Chapter 13: Nucleophilic Aromatic and Electrophilic Aromatic Substitution

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Contents

Introduction

Due to the stability of aromatic systems, it is not easy to conduct reactions with them that would break that aromaticity. We can, however, conduct reactions that *break and restore* aromaticity. Of these reactions, **substitution reactions** are the most prevalent.

Electrophilic Aromatic Substitution (EAS)

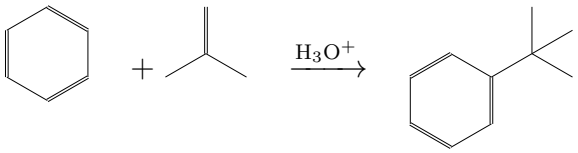
In this substitution reaction, the aromatic system acts as a **nucleophile** and attacks an **electrophilic species**.

General Two-Step Mechanism

1. **Attack (slow, rate-determining):** The π-electrons of the ring attack E^+, breaking aromaticity and forming the **arenium ion** (a cyclohexadienyl carbocation, also called the σ-complex).
2. **Deprotonation (fast):** A base removes the acidic proton from the sp^3 carbon, restoring the aromatic π-system.

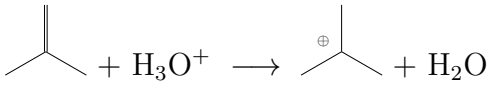
Example: Alkylation of Benzene under Acid Catalysis

Consider the reaction of benzene with an alkene in the presence of H_3O^+:



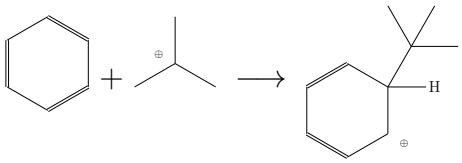
Step 1 – Generation of the carbocation electrophile.

The acid protonates the alkene double bond, producing a strongly electrophilic carbocation:



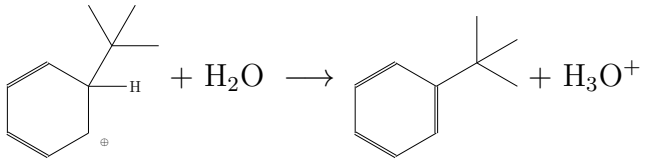
Step 2 – Benzene attacks the carbocation.

Benzene's π-electrons attack  forming the **arenium ion**:



Step 3 – Restoration of aromaticity.

The acidic proton on the arenium ion departs (it is a good leaving group), restoring aromaticity:

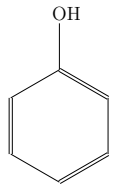


Rate of EAS: Activating and Deactivating Substituents

EAS reactions are **slow** because of the high-energy **arenium ion** intermediate. Substituents already on the ring can accelerate or retard the reaction.

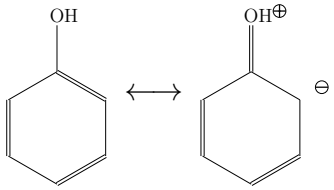
Phenol as an Activated Substrate

Consider **phenol**:



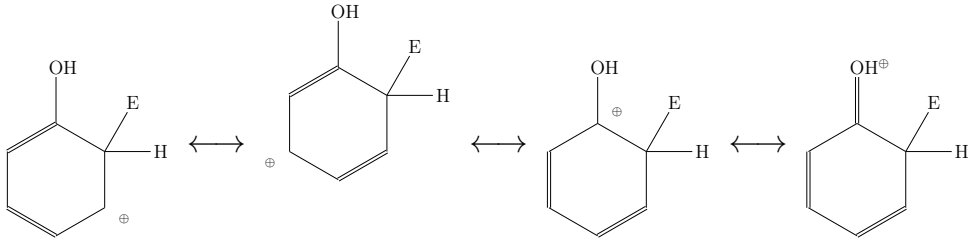
The oxygen in phenol serves **two purposes**:

1. **Increased nucleophilicity of the ring.** The lone pair on O donates into the aromatic π-system, raising the ring's electron density:

   This makes phenol a *much better* nucleophile than plain benzene.

2. **Stabilisation of the arenium ion.** After E^+ attacks, the resonance structures of the arenium ion include a contributor in which the positive charge sits **on oxygen**, greatly stabilising the intermediate:

Key point: The oxygen-stabilised resonance structure only appears when E^+ attacks at the **ortho** or **para** position, making $-$OH an **ortho/para-director**.

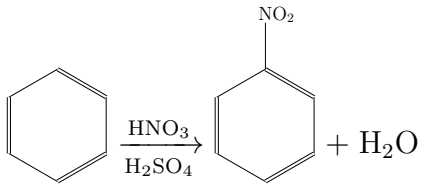
Regioselectivity of EAS

Group type	Direction	Effect on rate
$-$OH, $-$OR, $-NH_2$	Ortho / Para	Strongly activating
Alkyl ($-$R)	Ortho / Para	Weakly activating
Halogens ($-$F, $-$Cl, $-$Br)	Ortho / Para	Weakly deactivating
$-$CN, $-$COOH	Meta	Moderately deactivating
$-NO_2$, $-SO_3H$	Meta	Strongly deactivating

Common EAS Reactions

1. Nitration

Reagents: Concentrated HNO_3 + concentrated H_2SO_4.



Generation of the nitronium ion (NO_2^+):

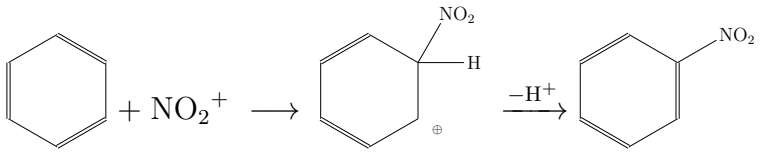
$$H_2SO_4 + HNO_3 \longrightarrow HSO_4^- + H_2NO_3^+ \quad (1)$$
$$H_2NO_3^+ \longrightarrow H_2O + NO_2^+ \quad (2)$$

Equivalently, using the proton-transfer picture:

$$HOSO_3H + HO{-}NO_2 \longrightarrow HOSO_3^- + [H_2O{-}NO_2]^+ \longrightarrow H_2O + {}^+NO_2$$

Mechanism:

1. NO_2^+ (the nitronium ion) is the electrophile.
2. Benzene attacks NO_2^+ via its π-electrons $\Rightarrow$ arenium ion.
3. HSO_4^- abstracts the acidic proton $\Rightarrow$ aromaticity restored, H_2SO_4 regenerated (catalytic role).



2. Sulfonation of Benzene

Reagents and Conditions

Benzene is treated with fuming sulfuric acid (oleum), which consists of sulfuric acid with dissolved sulfur trioxide (SO_3). Concentrated H_2SO_4 alone can be used, but the reaction is slow; excess SO_3 drives it efficiently. The reaction is reversible and proceeds at room temperature or with mild warming.

Step 1 — Generation of the Electrophile

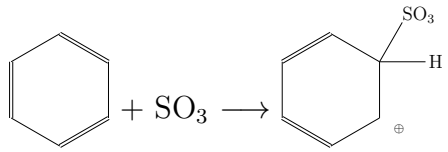
The active electrophile is sulfur trioxide itself. In oleum it is present directly. In concentrated H_2SO_4 it is generated by the equilibrium:

$$2\,H_2SO_4 \rightleftharpoons SO_3 + H_3O^+ + HSO_4^-$$

SO_3 is a powerful electrophile because sulfur bears a large partial positive charge: the three electronegative oxygen atoms withdraw electron density through both induction and resonance, leaving sulfur strongly electrophilic (δ^+).

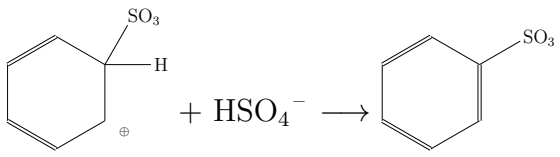
Step 2 — Electrophilic Attack on the π System

The electron-rich π system of benzene acts as a nucleophile and attacks the electrophilic sulfur of SO_3. One of the six π electrons forms a new σ bond to sulfur. This breaks the aromaticity of the ring and produces the **arenium ion**



Step 3 — Restoration of Aromaticity (Proton Transfer)

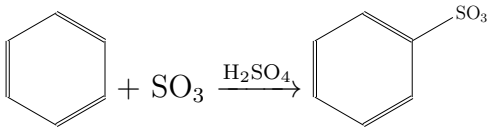
A base — HSO_4^- or H_2SO_4 acting as a proton acceptor — abstracts the proton from the sp^3 carbon of the arenium ion. The two electrons that had formed the C–H bond are returned to the ring, restoring the aromatic π system. The product at this stage is **benzenesulfonic acid** ($C_6H_5SO_3H$).



Overall Equation

$$C_6H_6 + SO_3 \longrightarrow C_6H_5SO_3H$$

One hydrogen of benzene is formally replaced by the sulfonic acid group ($-SO_3H$), and no other by-product is produced beyond the conjugate acid of whichever base accepted the proton in Step 3.



Reversibility

Sulfonation is unusual among electrophilic aromatic substitutions in being readily reversible. Heating benzenesulfonic acid with dilute aqueous H_2SO_4 or steam causes desulfonation: the $-SO_3H$ group is replaced by a proton, regenerating benzene and SO_3 (or H_2SO_4). This reversibility is synthetically useful: the sulfonic acid group can be installed to block a ring position during a subsequent substitution, then removed.

Regioselectivity on Substituted Benzenes

When the ring already bears a substituent, the sulfonic acid group is directed to the ortho and para positions by electron-donating groups (which activate those positions toward electrophilic attack) and to the meta position by electron-withdrawing groups (which deactivate ortho and para more than meta). The directing effect follows the same principles as for all electrophilic aromatic substitutions and arises from the relative stability of the three possible arenium ion intermediates.

3. Halogenation

Reagents and Conditions

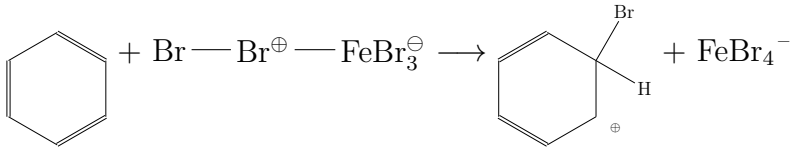
While halogens like bromine react readily with alkenes, their reactions with aromatic systems like benzene are really slow and, as such, need a catalyst to make the reaction feasible. The catalyst we use for bromination is ferric bromide, $FeBr_3$. $FeBr_3$ reacts with Br_2 to form a Lewis acid/Lewis base complex that looks like this.

$$Br - Br^{\oplus} - FeBr_3^{\ominus}$$

The bromine atom connected to the bromonium ion is attacked by the benzene ring to form the arenium ion and $FeBr_4^-$. To regenerate the aromatic system, the bromine atom that was the bromonium ion attacks the acidic hydrogen on the sp^3 carbon and breaks off from $FeBr_4^-$ to form $FeBr_3$ and HBr.

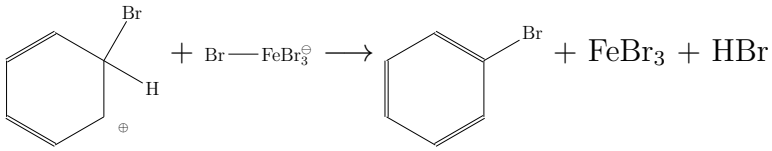
Step 1: Electrophilic Attack on the π-System

The π-electrons of the benzene ring attack the $Br—Br^{\oplus}—FeBr_3^{\ominus}$ complex.



Step 2: Aromatic Regeneration

The $FeBr_4^-$ complex attacks the acidic hydrogen to restore aromaticity and decomposes into hydrobromic acid and ferric bromide.



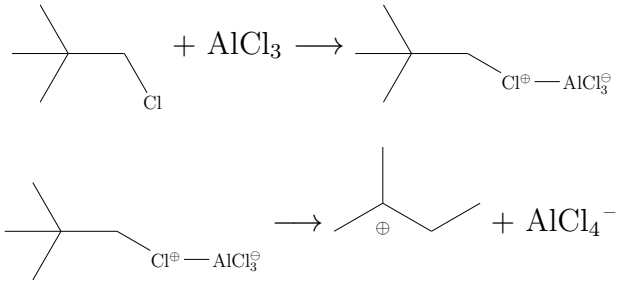
4. Friedel-Crafts Alkylation

Reagents and Conditions:

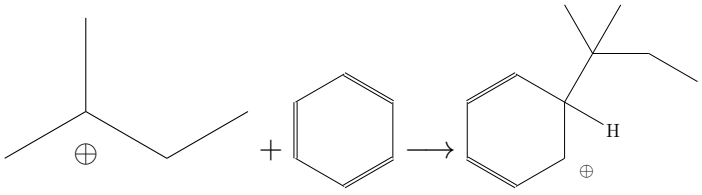
While normal alkanes are not electrophilic enough to be attacked by the π-system of a benzene ring, 2° and 3° alkyl halides can be converted into very highly electrophilic carbocations with the action of $AlCl_3$ as a catalyst. The mechanism of catalysis here is practically identical to the mechanism of catalysis in halogenation: the halogen in the alkyl halide bonds to $AlCl_3$ to form a Lewis Acid/Lewis Base complex which then dissociates to give $XAlCl_3^-$ and the 2° or 3° carbocation which then gets attacked by the π-system of the benzene ring to form the arenium ion. This then gets attacked by the X in $XAlCl_3^-$ to form HX and $AlCl_3$.

Step 1: Electrophile Generation

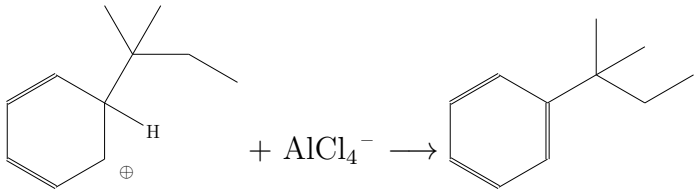
Let's take the example of isobutyl chloride.



Step 2: Electrophilic Attack on the π-System

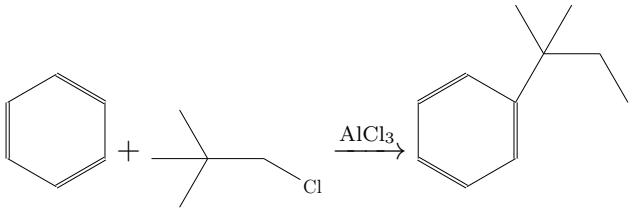


Step 3: Aromatic Regeneration



Overall Equation

$$C_6H_6 + C_5H_{11}Cl \xrightarrow{AlCl_3} C_{11}H_{15}$$



EAS on Heteroaromatic Rings

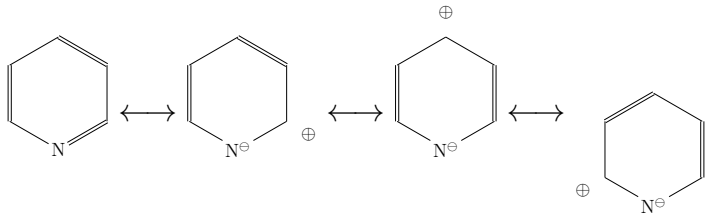
Heteroaromatic rings such as pyridine and furan undergo EAS, but their reactivity and regioselectivity differ significantly from benzene due to the electronic influence of the heteroatom.

EAS on Pyridine

Pyridine is a **strongly deactivated** aromatic system toward EAS. The ring nitrogen is **electron-withdrawing** by induction and resonance, pulling electron density away from the ring in a manner analogous to a nitro group on benzene. As a result, EAS on pyridine is extremely slow and requires very harsh conditions.

Electronic Character

The nitrogen lone pair in pyridine lies in the plane of the ring in an sp^2 orbital perpendicular to the π-system; it is *not* delocalised into the ring. The nitrogen therefore acts as a π-acceptor, withdrawing electron density through resonance and leaving the ring electron-poor:



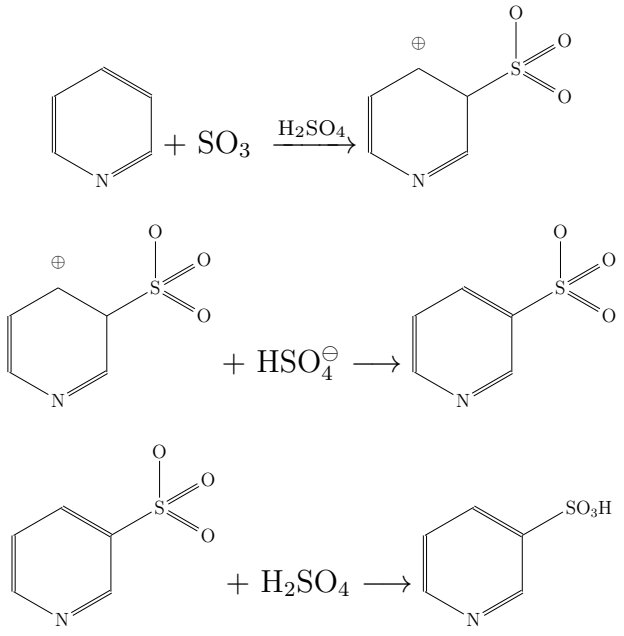
Regioselectivity

Because N withdraws electrons most strongly from the ortho (C-2, C-6) and para (C-4) positions, those positions are the most electron-poor. EAS therefore proceeds preferentially at the **meta** position (C-3) — directly analogous to a meta-directing electron-withdrawing group on benzene.

Practical Considerations

- Nitration and sulfonation of pyridine require very concentrated reagents at elevated temperatures and even then give low yields.
- Friedel-Crafts reactions fail entirely on pyridine because the Lewis acid catalyst ($AlCl_3$, $FeBr_3$, etc.) coordinates to the nitrogen lone pair, forming a stable adduct that prevents the catalyst from activating the electrophile.
- Halogenation proceeds under forcing conditions (neat halogen, high temperature) and gives predominantly the 3-halopyridine.

Example: Sulfonation of Pyridine

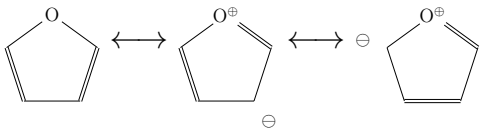


EAS on Furan

In contrast to pyridine, furan is **strongly activated** toward EAS. The oxygen heteroatom donates electron density into the π-system via resonance (its lone pair participates in the aromatic sextet), making furan considerably more reactive than benzene.

Electronic Character

Oxygen in furan contributes two electrons to the aromatic π-system. This donation enriches the ring with electron density and makes it a much better nucleophile:



Regioselectivity

The electron density from oxygen is donated preferentially to the **2- and 5-positions** (positions adjacent to oxygen), making those positions the most nucleophilic. EAS on furan therefore occurs at **C-2** (and the equivalent C-4) as the strongly preferred site.

Nucleophilic Aromatic Substitution (NAS)

In EAS, we saw the aromatic system act as a nucleophile. Here, it acts as an **electrophile**. Another key difference is that H is no longer a good leaving group: since the aromatic system is being attacked, it has excess electrons that have to leave the system. If H were to take those electrons, it would result in a hydride ion (H^-), which is extremely unstable.

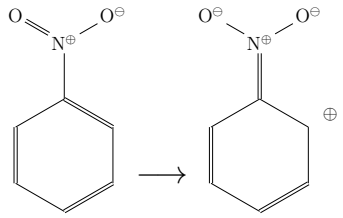
In NAS, there are two kinds of substitution:

- Addition–Elimination (A–E)
- Elimination–Addition (E–A)

Addition–Elimination (A–E)

Let's take on A–E first. This requires a halogen as your leaving group and an activator on the ortho or para positions. However, the activators of EAS like OH or OR or NH_2 make the system more nucleophilic, so they are strong deactivators in NAS. The deactivators in EAS become activators in NAS. Let's take NO_2 as an example. This is a strong deactivator in EAS for the same reason it is a strong activator in NAS.

The two oxygen atoms are electronegative and so pull electrons away from the system. The nitro group also acts as a π-acceptor through this resonance structure, pulling more electrons away:



This resonance structure is also why NO_2 is a meta director in EAS and an ortho/para director in NAS.

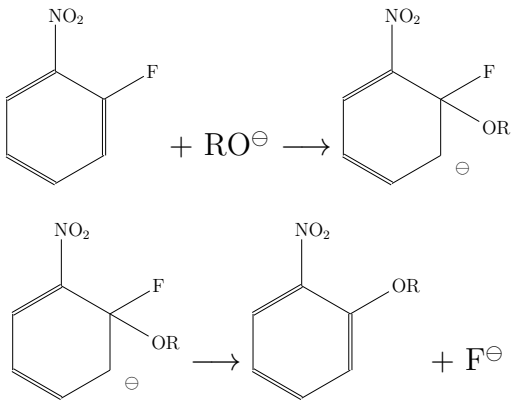
Rate of A–E with Halogens as the Leaving Group

The rate of reaction of A–E with halogens as the leaving group is as follows:

$$I < Br < Cl < F$$

The reason for this is that F is the most electronegative, so it makes the nucleophilic attack even easier.

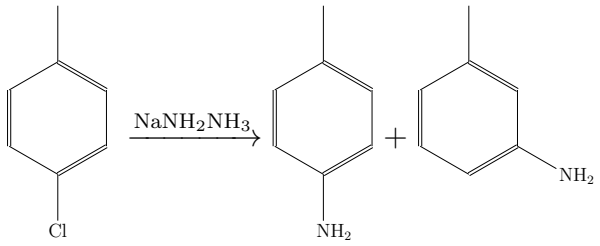
Worked Example: Nucleophilic Substitution with RO^-



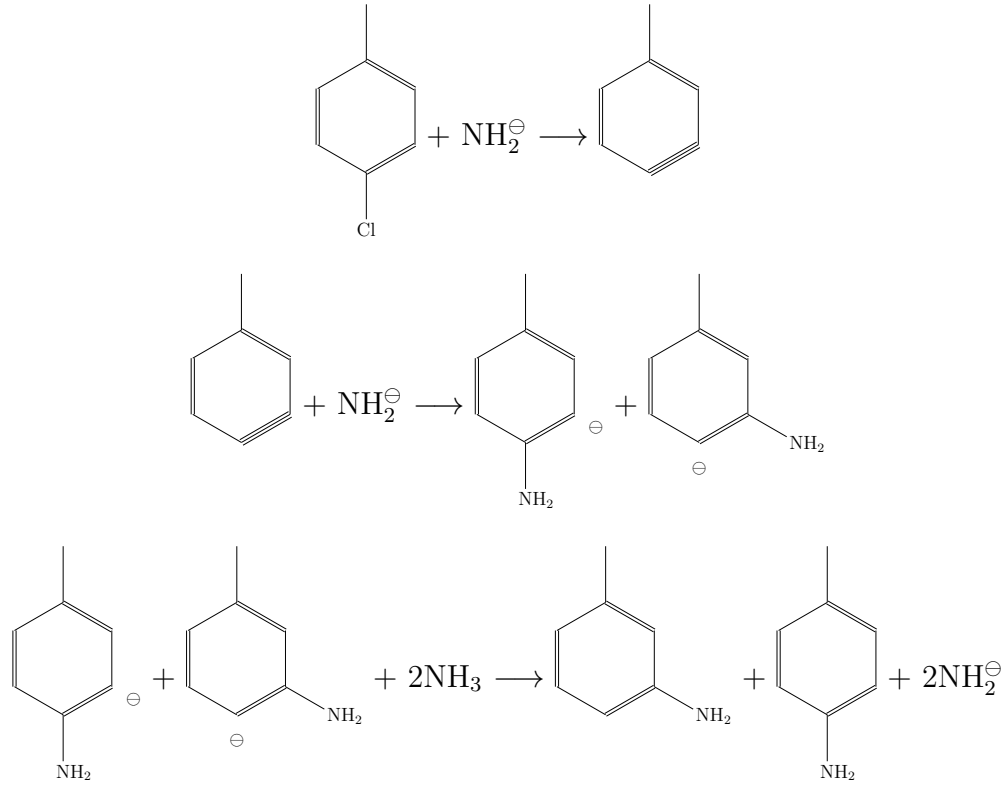
This mechanism applies to A–E reactions.

Elimination–Addition (E–A)

Now let's have a look at E–A reactions. These reactions only happen with nucleophiles at least as basic as $NH_2{}^-$ and require a halogen as a leaving group. They do not require strong activators like A–E does and can even be done with weakly deactivating alkyl groups. Let's take the example of para-chlorotoluene.



Why did we get two products? Let's look at the mechanism.



NAS on Pyridine

Pyridine is an excellent substrate for NAS via the A–E pathway because the ring nitrogen is strongly electron-withdrawing, activating the ring toward nucleophilic attack in the same way that NO_2 does on benzene. Crucially, the nitrogen activates the **2- and 4-positions** (ortho and para to N) most strongly, making those the preferred sites for nucleophilic attack.

Why Pyridine is Activated Toward NAS

The nitrogen lone pair pulls π-electron density away from C-2 and C-4 via resonance as seen above in the pyridine section in EAS. When a nucleophile attacks one of these positions, the resulting anionic intermediate (analogous to the Meisenheimer complex in benzene NAS) is particularly well stabilised because the negative charge can be delocalised directly onto the electronegative nitrogen:

Halopyridines and NAS

Halogen substituents on the ring further facilitate NAS when located at the 2- or 4-position (where the nitrogen already activates the ring). The combination of ring nitrogen and a halogen leaving group at C-2 or C-4 makes these substrates highly reactive toward even moderate nucleophiles: