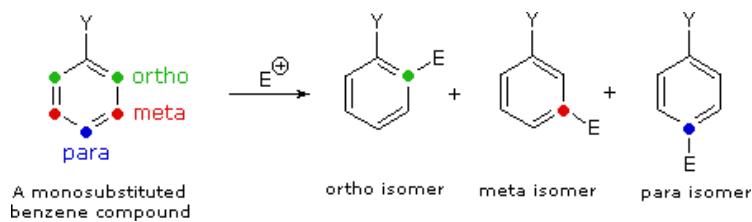


The Effect of Substituents on Orientation

The second factor that becomes important in reactions of substituted benzenes concerns the site at which electrophilic substitution occurs. Since a mono-substituted benzene ring has two equivalent ortho-sites, two equivalent meta-sites and a unique para-site, three possible constitutional isomers may be formed in such a substitution. If reaction occurs equally well at all available sites, the expected statistical mixture of isomeric products would be 40% ortho, 40% meta and 20% para. Again we find that the nature of the substituent influences this product ratio in a dramatic fashion. Bromination of methoxybenzene (anisole) is very fast and gives mainly the para-bromo isomer, accompanied by 10% of the ortho-isomer and only a trace of the meta-isomer. Bromination of nitrobenzene requires strong heating and produces the meta-bromo isomer as the chief product.



Some additional examples of product isomer distribution in other electrophilic substitutions are given in the table below. It is important to note here that the reaction conditions for these substitution reactions are not the same, and must be adjusted to fit the reactivity of the reactant C_6H_5-Y . The high reactivity of anisole, for example, requires that the first two reactions be conducted under very mild conditions (low temperature and little or no catalyst). The nitrobenzene reactant in the third example is very unreactive, so rather harsh reaction conditions must be used to accomplish that reaction.

Y in C_6H_5-Y	Reaction	% Ortho- Product	% Meta- Product	% Para- Product
$-O-CH_3$	Nitration	30–40	0–2	60–70
$-O-CH_3$	F-C Acylation	5–10	0–5	90–95
$-NO_2$	Nitration	5–8	90–95	0–5
$-CH_3$	Nitration	55–65	1–5	35–45
$-CH_3$	Sulfonation	30–35	5–10	60–65
$-CH_3$	F-C Acylation	10–15	2–8	85–90
$-Br$	Nitration	35–45	0–4	55–65
$-Br$	Chlorination	40–45	5–10	50–60

These observations, and many others like them, have led chemists to formulate an empirical classification of the various substituent groups commonly encountered in aromatic substitution reactions. Thus, substituents that activate the benzene ring toward electrophilic attack generally direct substitution to the ortho and para locations. With some exceptions, such as the halogens, deactivating substituents direct substitution to the meta location. The following table summarizes this classification.

Orientation and Reactivity Effects of Ring Substituents

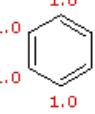
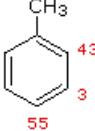
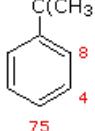
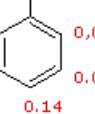
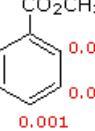
Activating Substituents ortho & para- Orientation	Deactivating Substituents meta-Orientation	Deactivating Substituents ortho & para- Orientation
$-O^{(-)}$	$-NH_2$	$-NO_2$
$-OH$	$-NR_2$	$-CO_2H$
$-OR$	$-$	$-CO_2R$
$-OC_6H_5$	$NHCOCH_3$	$-CONH_2$
$-$	$-R$	$-CHO$
$OCOCH_3$	$-C_6H_5$	$-COR$
		$-CN$
		$-F$
		$-Cl$
		$-Br$
		$-I$
		$-CH_2Cl$
		$-CH=CHNO_2$

The information summarized in the above table is very useful for rationalizing and predicting the course of aromatic substitution reactions, but in practice most

chemists find it desirable to understand the underlying physical principles that contribute to this empirical classification. We have already analyzed the activating or deactivating properties of substituents in terms of inductive and resonance effects, and these same factors may be used to rationalize their influence on substitution orientation.

The first thing to recognize is that the proportions of ortho, meta and para substitution in a given case reflect the relative rates of substitution at each of these sites. If we use the nitration of benzene as a reference, we can assign the rate of reaction at one of the carbons to be 1.0. Since there are six equivalent carbons in benzene, the total rate would be 6.0. If we examine the nitration of toluene, tert-butylbenzene, chlorobenzene and ethyl benzoate in the same manner, we can assign relative rates to the ortho, meta and para sites in each of these compounds. These relative rates are shown (colored red) in the following illustration, and the total rate given below each structure reflects the 2 to 1 ratio of ortho and meta sites to the para position. The overall relative rates of reaction, referenced to benzene as 1.0, are calculated by dividing by six. Clearly, the alkyl substituents activate the benzene ring in the nitration reaction, and the chlorine and ester substituents deactivate the ring.

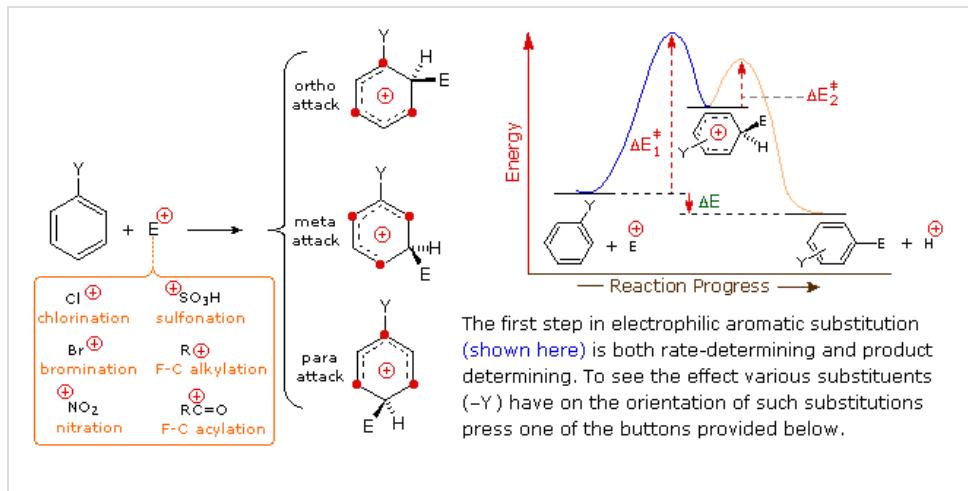
Rates of Nitration at Sites on the Benzene Ring

 1.0 1.0 1.0 1.0	 43 55 3	 8 75 4	 0.03 0.0 0.14	 0.0025 0.008 0.001
Total Rate	6.0	147	99	0.20
Relative Rate	1.0	24.5	16.5	0.033

From rate data of this kind, it is a simple matter to calculate the proportions of the three substitution isomers. Toluene gives 58.5% ortho-nitrotoluene, 37% para-nitrotoluene and only 4.5% of the meta isomer. The increased bulk of the tert-butyl group hinders attack at the ortho-sites, the overall product mixture being 16% ortho, 8% meta and 75% para-nitro product. Although chlorobenzene is much less reactive than benzene, the rate of ortho and para-substitution greatly exceeds that of meta-substitution, giving a product mixture of 30% ortho and 70% para-nitrochlorobenzene. Finally, the benzoic ester gave predominantly the meta-nitro product (73%) accompanied by the ortho (22%) and para (5%) isomers, as shown by the relative rates. Equivalent rate and product studies for other substitution reactions lead to similar conclusions. For example, electrophilic chlorination of

toluene occurs hundreds of times faster than chlorination of benzene, but the relative rates are such that the products are 60% ortho-chlorotoluene, 39% para and 1% meta-isomers, a ratio similar to that observed for nitration.

The manner in which specific substituents influence the orientation of electrophilic substitution of a benzene ring is shown in the following interactive diagram. As noted on the opening illustration, the product-determining step in the substitution mechanism is the first step, which is also the slow or rate determining step. It is not surprising, therefore, that there is a rough correlation between the rate-enhancing effect of a substituent and its site directing influence. The exact influence of a given substituent is best seen by looking at its interactions with the delocalized positive charge on the benzenonium intermediates generated by bonding to the electrophile at each of the three substitution sites. This can be done for seven representative substituents by using the selection buttons underneath the diagram.



In the case of alkyl substituents, charge stabilization is greatest when the alkyl group is bonded to one of the positively charged carbons of the benzenonium intermediate. This happens only for ortho and para electrophilic attack, so such substituents favor formation of those products. Interestingly, primary alkyl substituents, especially methyl, provide greater stabilization of an adjacent charge than do more substituted groups (note the greater reactivity of toluene compared with tert-butylbenzene).

Nitro (NO_2), sulfonic acid (SO_3H) and carbonyl ($\text{C}=\text{O}$) substituents have a full or partial positive charge on the atom bonded to the aromatic ring. Structures in which like-charges are close to each other are destabilized by charge repulsion, so these substituents inhibit ortho and para substitution more than meta substitution.

Consequently, meta-products predominate when electrophilic substitution is forced to occur.

Halogen (X), OR and NR₂ substituents all exert a destabilizing inductive effect on an adjacent positive charge, due to the high electronegativity of the substituent atoms. By itself, this would favor meta-substitution; however, these substituent atoms all have non-bonding valence electron pairs which serve to stabilize an adjacent positive charge by pi-bonding, with resulting delocalization of charge. Consequently, all these substituents direct substitution to ortho and para sites. The balance between inductive electron withdrawal and p-π conjugation is such that the nitrogen and oxygen substituents have an overall stabilizing influence on the benzenonium intermediate and increase the rate of substitution markedly; whereas halogen substituents have an overall destabilizing influence.

Contributors

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