a different Y group.

The CH_3 group (Y = H) *activates* and *o,p-directs* compared to unsubstituted benzene because CH_3 stabilizes the intermediate carbocation by hyperconjugation (Figures 14.25 and 14.33). However, as Y successively changes from H, to OCH_3, to Cl, to CN, and finally to NO_2, the rate ratio (k_S/k_H) decreases and the relative yield of *meta* product increases.

The rate decrease reflects an increase in the -I effect of the Y group. That increase in -I effect makes it harder for a CH_2-Y group to stabilize the carbocation intermediate by hyperconjugation. While such CH_2-Y hyperconjugation explains the *o,p*-directive effects of CH_2Cl and CH_2CN, the very strong -I effect of NO_2 significantly inhibits hyperconjugation causing *meta* direction and deactivation.

Reactions at the ortho Positions (14.4D)

We have discussed reactions at *ortho* and *para* positions of a substituted benzene as if they are equivalent to each other. However there are differences that we outline in this section.

Statistical Effects. One difference is that there are two *ortho* positions but only one *para* position in a monosubstituted benzene. As a result, we would expect the relative amounts of *ortho* and *para* product to be 2 to 1 in the absence of all other factors.

Product data for *o,p* directing substituents (Tables 14.10 and 14.11), however, show that this is rarely observed. Nitration of toluene (S = CH_3) is close with an *o/p* product ratio of 1.65 (61% *ortho* and 37% *para*), but the relative yield of *ortho* product is usually significantly lower then predicted by statistical considerations.

Steric Hindrance. A major reason for these non-statistical results is that the *ortho* position is more sterically hindered. For S = *alkyl* groups in Table 14.10, we see that the *o/p* product ratio decreases in the order *methyl (1.6) > ethyl (0.9) > isopropyl (0.4) > t-butyl (0.1)* directly paralleling an increase in the relative steric size of these groups (Figure 14.38).

Figure 14.38

Similarly, the *o/p* ratio decreases as we increase the size of alkyl group electrophiles (R_3C^+) as you can see in the data for reaction of three different size alkyl electrophiles with toluene (Table 14.11).

Additional Considerations. In addition to statistical and steric effects, *o/p* ratios also depend on other more complex factors.

Polar Effects. All of the halogens X are sterically smaller than the CH_3 group, but all halobenzenes have *o/p* ratios for nitration that are significantly less than that for S = CH_3 (Table 14.10). In addition, they decrease in an order *I (0.83) > Br (0.77) > Cl (0.55) > F (0.15)* that is opposite the order of the relative sizes of these halogens.

A complex explanation is based on the proposal that resonance structures (A) from *para* attack (Figure 14.39)[next page] are more energetically favorable than resonance structures (B) from *ortho* attack.

Figure 14.39

Since resonance, giving structures like A and B, is most important for F and least important for I (as we explained earlier in this chapter), the observed effect on product distribution of the differences in energy of A and B is most pronounced for S = F and least for S = I.

o,p Ratios for meta Directors. Our preceding discussions focused on *o/p* ratios for reactions where the substituents are *o,p* directors. In the case of *meta* directors, the *o/p* ratio varies dramatically. However, with the exception of NMe_3^+, these ratios are much greater than 2.0. Attack of the electrophile E^+ at the *ortho* position may sterically

interfere with resonance interactions of the S group with the aromatic ring causing *ortho* attack to be slightly less deactivated than *para* attack by resonance. However, since the total amount of *ortho* and *para* product is relatively small in these cases, small errors in their yields can lead to large errors in their ratios making these absolute ratios unreliable.

ipso Attack. A complication in interpretation of the *o/p* ratios can also arise from rearrangement of the first formed intermediate carbocation. If this occurs, the final product distribution does not accurately reflect the points of initial attack of the electrophile. While we have focused on *o*, *m*, and *p* substitution, electrophiles sometimes attack the C-S carbon (the ***ipso*** carbon) of the aromatic ring. The result of *ipso* attack often is reversible loss of the electrophile E^+ to regenerate the starting substituted aromatic system. However, sometimes it is possible for the E group in the cation intermediate to migrate to an *ortho* position (Figure 14.40).

Figure 14.40

This type of rearrangement is known to occur when E^+ is the nitronium ion (NO_2^+) and may explain the relatively high *o/p* ratios (Table 14.10) for nitration of benzenes substituted with *meta* directing deactivators.

Multiple Substituents (14.4E)

When a benzene ring has more than one substituent, their I and R effects can cooperate or conflict with each other. We will see in examples here that rates and product distributions depend on the number of substituents, their relative locations, the direction and strength of their I and R effects, and steric effects.

1,4-Dimethylbenzene. The product distribution is easy to predict for electrophilic substitution on any 1,4-disubstituted benzene where the two substitutents are identical such as 1,4-dimethylbenzene (*p*-xylene) (Figure 14.41).

Figure 14.41

All four unsubstituted positions are identical, so substitution by any electrophile at any of the four positions gives a single trisubstituted product no matter whether the substituents are activating or deactivating, or are *o,p* or *meta* directors.

1,3-Dinitrobenzene. The product distribution is also easy to predict for any 1,3-disubstituted benzene where both substituents are *meta* directors. There is only one unsubstituted position that is *meta* to either substituent so the attacking electrophile overwhelmingly prefers to react at that position (Figure 14.42).

Figure 14.42

For example, nitration of 1,3-dinitrobenzene gives exclusively 1,3,5-trinitro-benzene that we show in Figure 14.43 as the final product arising from "exhaustive" nitration of benzene.

Figure 14.43

> **Exhaustive Nitration of Benzene**. The intital formation of nitrobenzene from benzene is rapid since the nitronium ion is a powerful nucleophile. It is more difficult to add the second NO_2^+ because the nitro substitutent is a powerful deactivator. Since NO_2 is a *meta* director, the resultant dinitrobenzene is almost exclusively 1,3-dinitrobenzene.
>
> The third nitro group is very hard to add since the two NO_2 groups severely deactivate the ring. There are four unsubstituted positions on 1,3-dinitrobenzene, but it is easy to predict the structure of the product as 1,3,5-trinitrobenzene since C5 is the only position that is *meta* to both of the existing NO_2 groups.

1,3-Dimethylbenzene. In contrast to the results for 1,3-dinitrobenzene, electrophiles do <u>not</u> react at the C5 position of 1,3-dimethylbenzene (*m*-xylene). The two identical CH_3 substitutents are *o,p*-directors, so the three reactive positions (Figure 14.44) are in *ortho* or *para* relationships to each CH_3 group.

Figure 14.44

The C5 position is *meta* to each of those groups.

We show an actual product distribution for chlorination of 1,3-dimethyl-benzene in Figure 14.45 .

Figure 14.45

We see that the yield of 1-chloro-2,4-dimethylbenzene (A) (77%) is substantially higher than that of the isomeric product 2-chloro-1,3-dimethylbenzene (B) (23%).

While the relative product yields agree with our expectation that B should be harder to form than A for steric reasons, the actual effects of steric hindrance are

significantly smaller than they first appear. There are two different positions where an electrophile can react to give A, but only one where it can react to give B. As a result, the relative reactivities are much closer to each other after correction for statistical effects.

1,2-Benzenedicarboxylic Acid. When two identical groups groups are in a 1,2 relationship, their directive effects combine in such a way as to generally lead to formation of product at each unsubstituted position that is not sterically hindered. This is the case for 1,2-benzenedicarboxylic acid (phthalic acid) (Figure 14.46).

Figure 14.46

Nitration of phthalic acid (pronounced "thalic" acid) gives equal amounts of the two possible nitrobenzenedicarboxylic acids resulting from nitration at all four unsubstituted positions.

p-Chlorotoluene. When two substituents on a benzene ring are not the same, experimental results become more complex as we see for chlorination of *p*-chlorotoluene (Figure 14.47).

Figure 14.47

Chlorination occurs preferentially at the two equivalent positions (a) that are *ortho* to the CH_3 group rather than the two equivalent positions (b) *ortho* to the Cl. Both CH_3 and Cl are *o,p*-directing groups, but because of their relative positions on the benzene ring, these preferences conflict with each other. The *para* position for each group is blocked by the other group, and the positions *ortho* to CH_3 are *meta* to Cl and *vice-versa*.

The observed preference for chlorination *ortho* to CH_3 agrees with the general observation that when the directive effects of two groups conflict with each other, the influence of the more activating group is dominant. Alkyl groups are only weakly activating, but halogens are deactivators.

The relative reactivity order that we show here is useful for making these types of judgements.

NR_2 > OH > OR > R, Ar > X > *meta* directing groups
Decreasing Reactivity →

m-Chlorotoluene. In contrast to its *para* isomer, the substituent directive effects for *m*-chlorotoluene cooperate with each other. Chlorination does not occur at the single position *meta* to the two groups, but primarily at sites that are *o* and *p* to the two substituents (Figure 14.48).

Figure 14.48

However only a small amount of reaction occurs at the sterically hindered *ortho* position between the two groups.