

ELECTROPHILIC AROMATIC SUBSTITUTION III

Department of Pharmaceutical Chemistry

Dr. Husam Hamza

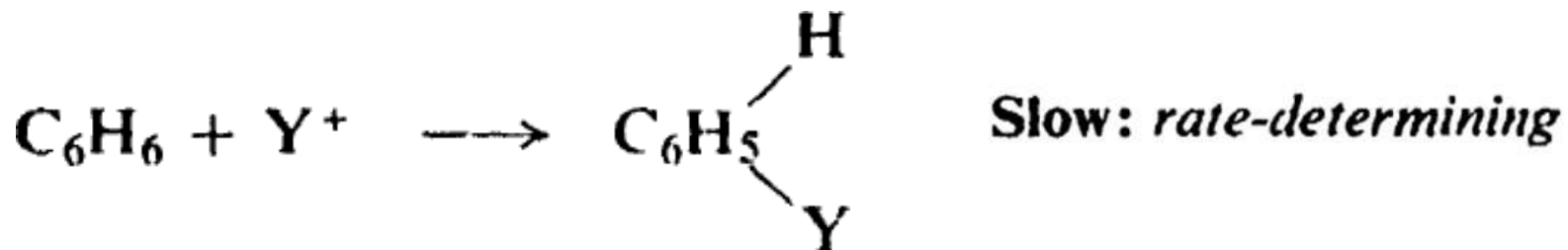
Reactivity and orientation

We have seen that certain groups activate the benzene ring and direct substitution to **ortho** and **para** positions, and that

Other groups deactivate the ring and (except halogens) direct substitution to **meta** positions.

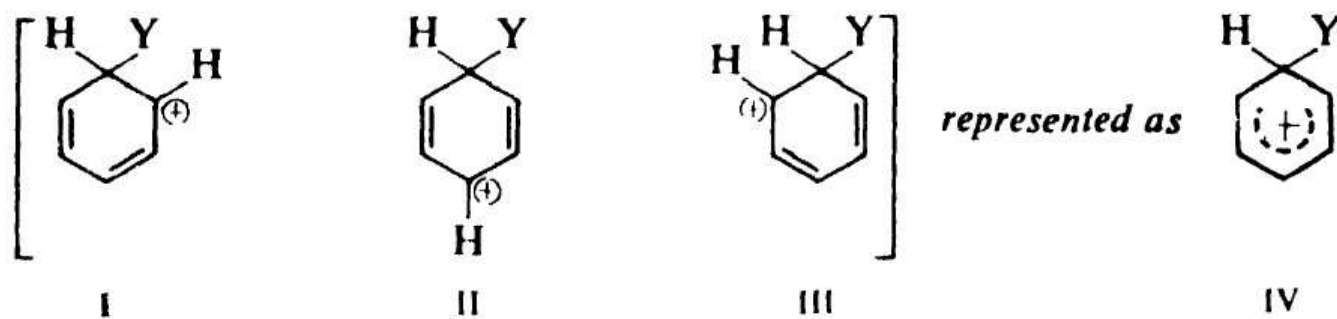
Methyl is said to activate the ring because it makes the ring react *faster* than benzene; it causes **ortho, para** orientation because it makes the **ortho** and **para** positions react faster than the **meta** positions.

***The rate of electrophilic aromatic substitution is determined by the same slow step-attack of the electrophile on the ring to form a **carbonium ion**:



***Any differences in rate of substitution must therefore be due to differences in the rate of this step.

In electrophilic aromatic substitution the intermediate carbonium ion is a hybrid of structures I, II, and III, in which the positive charge is distributed about the ring, being strongest as the positions **ortho** and **para** to the carbon atom being attacked.



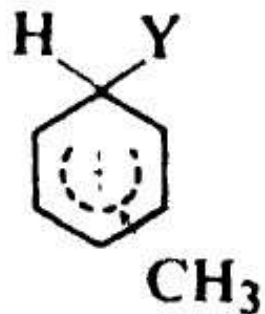
***A group already attached to the benzene ring should affect the stability of the carbonium ion by dispersing or intensifying the positive charge, depending upon its or electron-releasing(activating) electron-withdrawing nature (deactivating).

Theory of reactivity

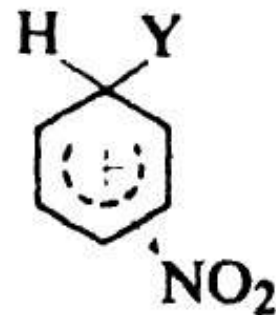
To compare rates of substitution in benzene, toluene, and nitrobenzene, we compare the structures of the carbonium ions formed from the three compounds:



I

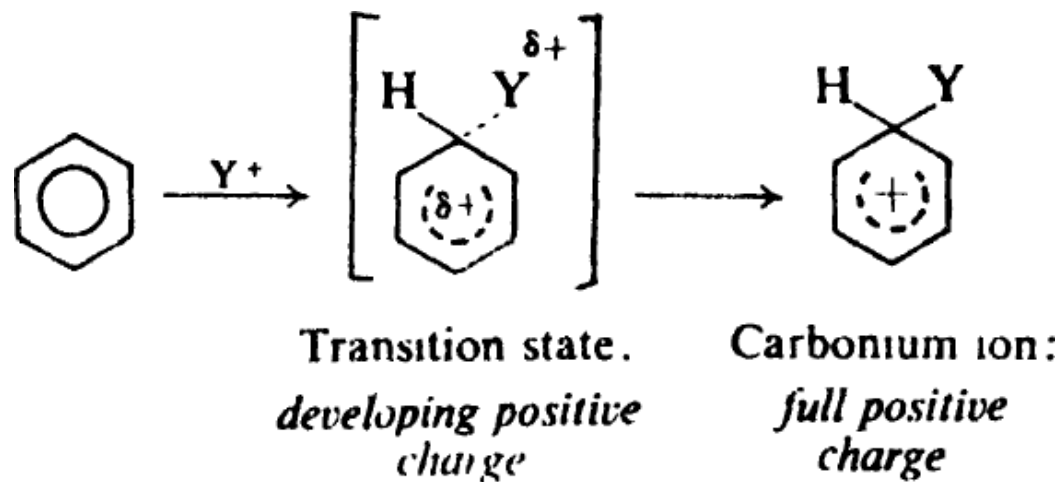


II



III

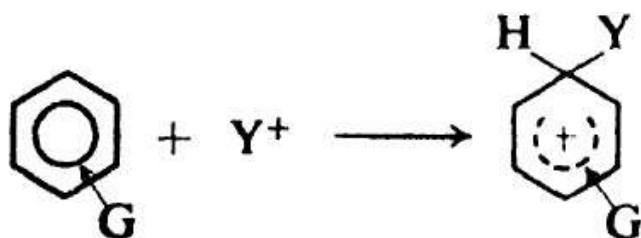
By releasing electrons, the methyl group (II) tends to neutralize the positive charge of the ring and so become more positive itself; this dispersal of the charge stabilizes the **carbonium ion**. In the same way the inductive effect stabilizes the developing positive charge in the transition state and thus leads to **a faster reaction**.



The -NO_2 group, on the other hand, has an electron- withdrawing inductive effect (III); this tends to intensify the positive charge, destabilizes the carbonium ion, and thus causes a slower reaction ➤

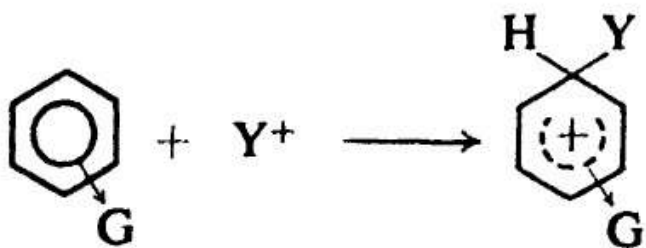
Reactivity in electrophilic aromatic substitution depends, then, upon the tendency of a substituent group to release or withdraw electrons. A group that releases electrons activates the ring; a group that withdraws electrons deactivates the ring.

Electrophilic Aromatic Substitution



*G releases electrons,
stabilizes carbonium ion,
activates*

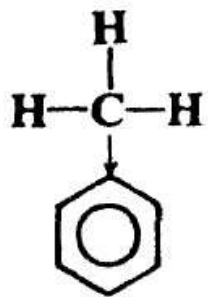
G = $-\text{NH}_2$
 $-\text{OH}$
 $-\text{OCH}_3$
 $-\text{NHCOCH}_3$
 $-\text{C}_6\text{H}_5$
 $-\text{CH}_3$



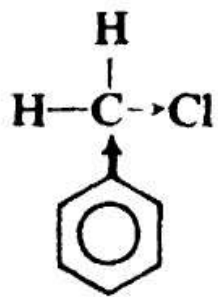
*G withdraws electrons,
destabilizes carbonium ion,
deactivates*

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

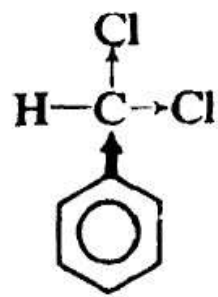
We might expect replacement of hydrogen in $-\text{CH}_3$ by halogen to decrease the electron-releasing tendency of the group, and perhaps to convert it into an electron-withdrawing group.



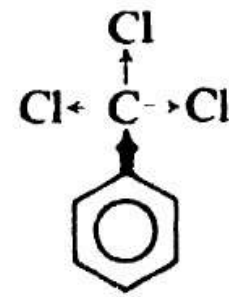
Activating



Weakly
deactivating



Moderately
deactivating



Strongly
deactivating

Theory of orientation

An activating group activates all positions of the benzene ring; even the positions meta to it are more reactive than any single position in benzene itself. It directs ***ortho*** and ***para*** simply because it activates the ***ortho*** and ***para*** positions much more than it does the ***meta***

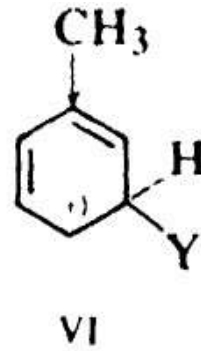
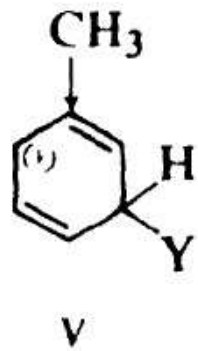
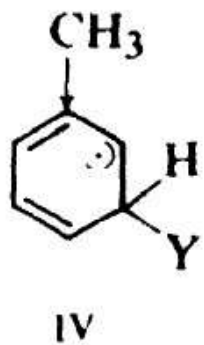
A deactivating group deactivates all positions in the ring, even the positions ***meta*** to it. It directs ***meta*** simply because it deactivates the ***ortho*** and ***para*** positions even more than it does the ***meta***.

Thus both ***ortho, para*** orientation and ***meta*** orientation arise in the same way: **the effect of any group whether activating or deactivating is strongest at the *ortho* and *para* positions.**

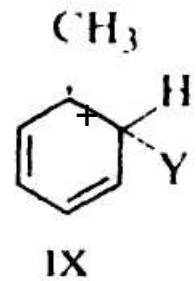
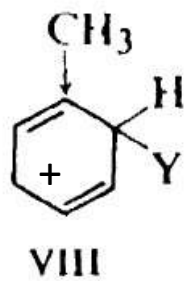
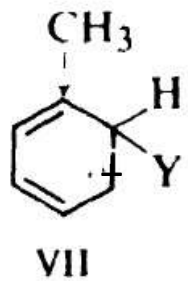


Para attack

*Especially stable:
charge on carbon
carrying substituent*



Meta attack

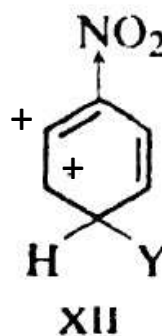
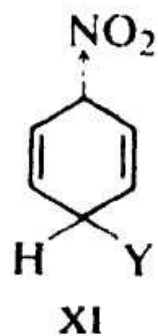
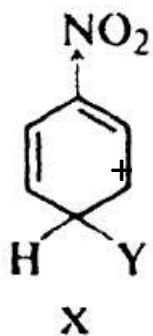


Ortho attack

*Especially stable:
charge on carbon
carrying substituent*

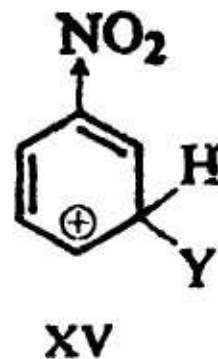
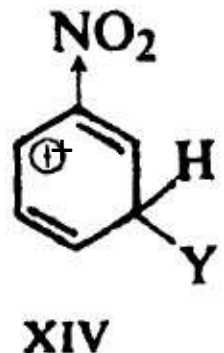
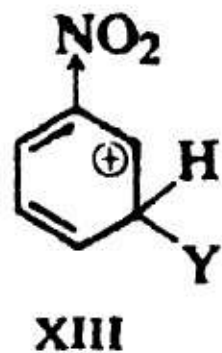
compare the carbonium ions formed by attack at the *para* and *meta* positions of nitrobenzene

Each of these is a hybrid of three structures, X-XII for *para* attack, XI II-XV for *meta* attack. In one of the six structures, XI, the positive charge is located on the

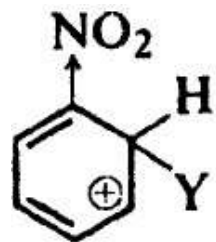


Para attack

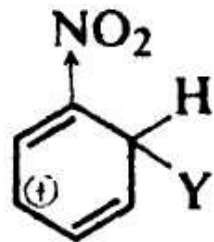
*Especially unstable:
charge on carbon
carrying substituent*



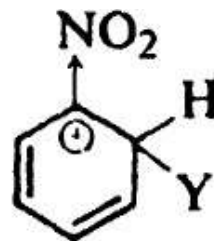
Meta attack



XVI



XVII



XVIII

Ortho attack

*Especially unstable:
charge on carbon
carrying substituent*

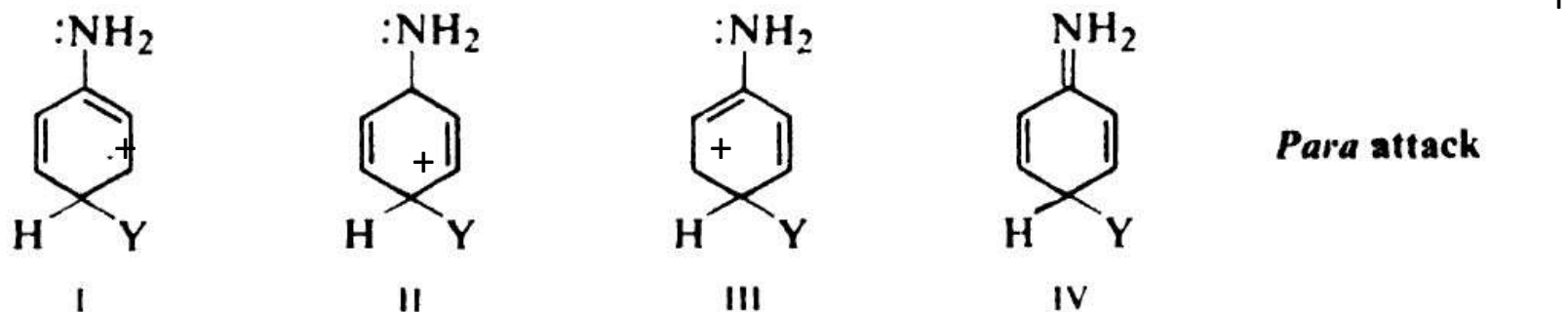
In nitrobenzene, **ortho. para** substitution is thus slower than **meta** substitution because electron withdrawal by $-\text{NO}_2$ is more effective during attack at the positions **ortho** and **para** to it. ➤

Electron release via resonance

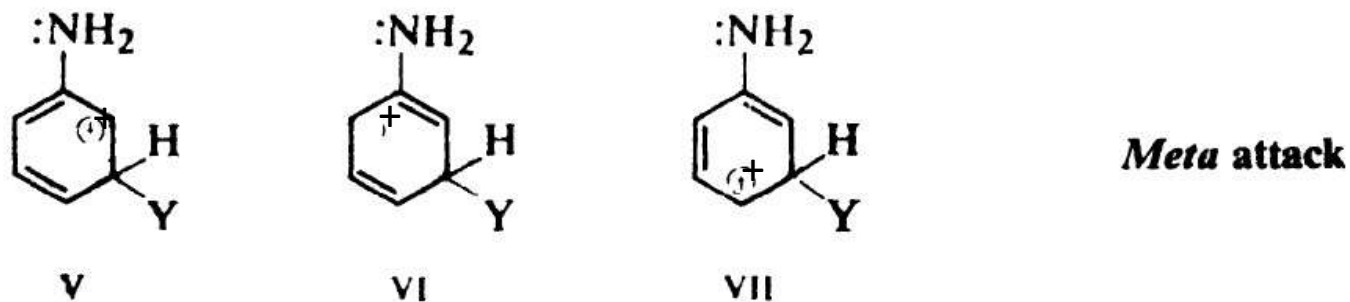
Groups ($-\text{NH}_2$ and $-\text{OH}$, and their derivatives) act as powerful activators toward electrophilic aromatic substitution, even though they contain electronegative atoms and can be shown in other ways to have electron-withdrawing inductive effects.

They are believed to do this by a resonance effect ➤

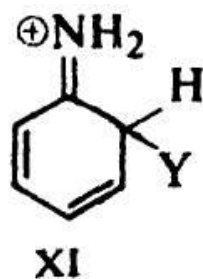
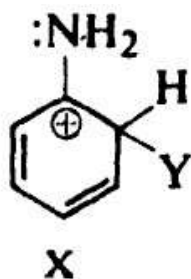
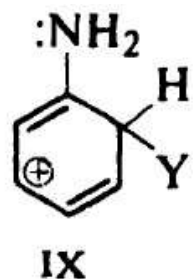
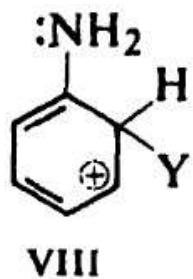
That nitrogen and oxygen can share more than a pair of electrons with the ring and can accommodate a positive charge. ➤



*Especially stable:
every atom has octet*



(VIII-XI) shows structures corresponding to the of Examination ➤ that **ortho** attack is much like para attack:

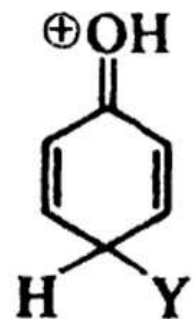


Ortho attack

*Epecially stable:
every atom has octet*

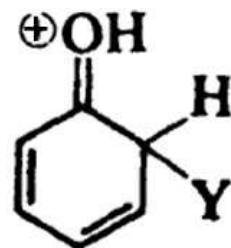
Thus substitution in aniline occurs faster than ➤ substitution in benzene, and occurs predominantly at the positions ortho and para to -NH_2 .

In the same way activation and **ortho, para** orientation by ➤ the -OH group is accounted for by contribution of structures like XII and XIII, in which every atom has a complete octet of electrons:



XII

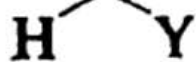
Para attack



XIII

Ortho attack

The similar effects of the derivatives of $-NH_2$ and $-OH$ are accounted for by similar structures (shown only for para attack):



$-NHCH_3$



$-N(CH_3)_2$



$-NHCOCH_3$



$-OCH_3$

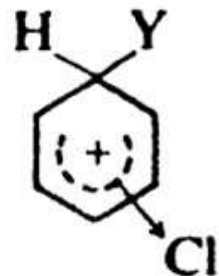
Effect of halogen on electrophilic aromatic substitution

Halogens are unusual in their effect on electrophilic aromatic substitution: they are deactivating yet ortho, para-directing

Can halogen both withdraw and release electrons?

Halogen withdraws electrons through its inductive effect, and releases electrons through its resonance effect.

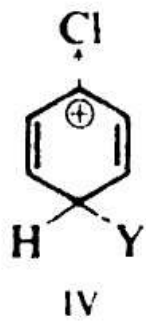
but there the much stronger resonance effect greatly outweighs the other.



— Cl withdraws electrons:
destabilizes carbonium ion,
deactivates ring

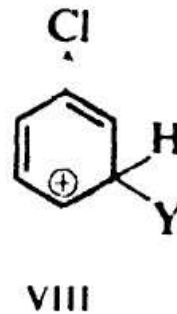
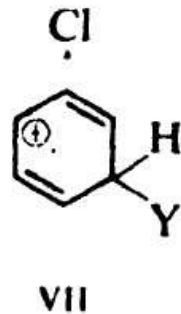
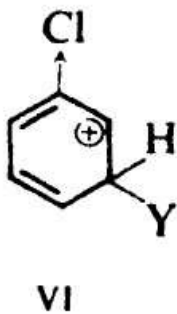
The electron withdrawing inductive effect of chlorine intensifies the positive charge in carbonium ion II, makes the ion less stable, and causes a slower reaction.

To understand orientation, we compare the structures of the carbonium ions formed by attack at the para and meta positions of chlorobenzene.



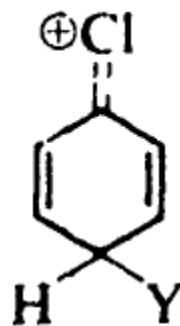
Para attack

*Especially unstable:
charge on carbon
bearing substituent*



Meta attack

the existence of halonium ions has shown us that halogen can share more than a pair of electrons and can accommodate a positive charge. ➤



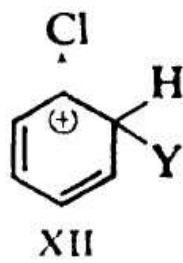
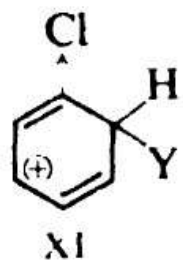
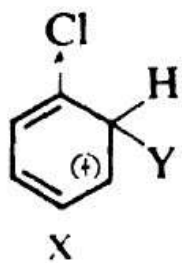
IX

*Comparatively stable:
every atom has octet*

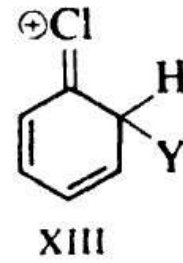
Para attack

This structure should be comparatively stable, since in it every atom (except hydrogen, of course) has a ***complete octet of electrons.*** ➤

In the same way it can be seen that attack at an ortho position also yields an ion (X-X1III) that can be stabilized by accommodation of the positive charge by chlorine ➤



*Especially unstable:
charge on carbon
bearing substituent*



*Comparatively stable:
every atom has octet*

Ortho attack