Nucleophilic Aromatic Substitution

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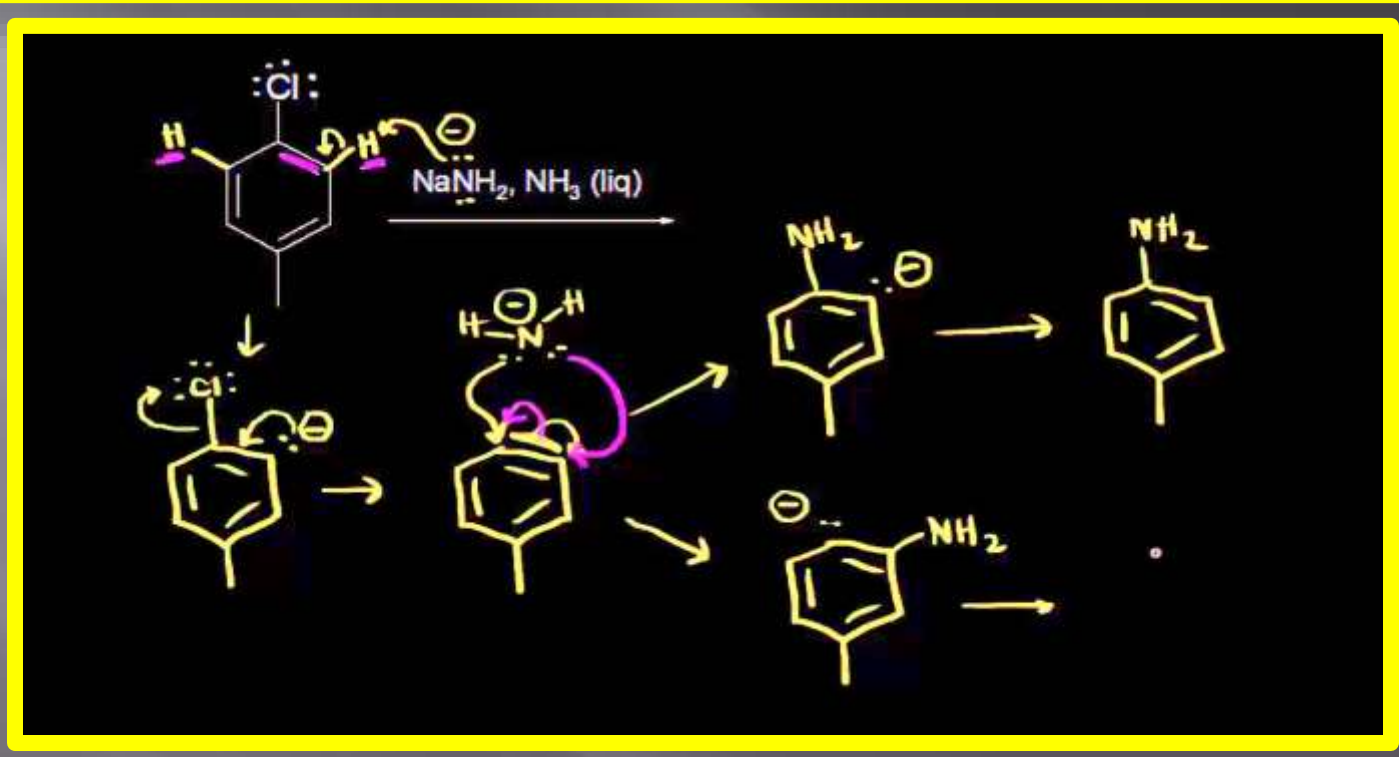


NUCLEOPHILIC AROMATIC SUBSTITUTION (NAS)

Here is a summary of NAS reactions

What are NAS Reactions?

How does it differ from EAS?

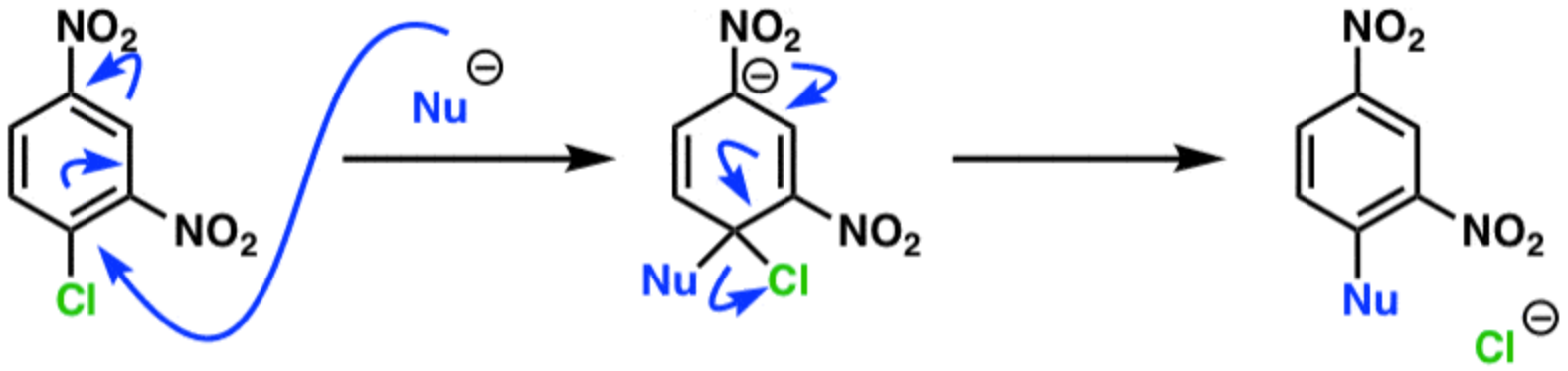
Why does it tend to work best with electron-poor aromatics and excellent nucleophiles?

Finally, how does it work?

In this presentation we will try to give answer to all of these important questions.!

Summary: Nucleophilic Aromatic Substitution

In this reaction, a nucleophile (Nu$^{\ominus}$) attacks an electron-poor aromatic molecule, resulting in the substitution of a leaving group:



The rate-determining step is attack of the aromatic ring by the nucleophile, which disrupts aromaticity.

Electron-withdrawing groups on the aromatic ring help to stabilize the negative charge of the intermediate.

Because loss of the leaving group is not the rate-determining step, fluorine is often used as a leaving group due to its high electronegativity

Let's review electrophilic aromatic substitution (EAS). What have we learned?

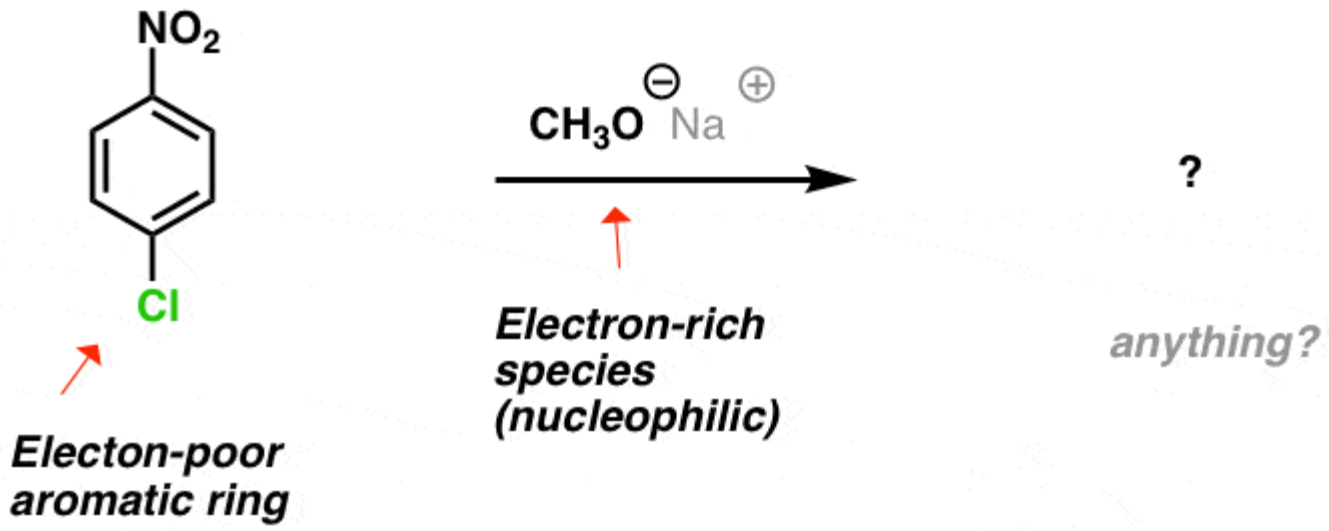
The **aromatic ring acts as a nucleophile**, and attacks an added electrophile E^+

An **electron-deficient carbocation intermediate is formed** (the rate-determining step) which is then deprotonated to restore aromaticity.

Electron-donating groups on the aromatic ring (such as OH, OCH_3, and alkyl) **make the reaction faster**, since they help to stabilize the electron-poor carbocation intermediate.

Lewis acids can make electrophiles even more electron-poor (reactive), increasing the reaction rate. For example $FeBr_3$ / Br_2 allows bromination to occur at a useful rate on benzene, whereas Br_2 by itself is slow).

How likely is this "electrophilic aromatic substitution" reaction?



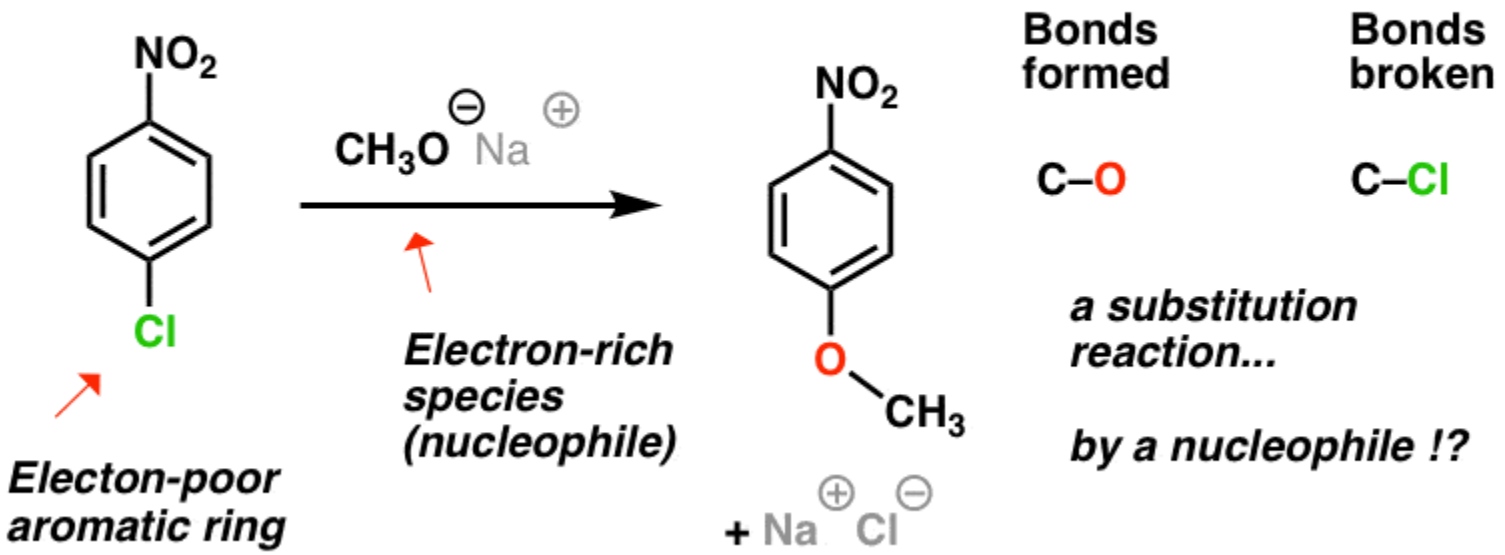
The aromatic ring is electron-poor and we are adding a nucleophile (electron rich). What could happen here?

Nothing, right?

Nucleophilic Aromatic Substitution

A substitution reaction may take place which **is not an electrophilic aromatic substitution reaction.** In this substitution reaction the C-Cl bond breaks, and a C-O bond forms on the same carbon.

Would you believe..



This substitution reaction has a few important differences:

- The species that attacks the ring is a nucleophile, not an electrophile.
- The aromatic ring is electron-poor (electrophilic), not electron rich (nucleophilic).
- The "leaving group" is chlorine, not H^+.
- The position where the nucleophile attacks is determined by where the leaving group is, not by electronic and steric factors (*i.e.* no mix of *ortho*– and *para*- products as with electrophilic aromatic substitution).

In short, **the roles of the aromatic ring and attacking species are reversed!** The attacking species (CH_3O^-) is the nucleophile, and the ring is the electrophile.

Since the nucleophile is the attacking species, this type of reaction has come to be known as **nucleophilic aromatic substitution.**

The Effect of Substituent's on the Ring

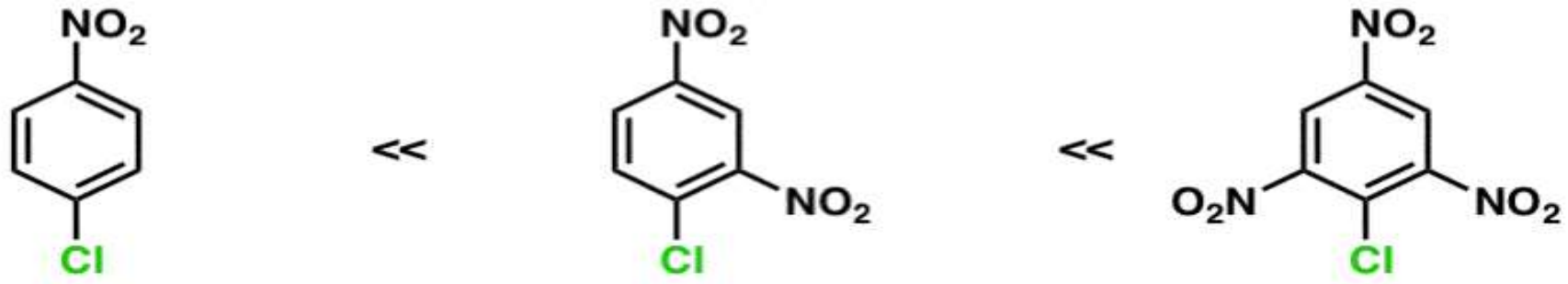
In nucleophilic aromatic substitution (NAS), all the trends you learned in electrophilic aromatic substitution operate, but *in reverse*. **Electron withdrawing groups (EWG's) increase** the rate of reaction, not decrease it. From this, it follows that the more EWG's there are, the faster the reaction.

For example, the rate of NAS for 2,4-dinitrophenyl chloride is about 10^5 times faster than for *p*-nitrophenyl chloride

Electron-Withdrawing Groups in Nucleophilic Aromatic Substitution:

one EWG	two EWGs	*three EWGs*
slowest	**faster**	**fastest**

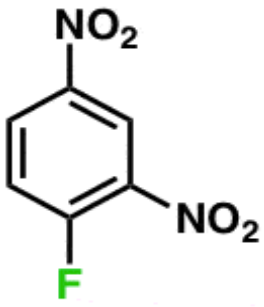
(by a factor of about 10^5)



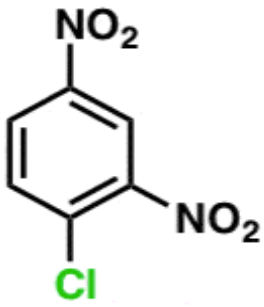
The Effect Of The Leaving Group

One of the most eye-opening aspects of nucleophilic aromatic substitution is noting that **fluorine is often used as a leaving group.** For one reaction studied, F as the leaving group was observed to be 3300 times faster than iodine. And between chlorine, bromine, and iodine, the difference was only by a factor of about 3.

Fluorine is actually a better leaving group than Cl, Br, and I



3300



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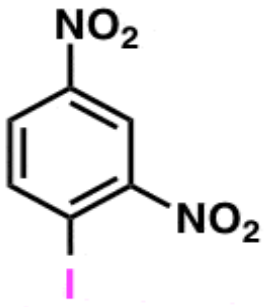
4.3



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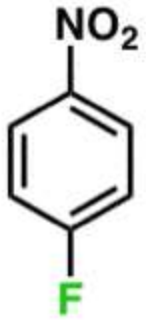
suggests that C–F bond cleavage is not involved in the rate-determining step!

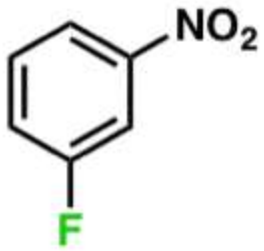
The Effect Of Substitution Pattern

There are no "*ortho*-,*para*-" or "*meta*-" directors. The position of substitution is controlled by the placement of the leaving group. The rate of the reaction is affected by the relative position of the leaving group and the electron-withdrawing group.

e.g., NAS of *p*-fluoronitrobenzene is faster than *m*-flouronitro-benzene, even though the NO_2 is closer to the leaving group and should presumably exert more of an inductive effect. The *ortho* isomer is also faster than the *meta* by a large margin.



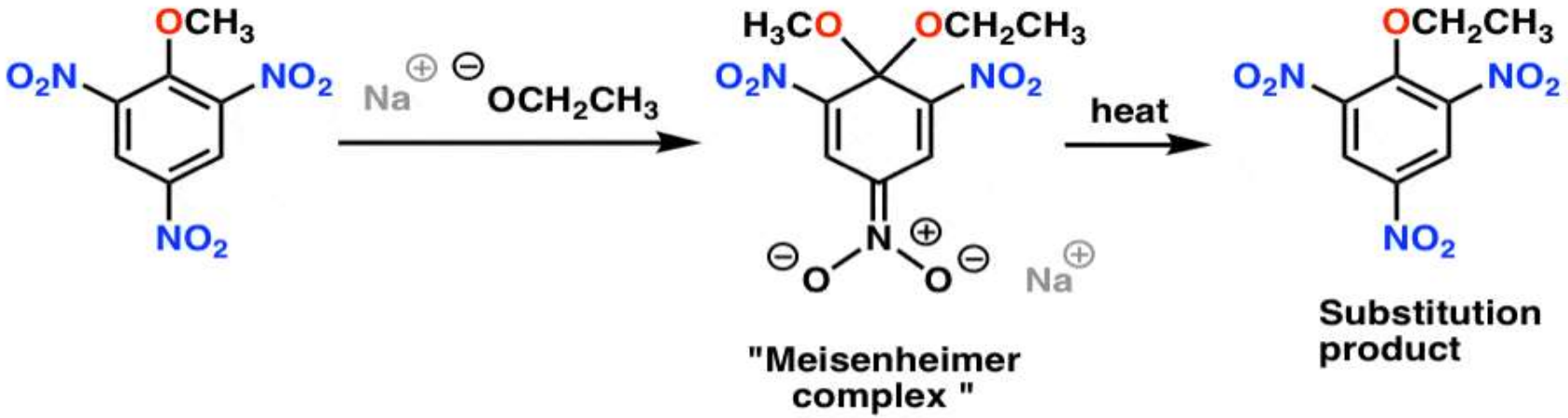
p-fluoronitrobenzene



m-fluoronitrobenzene

The “Meisenheimer” Intermediate.

It provides a clue to the Mechanism of **NAS.** During the addition nucleophiles to various electron-poor aromatic molecules with a leaving group, intermediates have been isolated. One of the first was isolated in 1902 by Jacob Meisenheimer, and the general name “**Meisenheimer complex**” is given to these intermediates. The intermediate is the (non-aromatic) addition product between the aromatic ring and the nucleophile. In the case below, the negative charge is delocalized to an oxygen on one of the nitro groups:



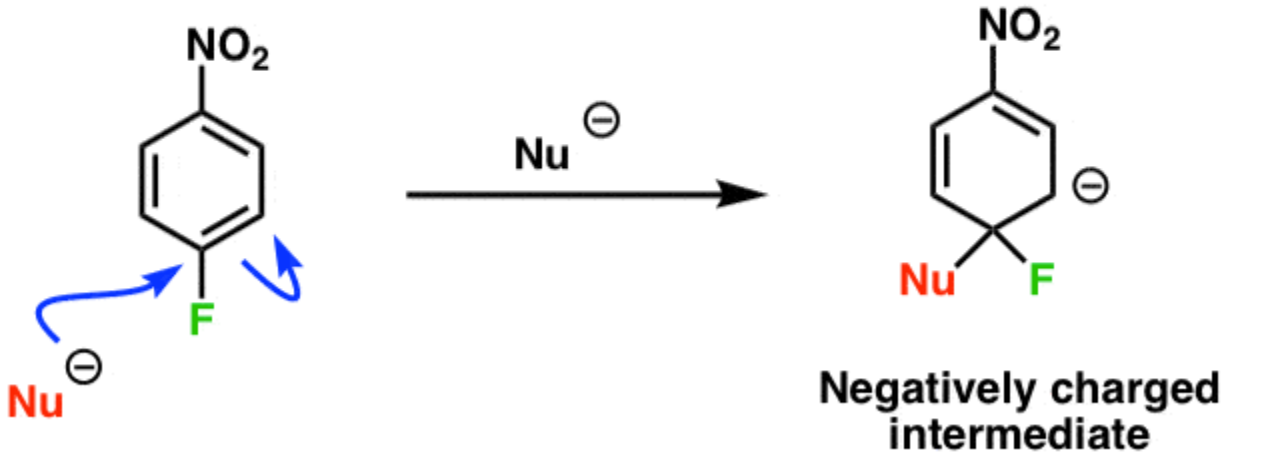
The Mechanism of NAS

The first step is **attack of the nucleophile on the electron-poor ring to generate a negatively charged intermediate** (*e.g.* the "Meisenheimer" intermediate)

Since this disrupts the aromaticity of the ring, it's also the rate-limiting step:

Nucleophilic Aromatic Substitution

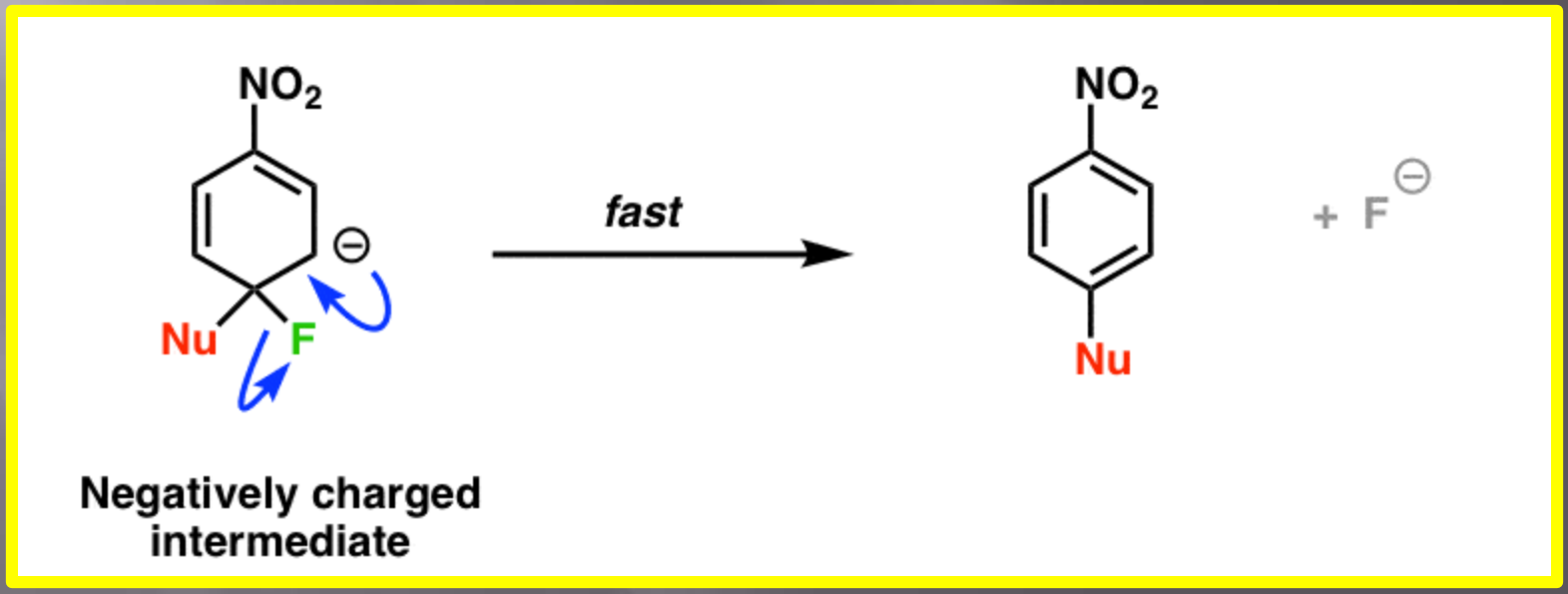
First step: Attack of electron-poor aromatic ring by nucleophile, forming a negatively charged intermediate:



In electrophilic aromatic substitution **(EAS)** we saw that electron-rich substituents stabilized the **electron-poor intermediate**.

But in nucleophilic aromatic substitution **(NAS)** the **intermediate is electron-rich**, and is stabilized by electron-withdrawing substituents, such as NO_2.

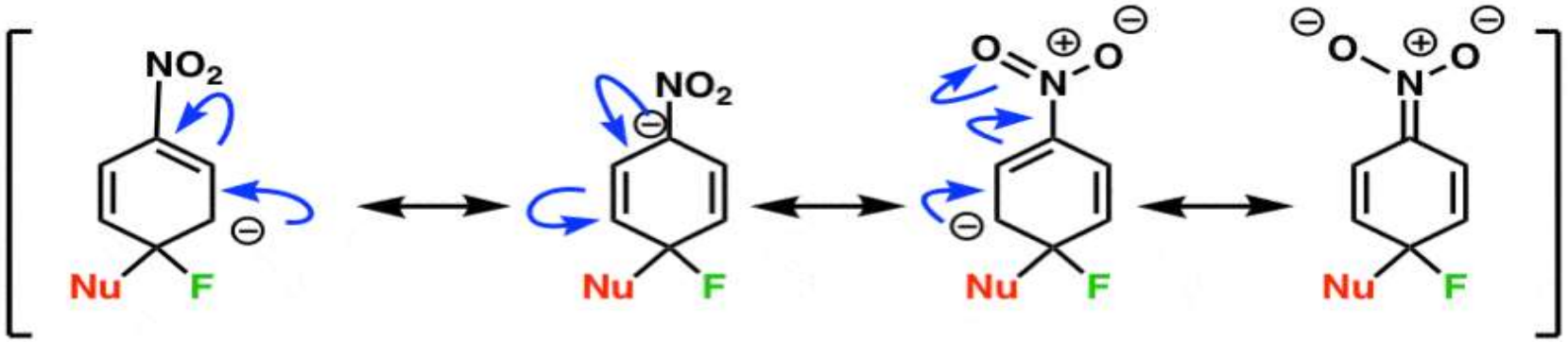
The second step in nucleophilic aromatic substitution is expulsion of the leaving group:



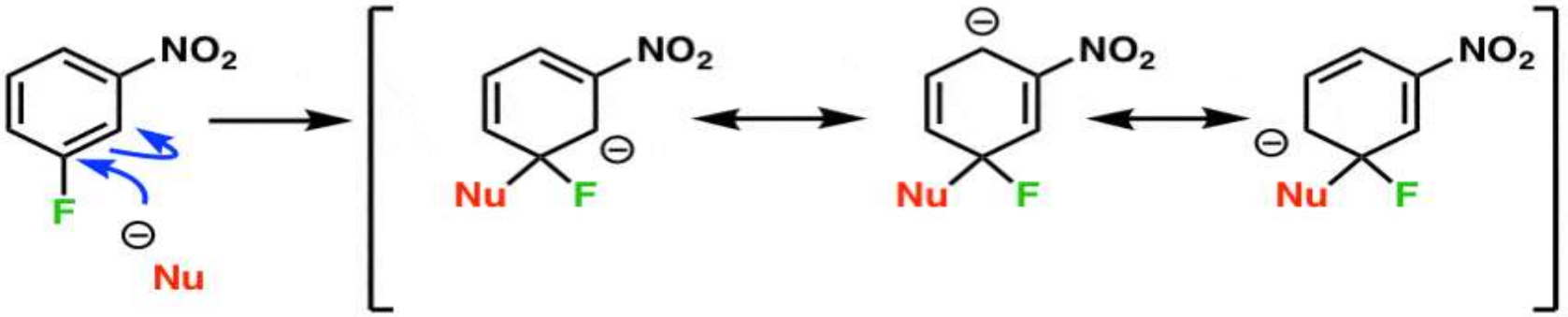
Why Is The *para-* Isomer Faster Than The *meta-* Isomer ?

The negatively charged intermediate is stabilized by electron withdrawing groups (such as NO_2)

In the attack of a nucleophile on *p*-nitrophenyl fluoride, the negative charge can be delocalized to the oxygen of the nitro group;



This isn't possible in the intermediate arising from attack on *m*-nitrophenyl fluoride:

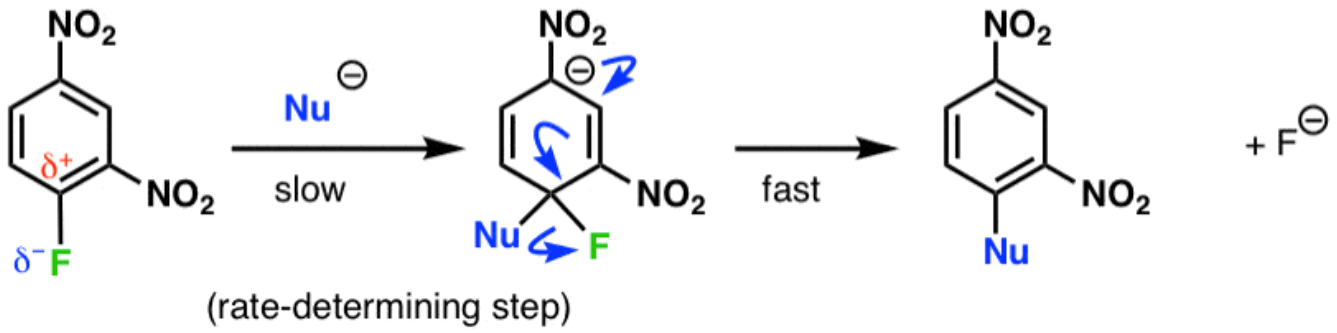


This explains why the rate of nucleophilic aromatic substitution is much faster with the *para* than the *meta* isomer.

Fluorine substituents increase the rate of nucleophilic aromatic substitution: **the rate determining step is attack on the aromatic ring, not breaking the very strong C-F bond.** The highly electronegative fluorine pulls electron density out of the ring, activating it towards attack.

So even though breaking a C-F bond is generally not energetically favorable, this is compensated by the fact that it restores aromaticity.

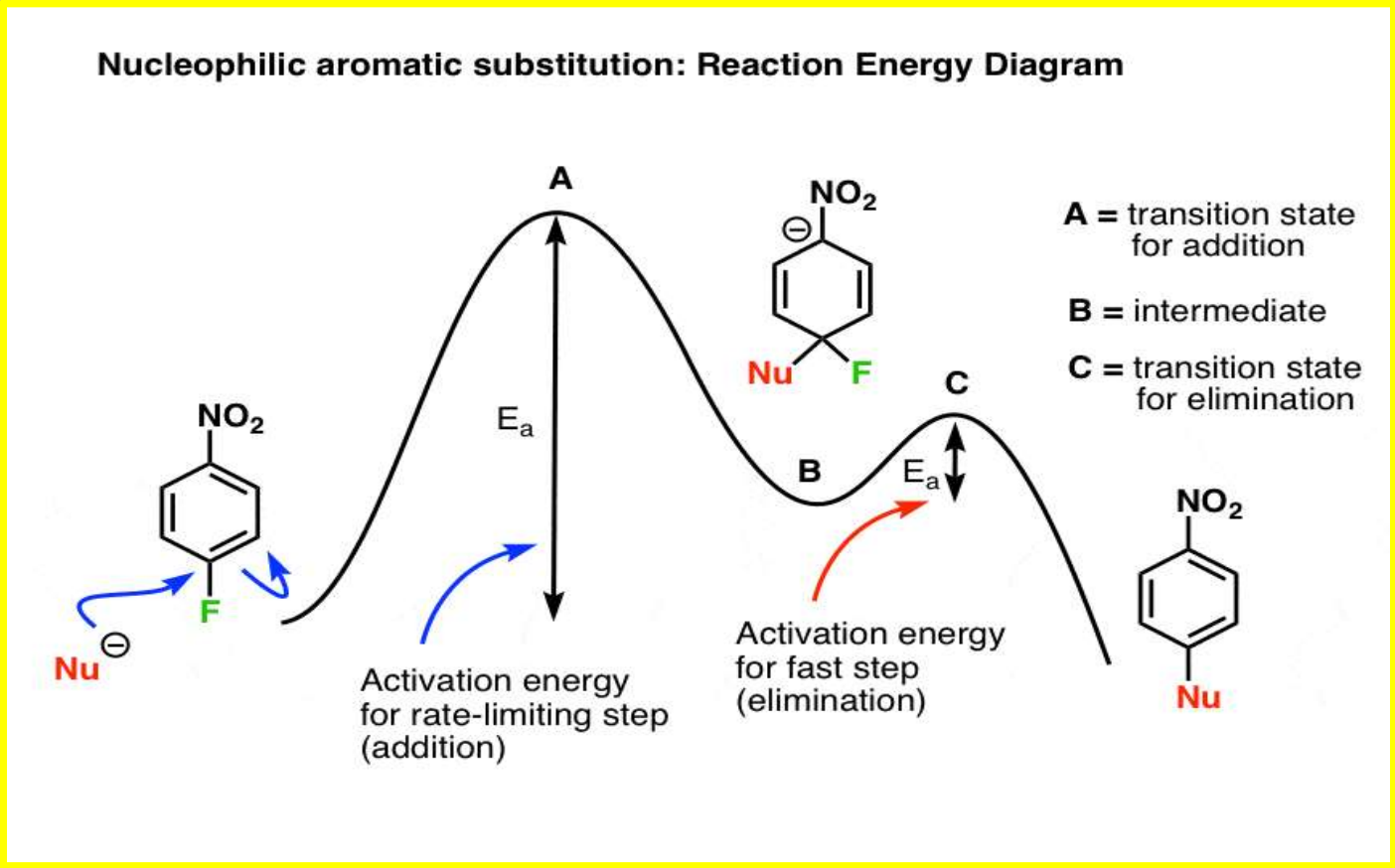
Highly electronegative fluorine helps to activate the ring toward attack:



(rate-determining step)

The Reaction Energy Diagram Of SNAr

We can sketch out a reaction-energy diagram for this mechanism: (*transitition states are "peaks", and intermediates are "valleys". Intermediates can (at least theoretically) be isolated; transition states have partial bonds, only last a femtosecond, and can't be isolated*).

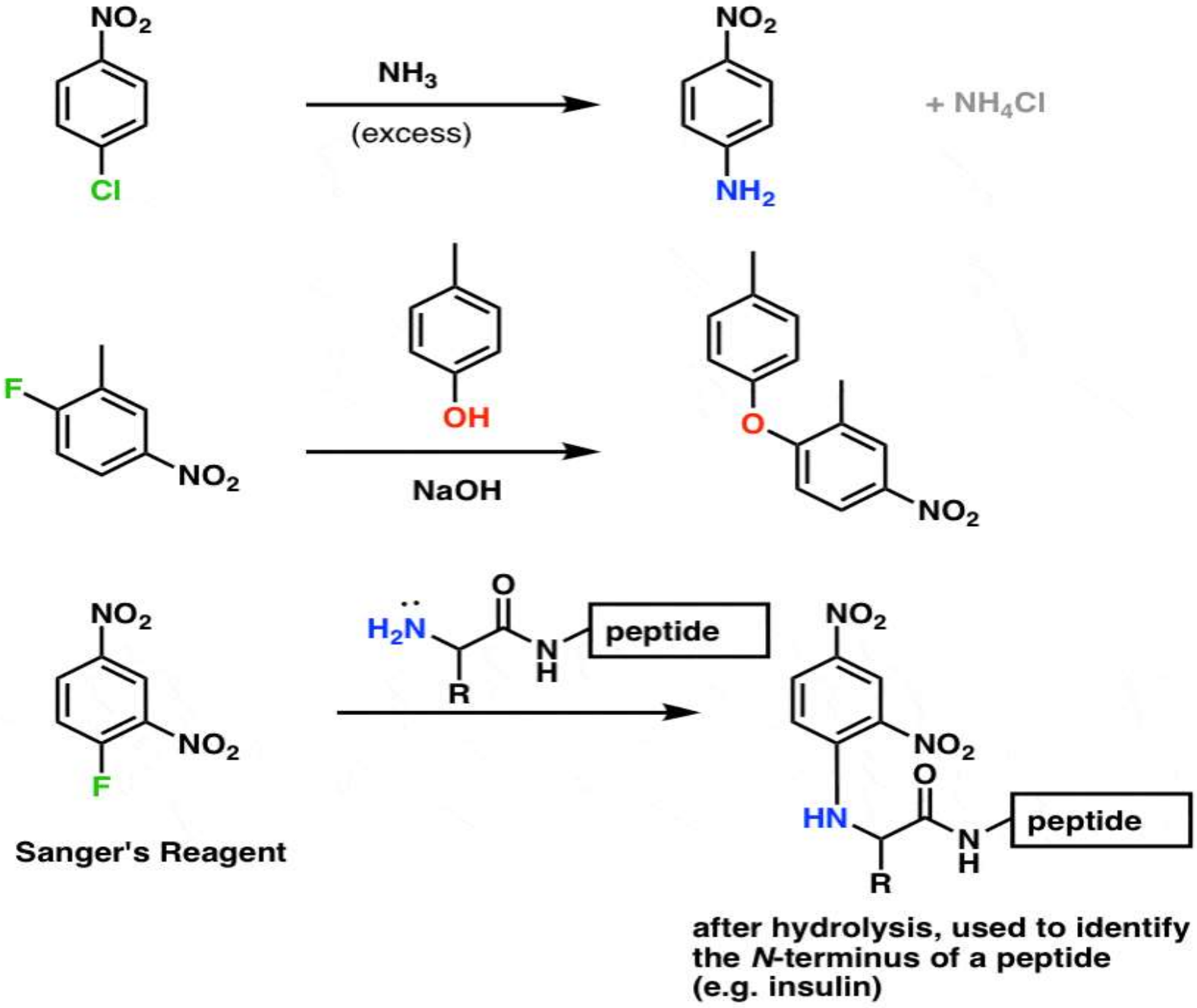


Importance

Three representative examples are given in next slide:

- The first is a straightforward nucleophilic aromatic substitution using an amine as a nucleophile.
- The second uses a stronger base (NaOH) to make a weaker base (the conjugate base of phenol) which attacks the electron-poor ring. (**A variation of this reaction was used in a synthesis of the antibiotic vancomycin**)
- The third example shows the *N*-terminus of a peptide reacting with 2,4-dinitrophenyl fluoride in a nucleophilic aromatic substitution reaction. Fred Sanger used this reagent to label the terminal residues in insulin, which led to the first reported sequence of a protein .

(Nobel Prize in chemistry 1958)


NO2
Cl
NH3
(excess)
NO2
NH2
+ NH4Cl
F
NO2
OH
NaOH
O
NO2
NO2
F
NO2
Sanger's Reagent
H2N
O
N
H
R
peptide
NO2
NO2
HN
O
N
H
R
peptide
after hydrolysis, used to identify
the N-terminus of a peptide
(e.g. insulin)