

St Peter's Institute of Pharmaceutical Sciences

Course : Bachelor of Pharmacy

Subject : Pharmaceutical Organic Chemistry II

Subject Code:BP301T

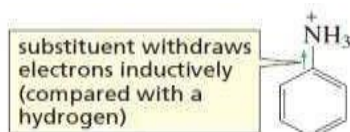
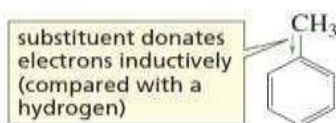
The Effect of Substituents on Reactivity

There are two ways substituents can donate electrons into a benzene ring: inductive electron donation and electron donation by resonance. There are also two ways substituents can withdraw electrons from a benzene ring: inductive electron withdrawal and electron withdrawal by resonance.

Inductive Electron Donation and Withdrawal

- It is a permanent effect
- It operates on sigma bonded electrons
- Electron shift take place towards more electro negative atom

If a substituent that is bonded to a benzene ring is less electron withdrawing than a hydrogen, the electrons in the sigma bond that attaches the substituent to the benzene ring will move toward the ring more readily. Such a substituent donates electrons inductively compared with a hydrogen.



If a substituent is more electron withdrawing than a hydrogen, it will withdraw the sigma electrons away from the benzene ring more strongly than will a hydrogen. Withdrawal of electrons through a sigma bond is called **inductive electron withdrawal**. The NH_3^+ group is a substituent that withdraws electrons inductively because it is more electronegative than a hydrogen.

Resonance Electron Donation and Withdrawal

If a substituent has a lone pair on the atom that is directly attached to the benzene ring, the lone pair can be delocalized into the ring; these substituents are said to donate electrons by resonance. Substituents such as OH, OR, and Cl donate electrons by resonance.

donation of electrons into a benzene ring by resonance



If a substituent is attached to the benzene ring by an atom that is doubly or triply bonded to a more electronegative atom, the pi electrons of the ring can be delocalized onto the substituent; these substituents are said to withdraw electrons by resonance. Substituents such as $\text{C}=\text{O}$, $\text{C}\equiv\text{N}$, $\text{O}=\text{N}-\text{O}$ (NO_2) and withdraw electrons by resonance.

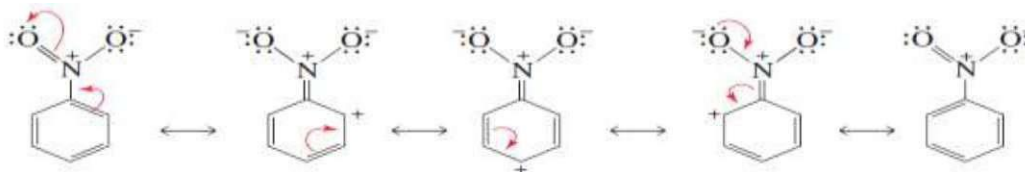


Table 1 EFFECT OF GROUPS ON ELECTROPHILIC AROMATIC SUBSTITUTION

Activating: *Ortho,para* Directors

Strongly activating

- $-\text{NH}_2$ ($-\text{NHR}$, $-\text{NR}_2$)
- $-\text{OH}$

Moderately activating

- $-\text{OCH}_3$ ($-\text{OC}_2\text{H}_5$, etc.)
- $-\text{NHCOCH}_3$

Weakly activating

- $-\text{C}_6\text{H}_5$
- $-\text{CH}_3$ ($-\text{C}_2\text{H}_5$, etc.)

Deactivating: *Meta* Directors

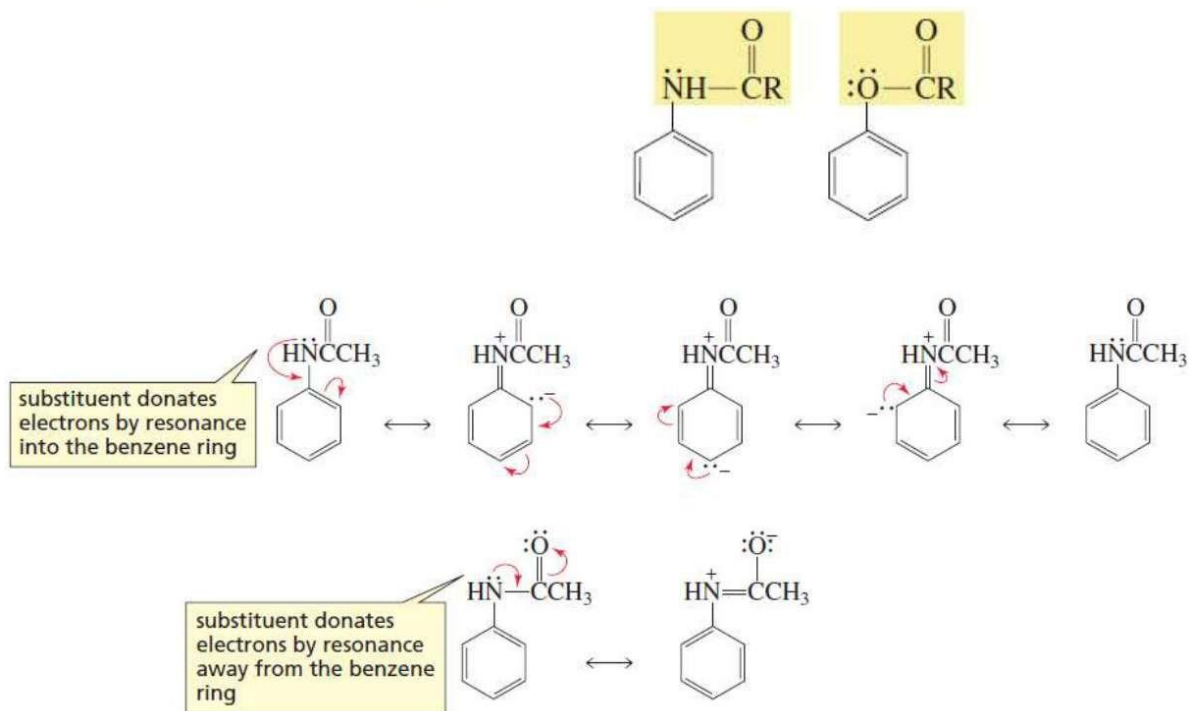
- $-\text{NO}_2$
- $-\text{N}(\text{CH}_3)_3^+$
- $-\text{CN}$
- $-\text{COOH}$ ($-\text{COOR}$)
- $-\text{SO}_3\text{H}$
- $-\text{CHO}$, $-\text{COR}$

Deactivating: *Ortho,para* Directors

- $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$

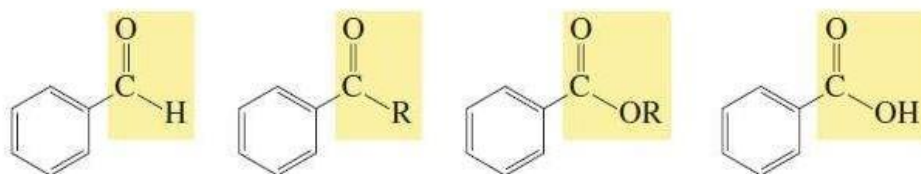
Note: The **moderately activating substituents** also donate electrons into the ring by resonance and withdraw electrons from the ring inductively. These substituents are less effective at donating electrons into the ring by resonance because, unlike the strongly activating substituents that donate electrons by resonance only into the ring, the moderately activating substituents can donate electrons by resonance in two competing directions: into the ring and away from the ring.

moderately activating substituents



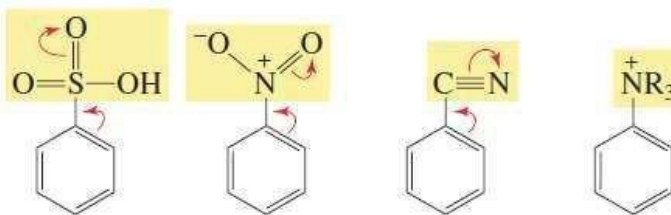
The moderately deactivating substituents all have carbonyl groups directly attached to the benzene ring. Carbonyl groups withdraw electrons both inductively and by resonance.

moderately deactivating substituents



The strongly deactivating substituents are powerful electron withdrawers. Except for the ammonium ions ($^+\text{NH}_3$, $^+\text{NH}_2\text{R}$, $^+\text{NHR}_2$ and $^+\text{NR}_3$), these substituents withdraw electrons both inductively and by resonance. The ammonium ions have no resonance effect, but the positive charge on the nitrogen atom causes them to strongly withdraw electrons inductively.

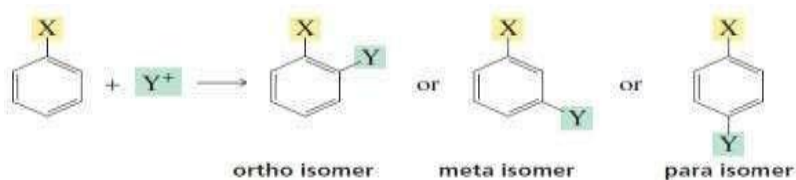
strongly deactivating substituents



The Effect of Substituents on Orientation

When a substituted benzene undergoes an electrophilic substitution reaction, The substituent already attached to the benzene ring determines the location of the new substituent.

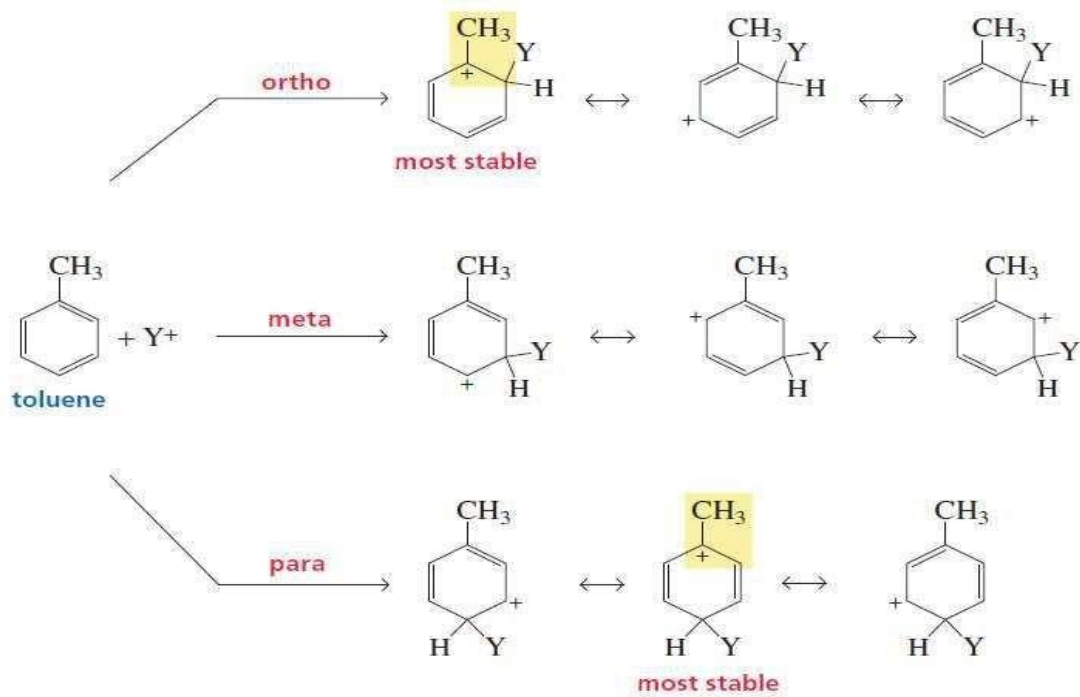
All activating substituents and the weakly deactivating halogens are ortho-para directors, and all substituents that are more deactivating than the halogens are meta directors. Thus, the substituents can be divided into three groups:



The above classification is based on the stability of the carbocation intermediate that is formed in the rate-determining step.

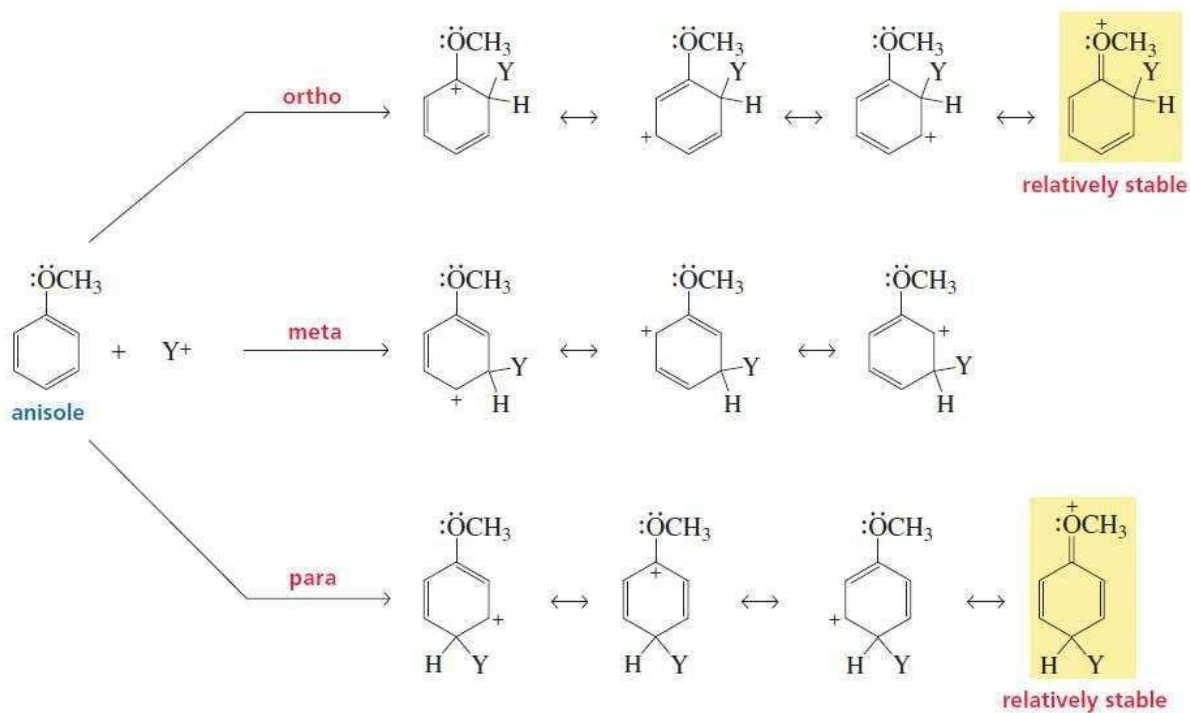
Example:

If a substituent donates electrons inductively like a methyl group, for example in Toluene, the substituent is attached directly to the positively charged carbon, which the substituent can stabilize by inductive electron donation. These relatively stable resonance contributors are obtained only when the incoming group is directed to an ortho or para position.



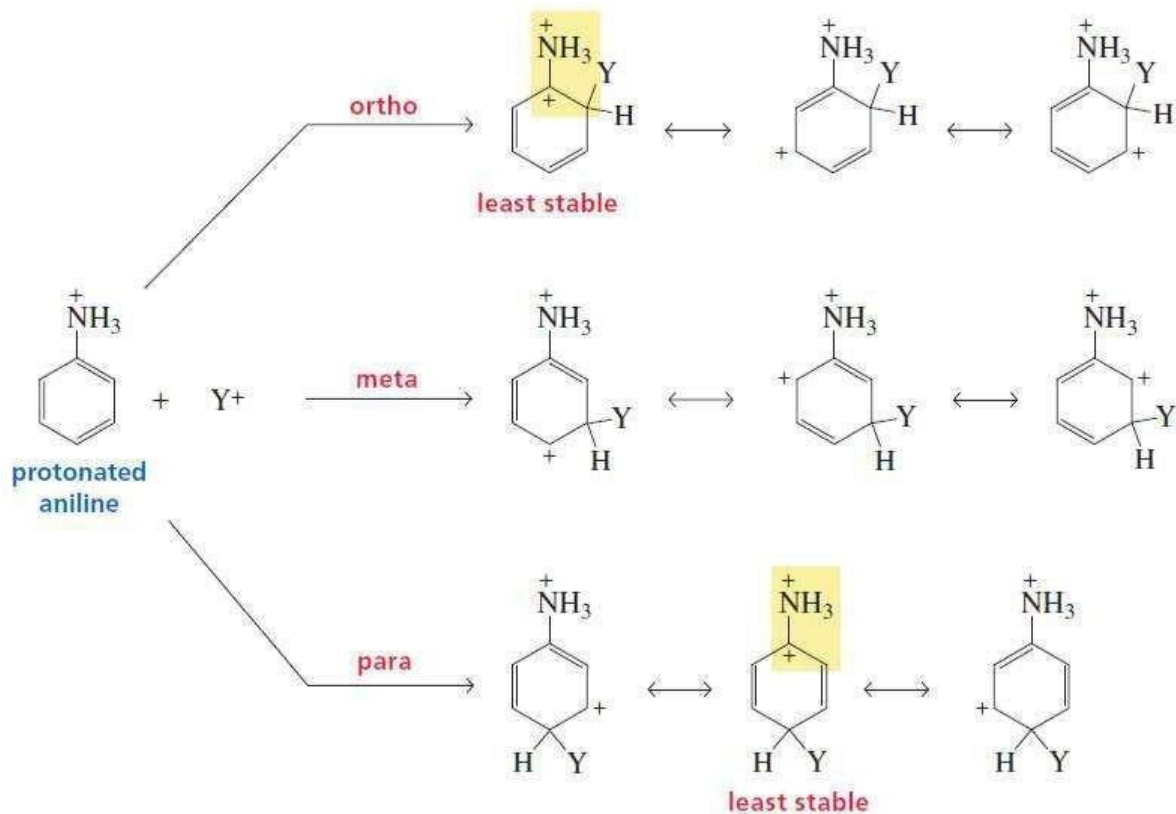
Example:

If a substituent donates electrons by resonance, like a methoxy group, for example in Anisole, the carbocations formed by putting the incoming electrophile on the ortho and para positions have a fourth resonance contributor. This is an especially stable resonance contributor because it is the only one whose atoms (except for hydrogen) all have complete octets. Therefore, all substituents that donate electrons by resonance are ortho-para directors.



Example:

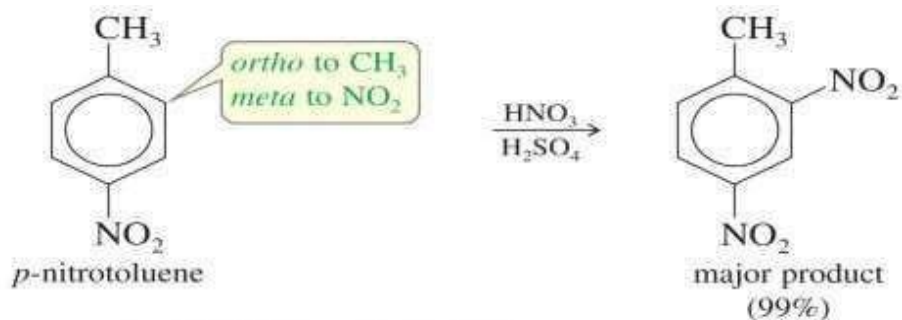
Substituents with a positive charge or a partial positive charge on the atom attached to the benzene ring, withdraw electrons inductively from the benzene ring, and most withdraw electrons by resonance as well. For all such substituents, the indicated resonance contributors in Figure below are the least stable because they have a positive charge on each of two adjacent atoms, so the most stable carbocation is formed when the incoming electrophile is directed to the meta position. Thus, all substituents that withdraw electrons (except for the halogens, which are ortho-para directors because they donate electrons by resonance) are meta directors.



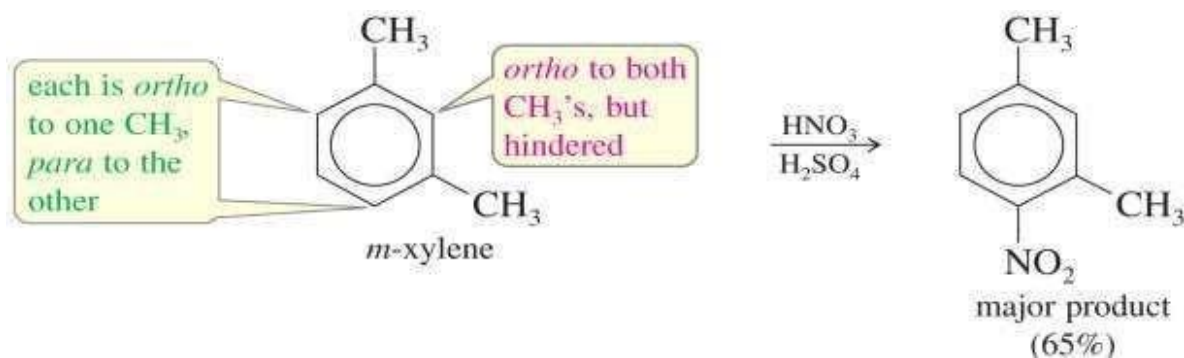
Effect of Multiple Substituents on Electrophilic Aromatic Substitution

When 2 substituents are already on the ring

- the stronger activator usually predominates.
- Steric factors will also play a role in determining the structure of the new product.



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- Practical Organic Chemistry by Mann and Saunders.
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