Analysis of Electrophilic Aromatic Substitution in Aromatic Nitration, Aromatic Halogenation – An Analysis

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Abstract

This paper attempts to study how **electrophilic aromatic substitution reactions** organic reactions wherein an electrophile replacing an **atom with nitration, aromatic halogenation** . The **Electrophilic aromatic** reaction mechanism, denoted by the Hughes–Ingold mechanistic symbol **S_EAr**, begins with the aromatic ring attacking the electrophile E^+. This step leads to the formation of a positively charged and delocalized cyclohexadienyl cation, also known as an arenium ion, Wheland intermediate, or arene σ-complex. Many examples of this carbocation have been characterized, but under normal operating conditions these highly acidic species will donate the proton attached to the sp^3 carbon to the solvent (or any other weak base) to reestablish aromaticity. The net result is the replacement of H by E in the aryl ring. Occasionally, other electrofuges (groups that can leave *without their electron pair*) beside H^+ will depart to reestablish aromaticity; these species include silyl groups (as SiR_3^+), the carboxy group (as CO_2 + H^+), the iodo group (as I^+), and tertiary alkyl groups like *t*-butyl (as R^+). The capacity of these types of substituents to leave is sometimes exploited synthetically, particularly the case of replacement of silyl by another functional group (*ipso* attack). However, the loss of groups like iodo or alkyl is more often an undesired side reaction. In an electrophilic aromatic substitution reaction, existing substituent groups on the aromatic ring influence the overall reaction rate or have a directing effect on positional isomer of the products that are formed.

An **electron donating group** (**EDG**) or **electron releasing group** (**ERG**, **Z** in structural formulas) is an atom or functional group that donates some of its electron density into a conjugated π system via resonance (mesomerism) or inductive effects (or induction)—called **+M** or **+I** effects, respectively—thus making the π system more nucleophilic. As a result of these electronic effects, an aromatic ring to which such a group is attached is more likely to participate in electrophilic substitution reaction. EDGs are therefore often known as **activating groups**, though steric effects can interfere with the reaction. An **electron withdrawing group** (EWG) will have the opposite effect on the nucleophilicity of the ring. The EWG removes electron density from a π system, making it less reactive in this type of reaction, and therefore called **deactivating groups**.EDGs and EWGs also determine the positions (relative to themselves) on the aromatic ring where substitution reactions are most likely to take place; this property is therefore important in processes of organic synthesis.

Key words: Aromatic electrophilic substitution, Directing effect, functional groups deactivating groups

Introduction

Weakly deactivating groups direct electrophiles to attack the benzene molecule at the *ortho*- and *para*- positions, while strongly and moderately deactivating groups direct attacks to the *meta*- position. This is not a case of favoring the meta- position like para- and ortho- directing functional groups, but rather disfavouring the *ortho*- and *para*-positions more than they disfavour the *meta*- position.

The activating groups are mostly resonance donors (+M). Although many of these groups are also inductively withdrawing (–I), which is a deactivating effect, the resonance (or mesomeric) effect is almost always stronger, with the exception of Cl, Br, and I.

Magnitude of activation	**Substituent Name (in approximate order of activating strength)**	**Structure**	**Type of electronic effect**	**Directing effect**
Extreme	oxido group	-O^-	+I, +M	*ortho, para*
Strong	(substituted) amino groups	-NH_2, -NHR, -NR_2	–I, +M	
	hydroxy and alkoxy groups	-OH, -OR		
Moderate	acylamido groups	-NHCOR		
	acyloxy groups	-OCOR		
	(di)alkylphosphino, alkylthio, and sulfhydryl groups	-PR_2, -SR, -SH	+M (weak)	
Weak	phenyl (or aryl) group	-C_6H_5		

	vinyl group	-CH=CH$_2$	–I, +M; though other interactions may be involved as well	
	alkyl groups (e.g. -CH$_3$, -C$_2$H$_5$)	-R		
	carboxylate group	-CO$_2^-$	+I	
	fluoro group (*para* position)	-F	–I, +M	*para*

In general, the resonance effect of elements in the third period and beyond is relatively weak. This is mainly because of the relatively poor orbital overlap of the substituent's 3p (or higher) orbital with the 2p orbital of the carbon.

Due to a stronger resonance effect and inductive effect than the heavier halogens, fluorine is anomalous. The partial rate factor of electrophilic aromatic substitution on fluorobenzene is often larger than one at the *para* position, making it an activating group. Conversely, it is moderately deactivated at the *ortho* and *meta* positions, due to the proximity of these positions to the electronegative fluoro substituent.

Deactivating groups

While all deactivating groups are inductively withdrawing (–I), most of them are also withdrawing through resonance (–M) as well. Halogen substituents are an exception: they are resonance donors (+M). With the exception of the halides, they are *meta* directing groups.

Halides are *ortho*, *para* directing groups but unlike most *ortho*, *para* directors, halides mildly deactivate the arene. This unusual behavior can be explained by two properties:

1. Since the halogens are very electronegative they cause inductive withdrawal (withdrawal of electrons from the carbon atom of benzene).
2. Since the halogens have non-bonding electrons they can donate electron density through pi bonding (resonance donation).

The inductive and resonance properties compete with each other but the resonance effect dominates for purposes of directing the sites of reactivity. For nitration, for example, fluorine directs strongly to the *para* position because the *ortho* position is inductively deactivated (86% *para*, 13% *ortho*, 0.6% *meta*). On the other hand, iodine directs to *ortho* and *para* positions comparably (54% *para* and 45% *ortho*, 1.3% *meta*).

Fluorine is something of an anomaly in this circumstance. Above, it is described as a weak electron withdrawing group but this is only partly true. It is correct that fluorine has a -I effect, which results in electrons being withdrawn inductively. However, another effect that plays a role is the +M effect which adds electron density back into the benzene ring (thus having the opposite effect of the -I effect but by a different mechanism). This is called the mesomeric effect (hence +M) and the result for fluorine is that the +M effect approximately cancels out the -I effect. The effect of this for fluorobenzene at the *para* position is reactivity that is comparable to (or even higher than) that of benzene. Because inductive effects depends strongly on proximity, the *meta* and *ortho* positions of fluorobenzene are considerably less reactive than benzene.

Notice that iodobenzene is still less reactive than fluorobenzene because polarizability plays a role as well. This can also explain why phosphorus in phosphanes can't donate electron density to carbon through induction (i.e. +I effect) although it is less electronegative than carbon (2.19 vs 2.55, see electronegativity list) and why hydroiodic acid (pKa = -10) being much more acidic than hydrofluoric acid (pKa = 3). (That's 10^{13} times more acidic than hydrofluoric acid)

Objective:

This paper intends to explore and analyze aromatic compounds react by **electrophilic aromatic substitution reactions**, in which the aromaticity of the ring system is preserved. Also Many functional groups can be added via **nitration, aromatic halogenation** to aromatic compounds via electrophilic aromatic substitution reactions.

Electrophilic Aromatic Substitution Reactions

Both the regioselectivity—the diverse arene substitution patterns—and the speed of an electrophilic aromatic substitution are affected by the substituents already attached to the benzene ring. In terms of regioselectivity, some groups promote substitution at the ortho or para positions, whereas other groups favor substitution at the meta position. These groups are called either ortho–para directing or meta directing, respectively. In addition, some groups will increase the rate of reaction (activating) while others will decrease the rate (deactivating). While the patterns of regioselectivity can be explained with resonance structures, the influence on kinetics can be explained by both resonance structures and the inductive effect.

Reaction rate

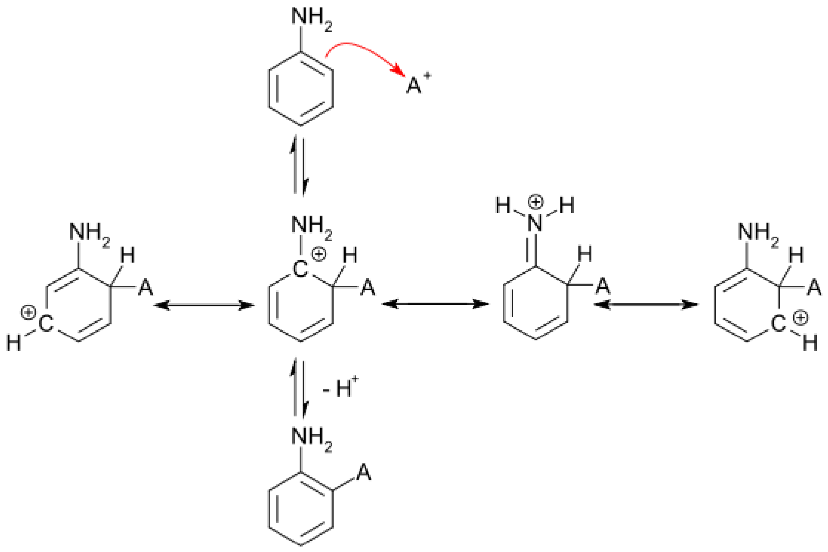
Substituents can generally be divided into two classes regarding electrophilic substitution: activating and deactivating towards the aromatic ring. Activating substituents or activating groups stabilize the cationic intermediate formed during the substitution by donating electrons into the ring system, by either inductive effect or resonance effects. Examples of activated aromatic rings are toluene, aniline and phenol.

The extra electron density delivered into the ring by the substituent is not distributed evenly over the entire ring but is concentrated on atoms 2, 4 and 6, so activating substituents are also ortho/para directors (see below).

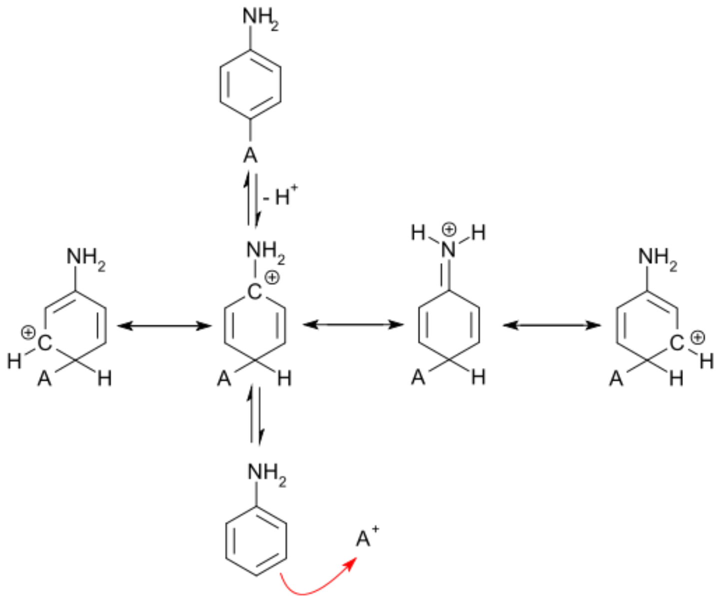
On the other hand, deactivating substituents destabilize the intermediate cation and thus decrease the reaction rate by either inductive or resonance effects. They do so by withdrawing electron density from the aromatic ring. The deactivation of the aromatic system means that generally harsher conditions are required to drive the reaction to completion. An example of this is the nitration of toluene during the production of trinitrotoluene (TNT). While the first nitration, on the activated toluene ring, can be done at room temperature and with dilute acid, the second one, on the deactivated nitrotoluene ring, already needs prolonged heating and more concentrated acid, and the third one, on very strongly deactivated dinitrotoluene, has to be done in boiling concentrated sulfuric acid. Groups that are electron-withdrawing by resonance decrease the electron density especially at positions 2, 4 and 6, leaving positions 3 and 5 as the ones with comparably higher reactivity, so these types of groups are meta directors (see below). Halogens are electronegative, so they are deactivating by induction, but they have lone pairs, so they are resonance donors and therefore ortho/para directors.

Ortho/para directors

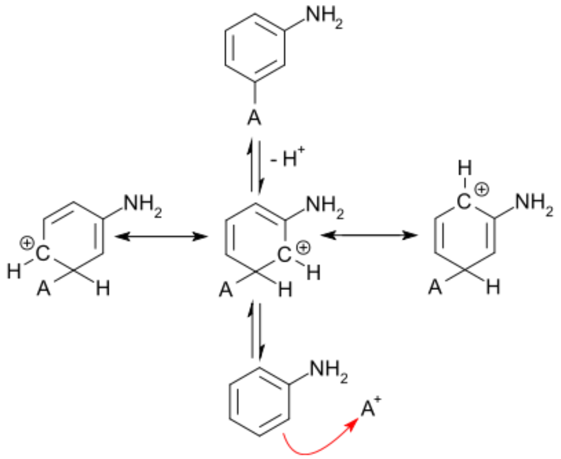
Groups with unshared pairs of electrons, such as the amino group of aniline, are strongly activating and ortho/para-directing by resonance. Such activating groups donate those unshared electrons to the pi system, creating a negative charge on the ortho and para positions. These positions are thus the most reactive towards an electron-poor electrophile. The highest electron density is located on both ortho and para positions, although this increased reactivity might be offset by steric hindrance between substituent and electrophile. The final result of the electrophilic aromatic substitution might thus be hard to predict, and it is usually only established by doing the reaction and determining the ratio of ortho versus para substitution.



In addition to the increased nucleophilic nature of the original ring, when the electrophile attacks the ortho and para positions of aniline, the nitrogen atom can donate electron density to the pi system (forming an iminium ion), giving four resonance structures (as opposed to three in the basic reaction). This substantially enhances the stability of the cationic intermediate.



When the electrophile attacks the meta position, the nitrogen atom cannot donate electron density to the pi system, giving only three resonance contributors. This reasoning is consistent with low yields of meta-substituted product.



Other substituents, such as the alkyl and aryl substituents, may also donate electron density to the pi system; however, since they lack an available unshared pair of electrons, their ability to do this is rather limited. Thus, they only weakly activate the ring and do not strongly disfavor the meta position. Directed ortho metalation is a special type of EAS with special ortho directors.

Non-halogen groups with atoms that are more electronegative than carbon, such as a carboxylic acid group (-CO2H), withdraw substantial electron density from the pi system. These groups are strongly deactivating groups. Additionally, since the substituted carbon is already electron-poor, any structure having a resonance contributor in which there is a positive charge on the carbon bearing the electron-withdrawing group (i.e., ortho or para attack) is less stable than the others. Therefore, these electron-withdrawing groups are meta directing because this is the position that does not have as much destabilization.

The reaction is also much slower (a relative reaction rate of 6×10^{-8} compared to benzene) because the ring is less nucleophilic.

Reaction on pyridine

Compared to benzene, the rate of electrophilic substitution on pyridine is much slower, due to the higher electronegativity of the nitrogen atom. Additionally, the nitrogen in pyridine easily gets a positive charge either by protonation (from nitration or sulfonation) or Lewis acids (such as AlCl3) used to catalyze the reaction. This makes the reaction even slower by having adjacent formal charges on carbon and nitrogen or 2 formal charges on a localised atom. Doing an electrophilic substitution directly in pyridine is nearly impossible.

In order to do the reaction, they can be made by 2 possible reactions, which are both indirect.

One possible way to do a substitution on pyridine is nucleophilic aromatic substitution. Even with no catalysts, the nitrogen atom, being electronegative, can hold the negative charge by itself. Another way is to do an oxidation before the electrophilic substitution. This makes pyridine N-oxide, which due to the negative oxygen atom, makes the reaction faster than pyridine, and even benzene. The oxide then can be reduced to the substituted pyridine.

Ipso attack

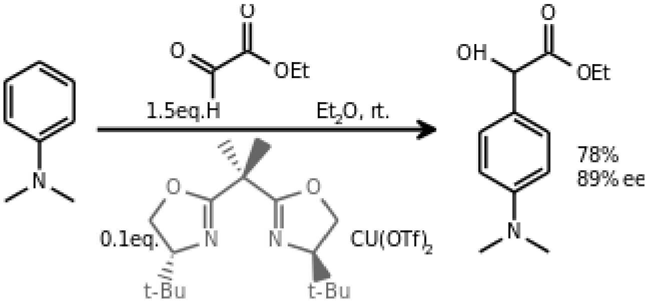
The attachment of an entering group to a position in an aromatic compound already carrying a substituent group (other than hydrogen). The entering group may displace that substituent group but may also itself be expelled or migrate to another position in a subsequent step. The term 'ipso-substitution' is not used, since it is synonymous with substitution. A classic example is the reaction of salicylic acid with a mixture of nitric and sulfuric acid to form picric acid. The nitration of the 2 position involves the loss of CO2 as the leaving group. Desulfonation in which a sulfonyl group is substituted by a proton is a common example. See also Hayashi rearrangement. In aromatics substituted by silicon, the silicon reacts by ipso substitution.

Five membered heterocycles

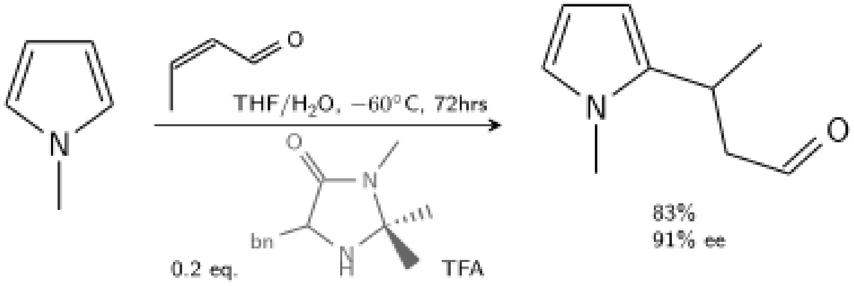
Compared to benzene, furans, thiophenes, and pyrroles are more susceptible to electrophilic attack. These compounds all contain an atom with an unshared pair of electrons (oxygen, sulfur, or nitrogen) as a member of the aromatic ring, which substantially stabilizes the cationic intermediate. Examples of electrophilic substitutions to pyrrole are the Pictet–Spengler reaction and the Bischler–Napieralski reaction.

Asymmetric electrophilic aromatic substitution

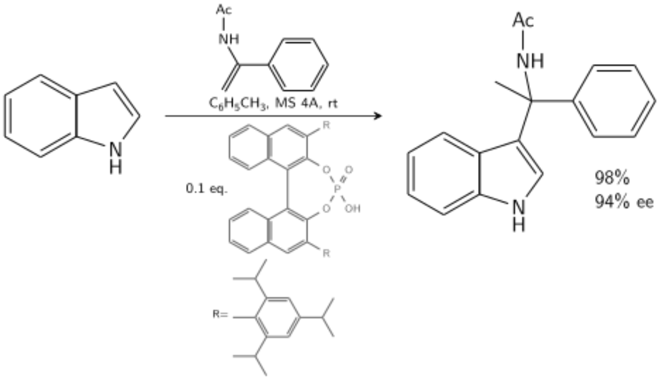
Electrophilic aromatic substitutions with prochiral carbon electrophiles have been adapted for asymmetric synthesis by switching to chiral Lewis acid catalysts especially in Friedel–Crafts type reactions. An early example concerns the addition of chloral to phenols catalyzed by aluminium chloride modified with (–)-menthol. A glyoxylate compound has been added to N,N-dimethylaniline with a chiral bisoxazoline ligand–copper(II) triflate catalyst system also in a Friedel–Crafts hydroxyalkylation:



In another alkylation N-methylpyrrole reacts with crotonaldehyde catalyzed by trifluoroacetic acid modified with a chiral imidazolidinone:



Indole reacts with an enamide catalyzed by a chiral BINOL derived phosphoric acid:



In the presence of 10–20 % chiral catalyst, 80–90% ee is achievable.

Conclusion

Electron donating groups are generally ortho/para directors for electrophilic aromatic substitutions, while electron withdrawing groups are generally meta directors with the exception of the halogens which are also *ortho*/*para* directors as they have lone pairs of electrons that are shared with the aromatic ring. Electron donating groups are typically divided into three levels of activating ability (The "extreme" category can be seen as "strong".) Electron withdrawing groups are assigned to similar groupings. Activating substituents favour electrophilic substitution about the *ortho* and *para* positions. Thus, electrophilic aromatic substitution on fluorobenzene is strongly *para* selective.

This -I and +M effect is true for all halides - there is some electron withdrawing and donating character of each. To understand why the reactivity changes occur, we need to consider the orbital overlaps occurring in each.

The valence orbitals of fluorine are the 2p orbitals which is the same for carbon - hence they will be very close in energy and orbital overlap will be favourable. Chlorine has 3p valence orbitals, hence the orbital energies will be further apart and the geometry less favourable, leading to less donation the stabilize the carbocationic intermediate, hence chlorobenzene is less reactive than fluorobenzene. However, bromobenzene and iodobenzene are about the same or a little more reactive than chlorobenzene, because although the resonance donation is even worse, the inductive effect is also weakened due to their lower electronegativities. Thus the overall order of reactivity is U-shaped, with a minimum at chlorobenzene/bromobenzene (relative nitration rates compared to benzene = 1 in parentheses): PhF (0.18) > PhCl (0.064) ~ PhBr (0.060) < PhI (0.12). But still, all halobenzenes reacts slower than benzene itself.

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