

Aromatic electrophilic substitution (Ar-S_E) Reactions

The special reactivity of aromatic systems towards electrophiles arises mainly from two factors: the presence of π electron density above and below the plane of the ring - making it nucleophilic, and the drive to regain the aromatic character by opting for substitution as opposed to a simple addition reaction. Preference towards addition reactions in the case of alkenes and substitution in the case of aromatic compounds becomes evident if we analyze the energy profiles of these reactions (Figures 1 and 2).

Energy profile in the case of Olefins – Addition vs. Substitution

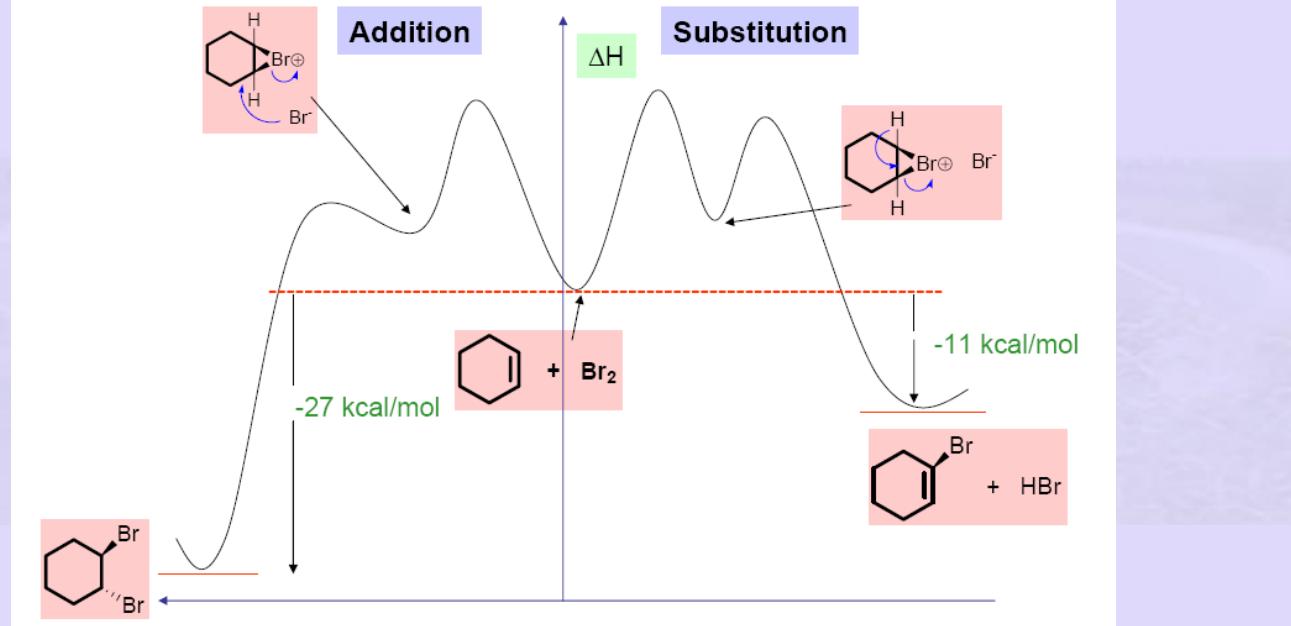


Figure 1.

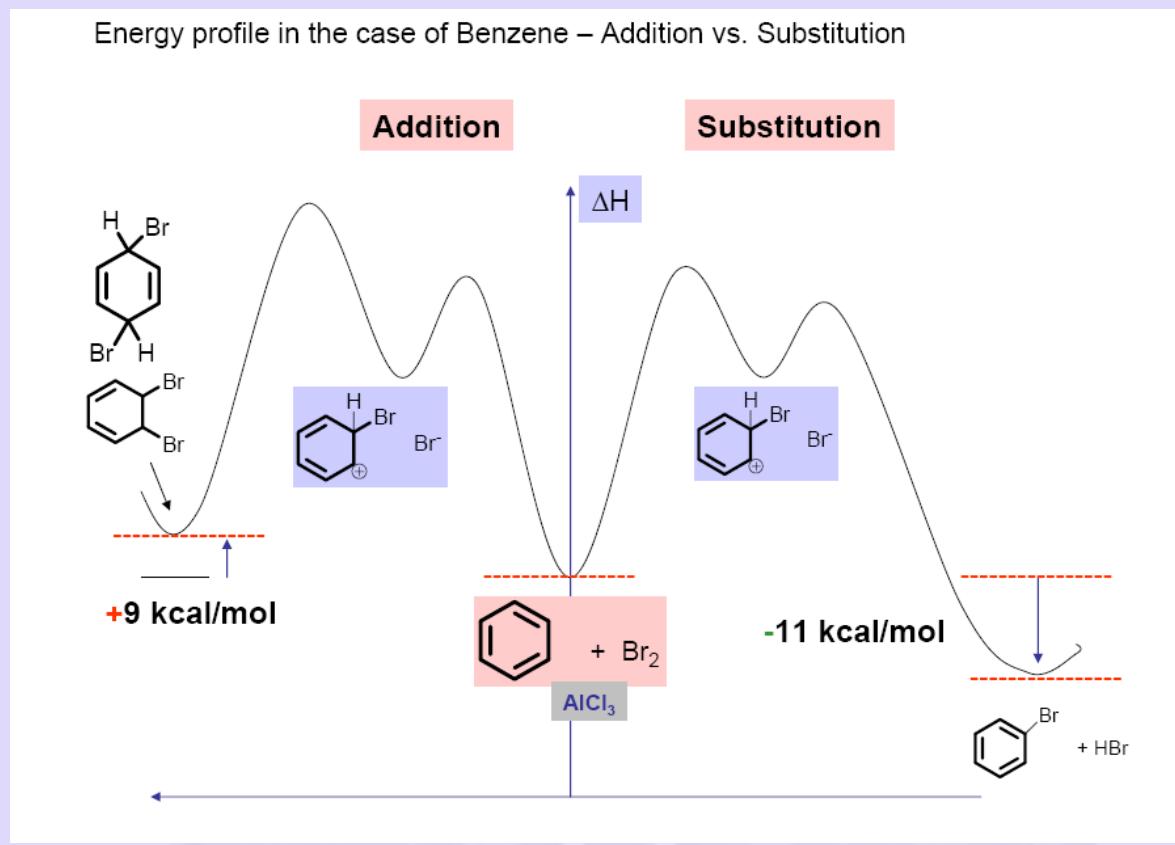


Figure 2.

Note: consider all the resonance structures of the wheland complex

The mechanism of electrophilic aromatic substitution involves an initial rate determining interaction of the π system with the electrophile to give a benzenonium ion intermediate (σ -complex or wheland complex), which undergoes a rapid de-protonation by the base in the second step to restore aromaticity (Figure 3).

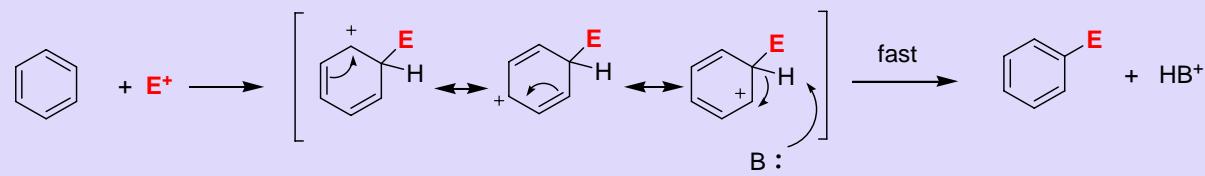


Figure 3.

Some common electrophilic aromatic substitution reactions are: halogenation, nitration, sulfonation, Friedel-Crafts Acylation and Friedel-Crafts alkylation. These differ only in the

nature and mode of generation of electrophiles, but in general follow the same two-step mechanism described above. Reagent combinations that lead to the generation of electrophiles in these reactions are shown in Figure 4.



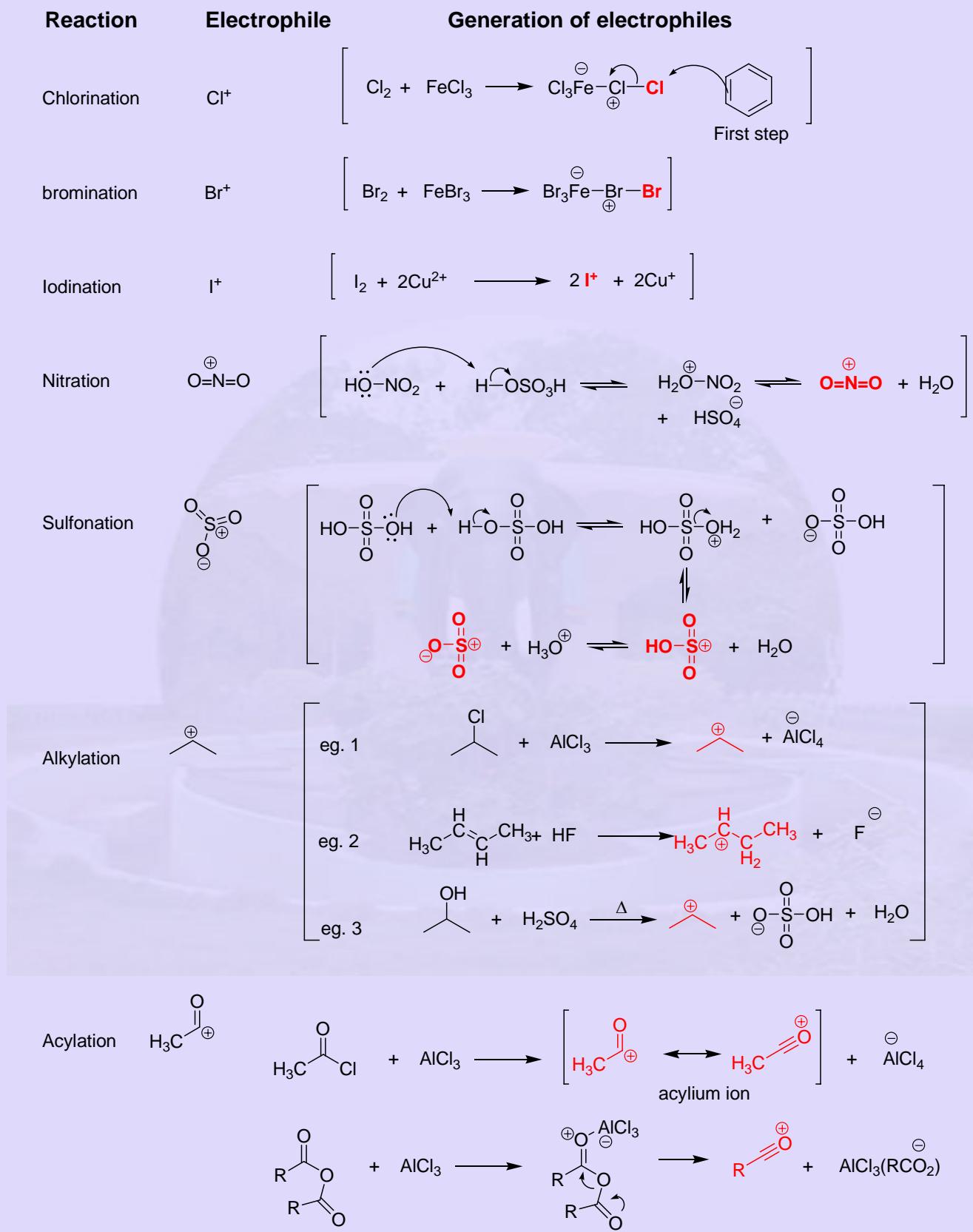


Figure 4

Note: since the product of acylation is a ketone which can complex with AlCl_3 , two equivalents of the Lewis acid is necessary to bring about the conversion efficiently. The complex can later be hydrolyzed using water

Among the reactions mentioned above, Friedel crafts alkylation suffers from two main draw backs: a) the possibility of multiple substitutions due to ring activation on mono-alkylation and b) the formation of products arising from rearranged electrophiles (carbocations) to more stable ones (Figure 5). Multiple substitutions can be avoided by using a large excess of the substrate (aromatic system) to ensure the collision of the electrophile with an un-substituted substrate and not a mono-substituted one.

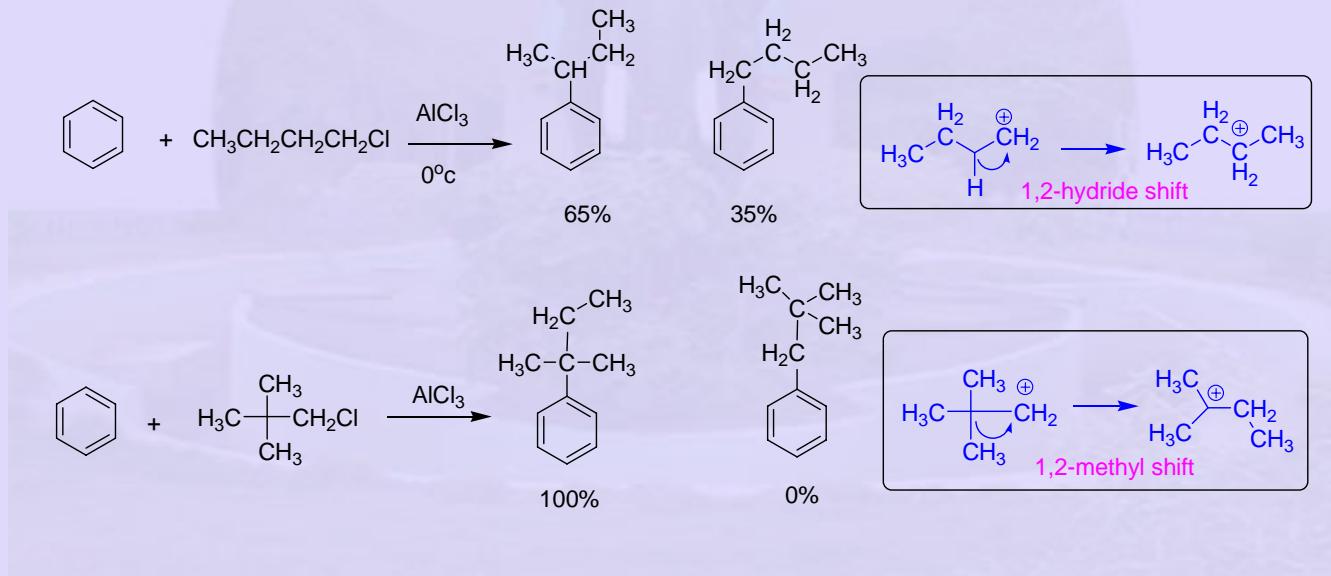


Figure 5.

Since acylium ions do not undergo rearrangement, an acylation-reduction strategy can be conveniently used to introduce alkyl groups which are prone to rearrangement as demonstrated by the example below (Figure 6)

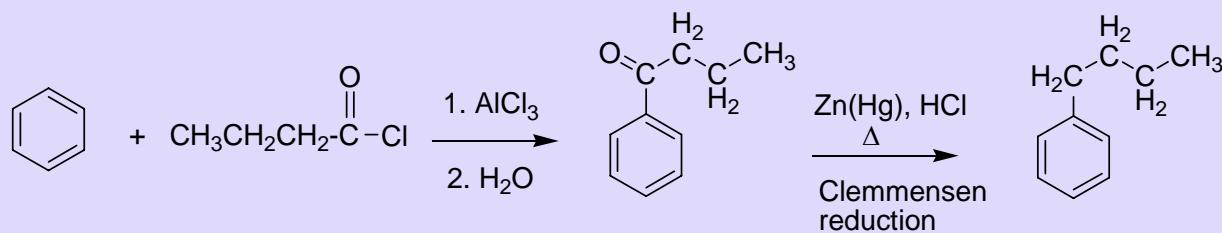


Figure 6.

Reversibility in Ar-S_E Reactions

Sulfonation of aromatic compounds is reversible and generally follows the following path (Figure 7). Similar equilibration is possible with electrophilic species such as HSO_3^+ as well.

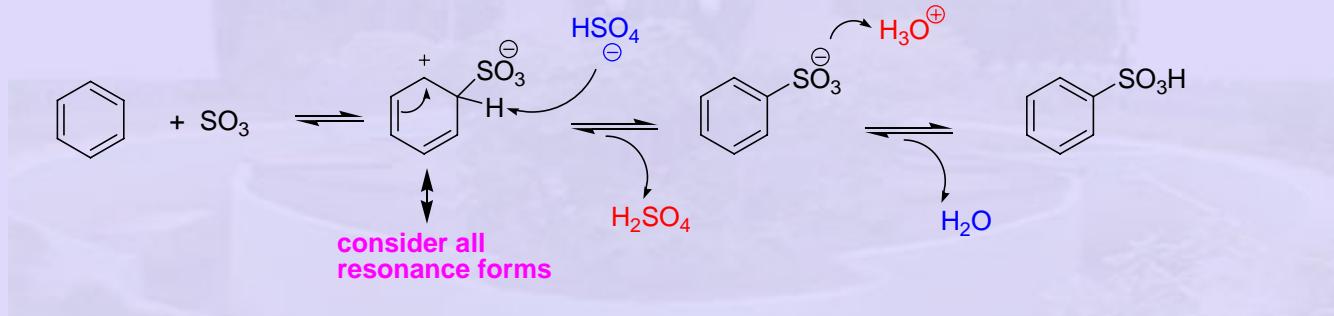
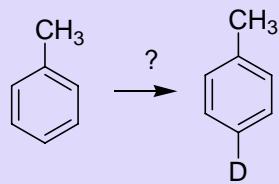


Figure 7.

To drive the equilibrium forward, we can use large excess of the sulfonating agent with minimum amount of water at lower temperature. Likewise, the reverse reaction will be facilitated by using dilute acids at higher temperatures with excess of water or passing superheated steam through the reaction mixture to remove the volatile de-sulfonated product.

Problem: How would you bring about the following transformation



As per the *principle of microscopic reversibility*, the desulfonylation should follow the same path in the reverse direction and energies of transition states and intermediates should remain the same. That is, the rate determining step here would involve the loss of $^+SO_3H$ from the protonated intermediate as shown below (Figures 8 and 9).

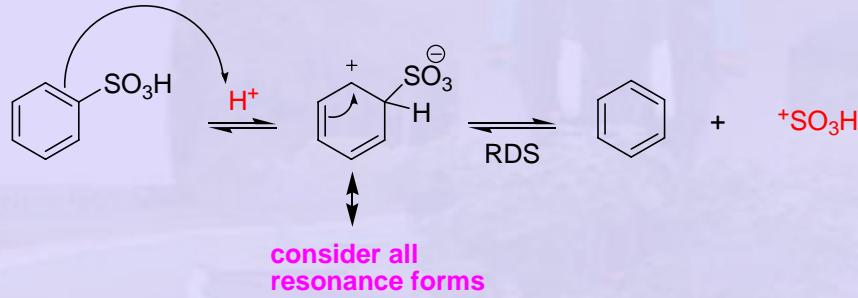


Figure 8.

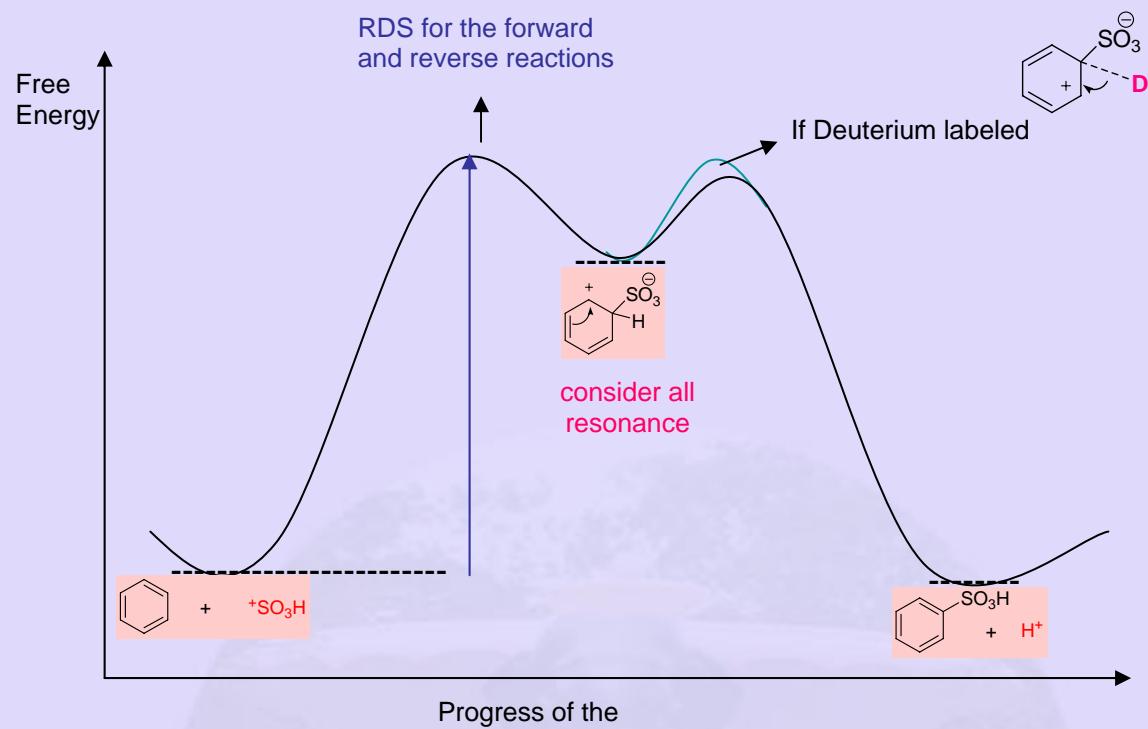


Figure 9.

Note: The energy barrier in the second step (deprotonation) would be slightly higher for deuterated benzenonium ion intermediate compared to protonated one. This leads to a moderate isotope effect, where H^+ is displaced almost twice as fast compared to D^+ from the corresponding analogs. Forward reaction in the case of protonated species becomes more feasible due to relatively lower energy barrier, where as larger fraction of deuterated ones revert back to the starting material, thus decreasing the overall rate.

Reactivity of substituted aromatics

Electron donating substituents usually activate the ring towards substitution where as electron withdrawing groups deactivate it. Compounds with activating groups react faster compared to benzene where as the ones with deactivating substituents react slower. This trend can be explained if we analyze the energy profile of the reaction and compare the stabilities of

the benzenonium ion intermediates involved (Figure 10). Since factors that stabilize the benzenonium ion intermediate should stabilize the transition-state as well (late transition-state) the activation energy in the case of aromatics with electron donating substituents will be lower than that for benzene. Due to the same reason, activation energy for derivatives with electron withdrawing substituents will be higher than that for benzene, leading to deactivation. The effects of these groups become very prominent if they are located at ortho or para positions with respect to the incoming electrophile.

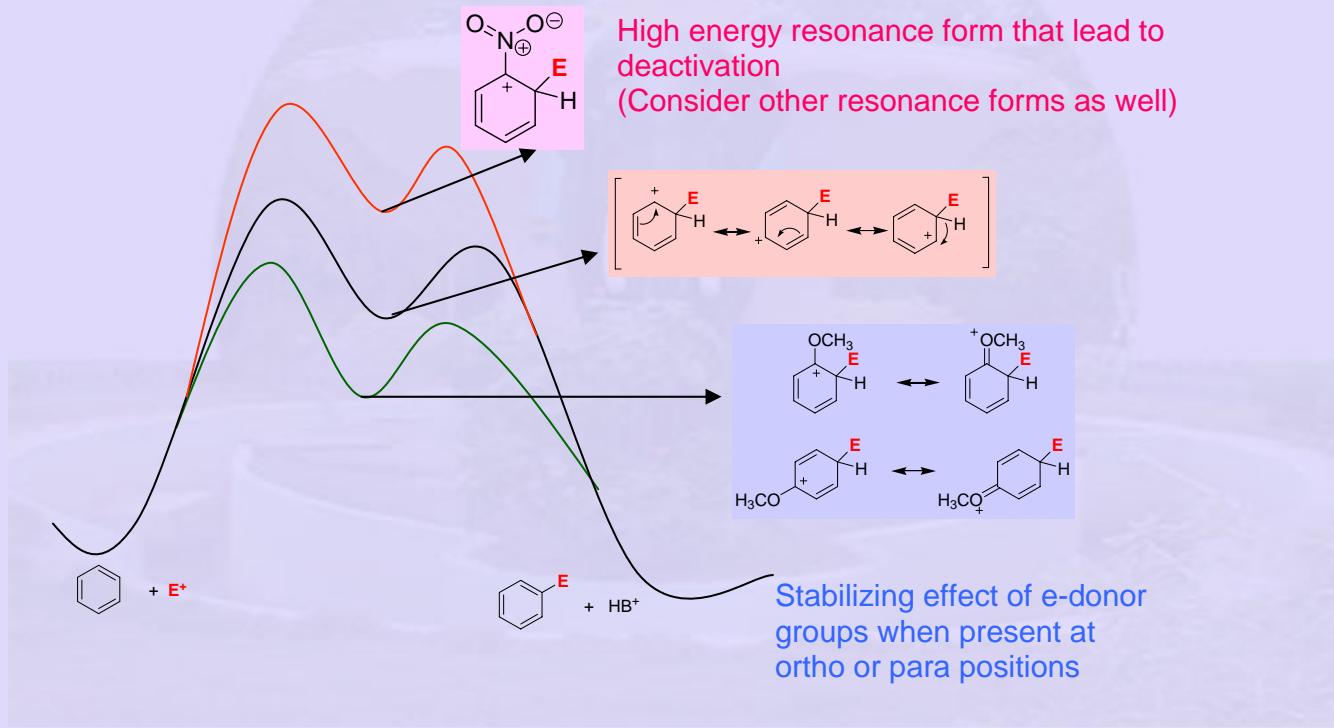


Figure 10.

Note: relative energies of *starting materials* and *products* are NOT clearly defined in the above figure. Only the intermediates and transition states need to be considered.

The same concept can be extended to explain the ability of pre-existing substituents to orient the incoming electrophiles. Typically, an electron donating group activate the ring towards substitution at ortho and para positions and electron withdrawing groups orient them to meta position. Taking benzene as the reference, it can be stated that an activating group activates all positions in the ring (ortho, meta and para), but substitution predominantly takes place at ortho and para positions as these positions are activated to a larger extent compared to meta. Similarly, an electron withdrawing group deactivates all positions in the ring (including meta), but substitution takes place at meta position as other locations in the ring are deactivated even more. This trend becomes clear if we look at the reaction conditions and product distributions in the sets of reactions presented in Figure 11. Various substituents and the nature of their electronic influences that lead to activation/deactivation are summarized in Figure 12.



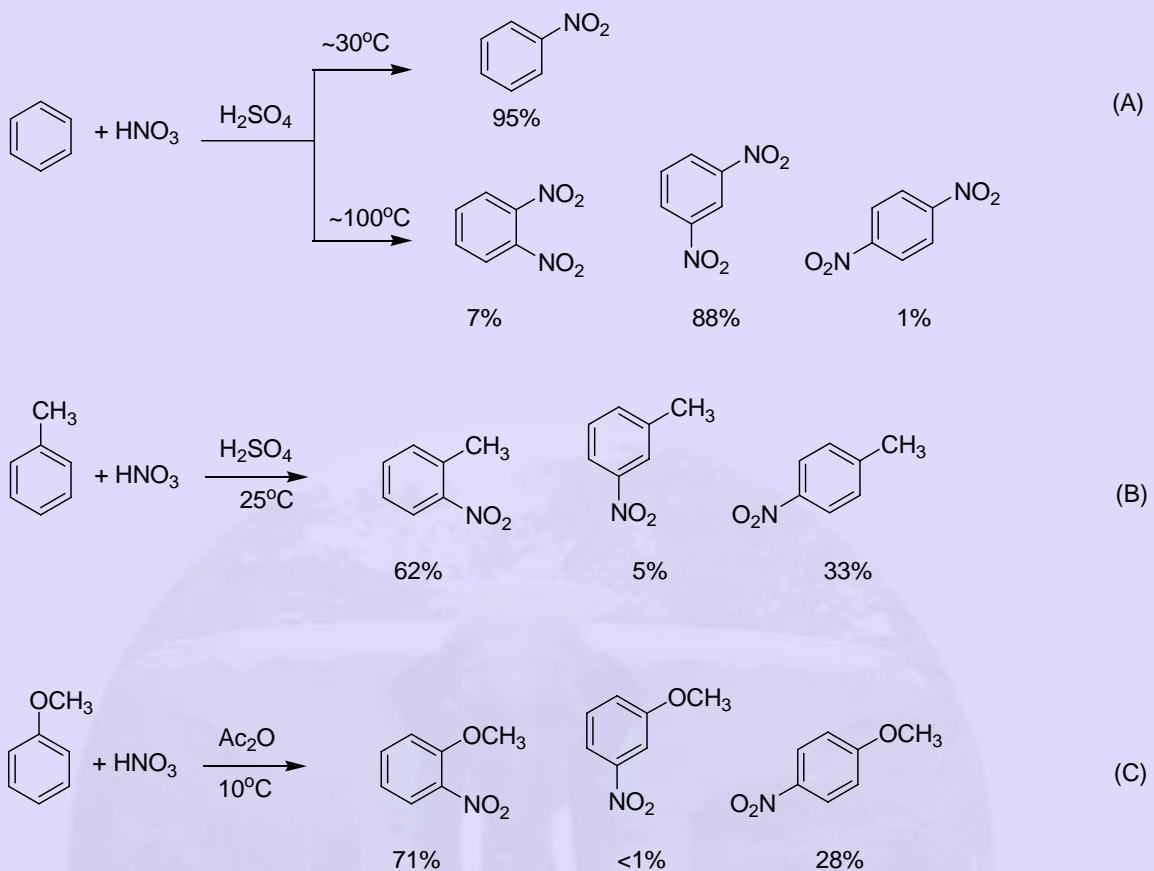


Figure 11.

$-\ddot{\text{O}}^-$	$+M, +I$ (activation of the ring by $+M$ groups are stronger than that by $+I$ groups)
$-\text{NR}_2, -\text{NH}_2,$ $-\text{OR}, -\text{OH}, -\text{SR},$ $-\text{H}^{\text{N}}-\text{CO}-\text{R}, -\text{O}-\text{CO}-\text{R},$	$+M, -I$
-Alkyl (eg. CH_3)	$+I$
-H	Standard
$-\text{CH}_2\text{Cl}$ $-\text{Cl}, -\text{Br}$	$-I, +I$ $-I, +M$
$-\text{NR}_3^+, -\text{NH}_3^+$	$-I$
$-\text{CO}-\text{R}, -\text{CO-OR}, -\text{C}\equiv\text{N}$ $-\text{NO}_2, \text{SO}_3\text{H}$	$-M, -I$

Figure 12.

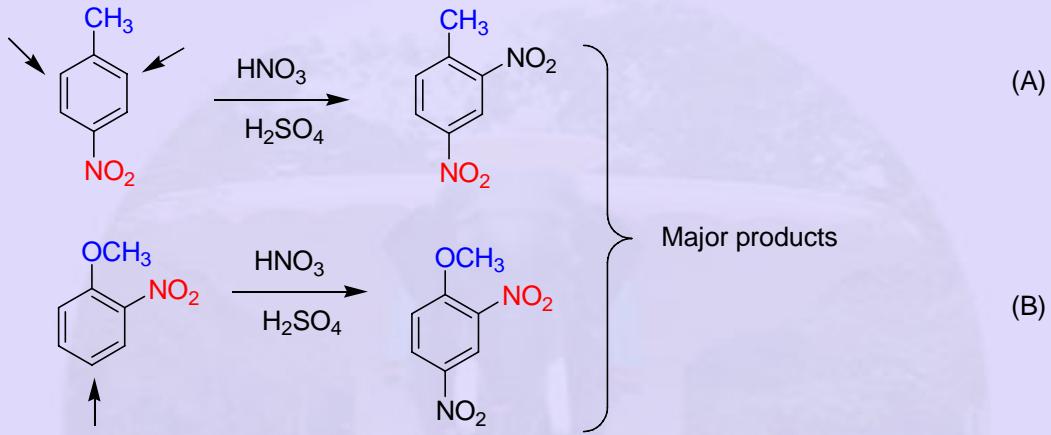
As mentioned, electron donating substituents direct the incoming electrophile to ortho/para positions and electron withdrawing groups direct them to meta. The site of substitution if the ring possesses more than one substituent can be predicted by analyzing their relative stereo-electronic influences. The following general rules can be used to predict the outcome.

1. The effect of activating groups (o/p directors) with $+M$ or $+I$ effects dominate over those with $-M$ or $-I$ groups.
2. Resonance effects ($+R$) override inductive effects ($+I$).
3. Steric crowding may thwart the formation of 1,2,3-trisubstituted products.
4. If the directing group is bulky, more para product would arise to avoid steric clash.

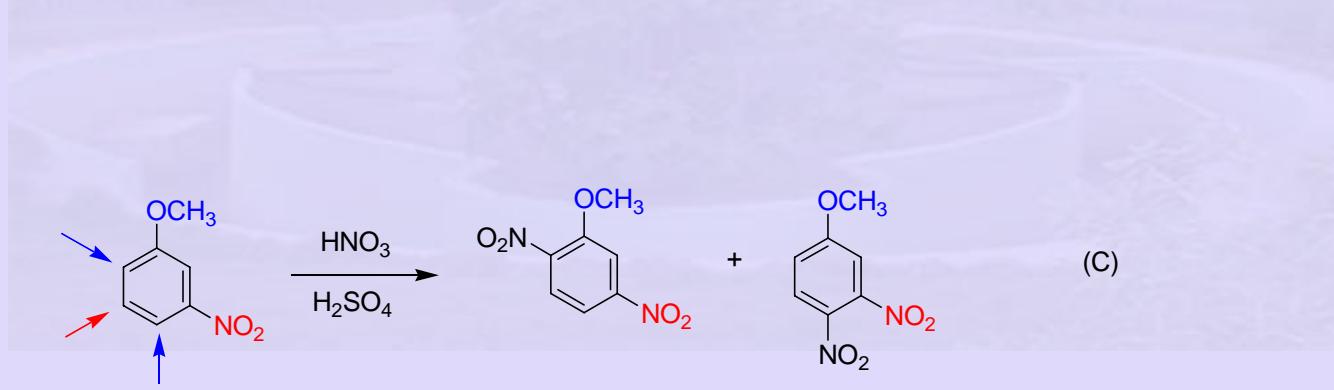
5. If the substituents present have similar activating propensities, a mixture of products result.

Some examples to illustrate the directivities are given below:

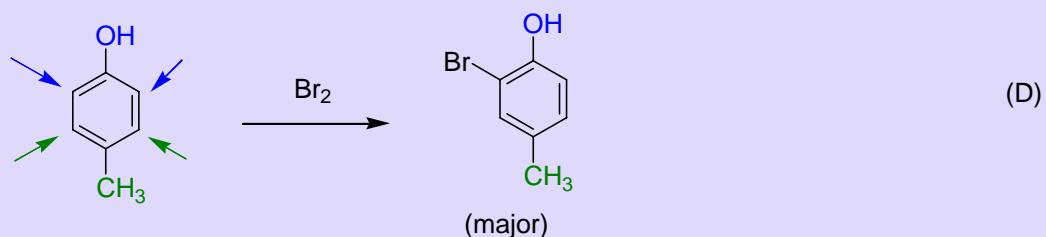
Case I. both substituents direct the incoming electrophile to the same position



Case II. Existing substituents direct the electrophile to different positions



Case III. Resonance vs. inducting effects



Case IV. Substituents with similar activating properties

