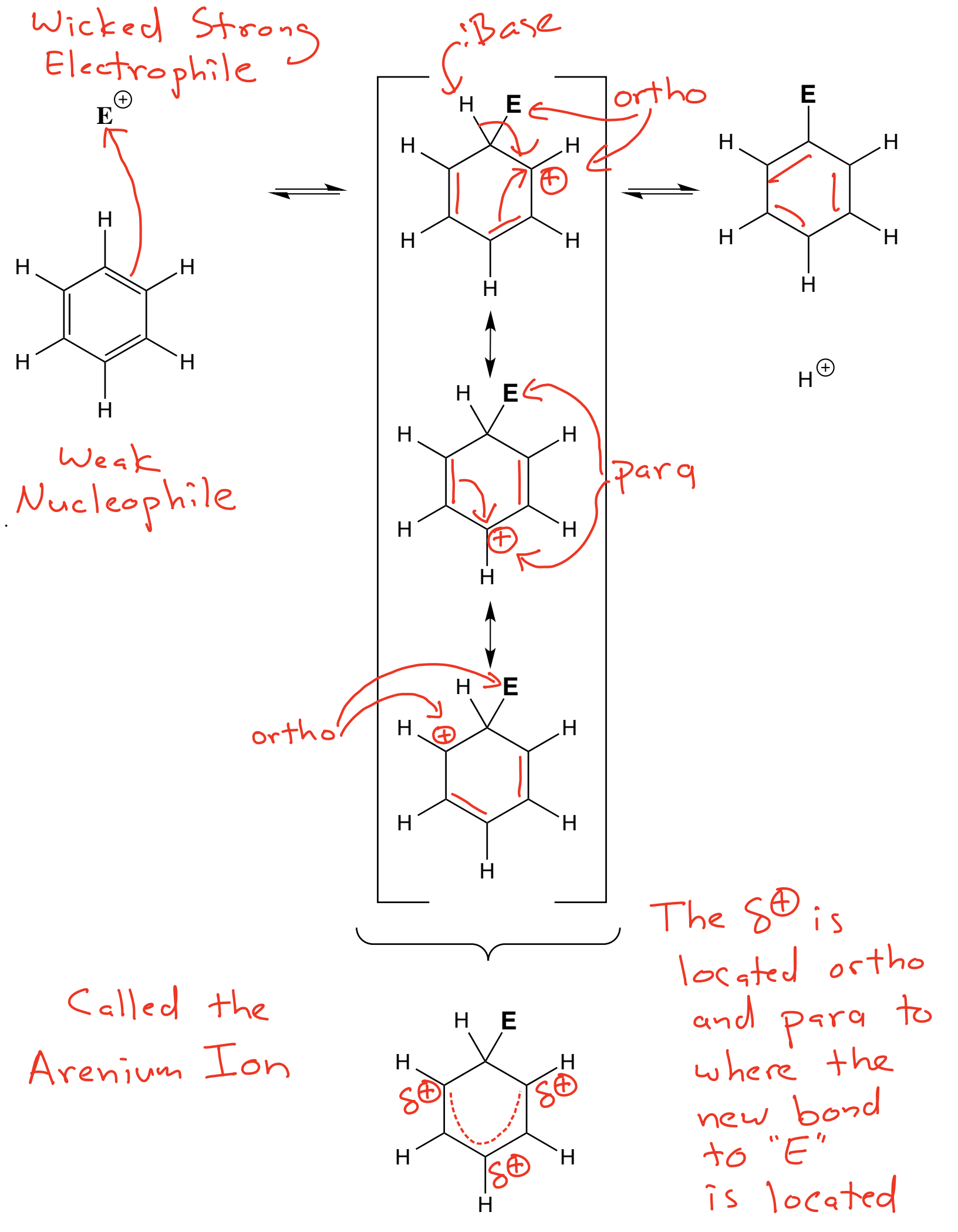
Now get ready to smile!


SKIP HOP
CHICKEN

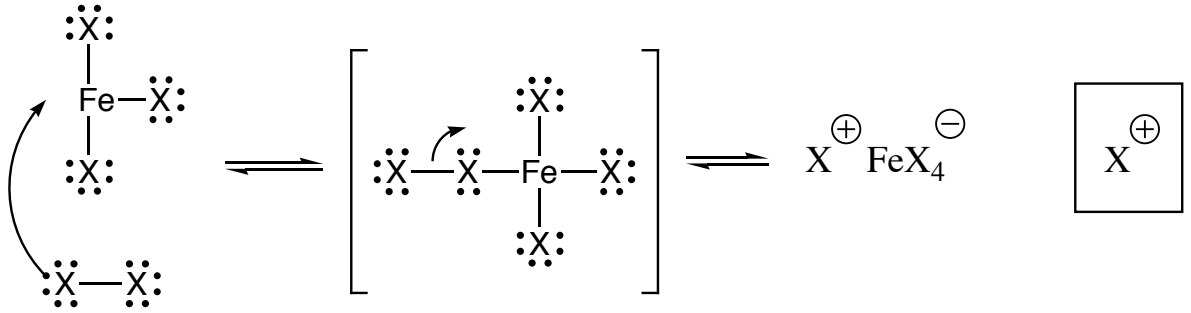

Wicked Strong Electrophile
:Base
ortho
Weak Nucleophile
para
ortho
Called the Arenium Ion
The δ⊕ is located ortho and para to where the new bond to "E" is located

Reagents

Wicked strong electrophile

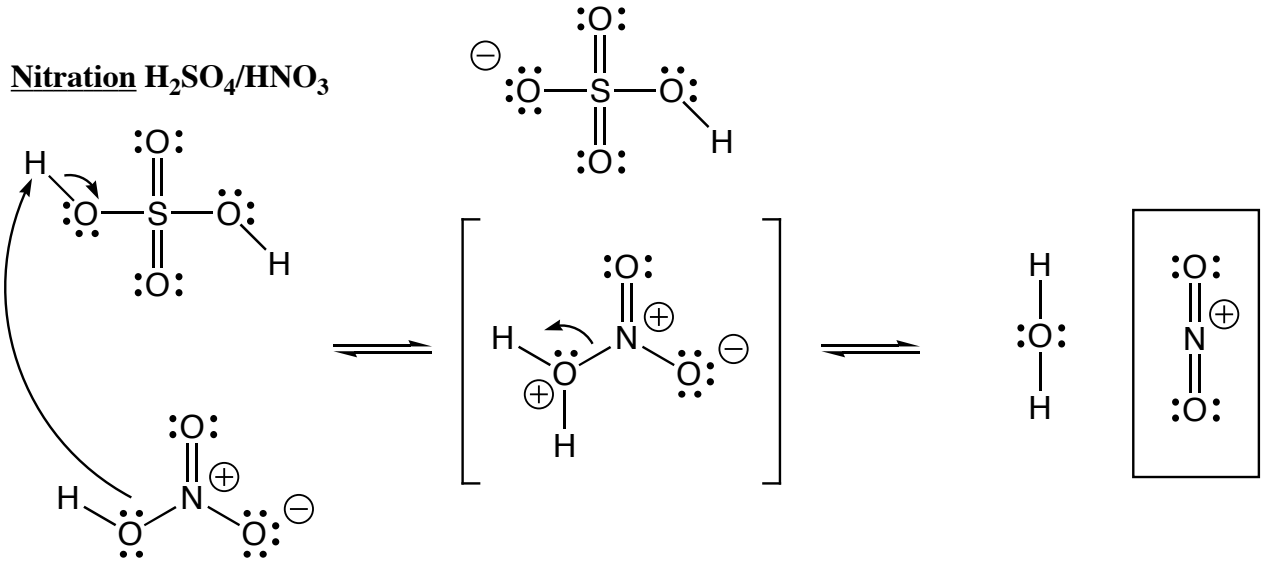
$\mathbf{E^{\oplus}}$

Halogenation $\mathbf{X_2, FeX_3}$



X = Br, Cl

Nitration $\mathbf{H_2SO_4/HNO_3}$



Sulfonation $\mathbf{H_2SO_4/SO_3}$

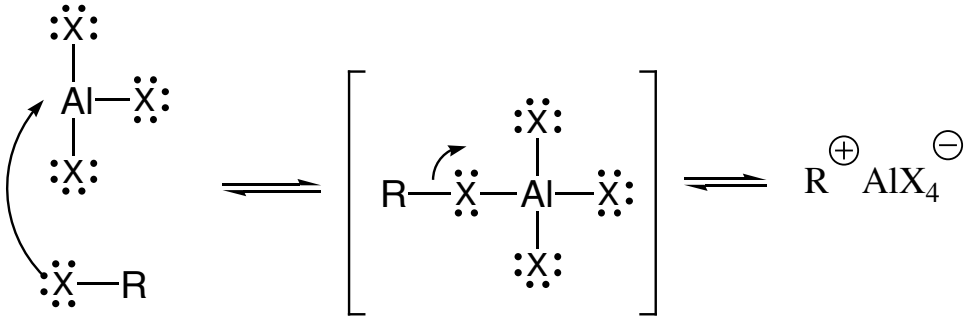
Fuming sulfuric acid contains both of the above reagents, the SO_3 is the important one

Wicked strong electrophile

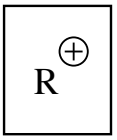
$\mathbf{E^{\oplus}}$

Reagents

Friedel-Crafts Alkylation **R-X, AlX_3**

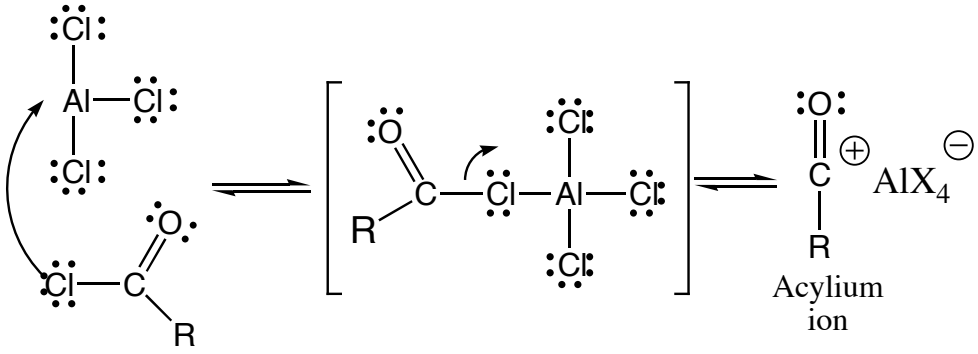


X = Br, Cl

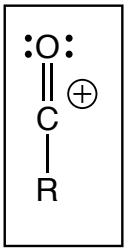


Note this is a carbocation, so it will rearrange if it is a primary or a rearrangment-prone secondary cation

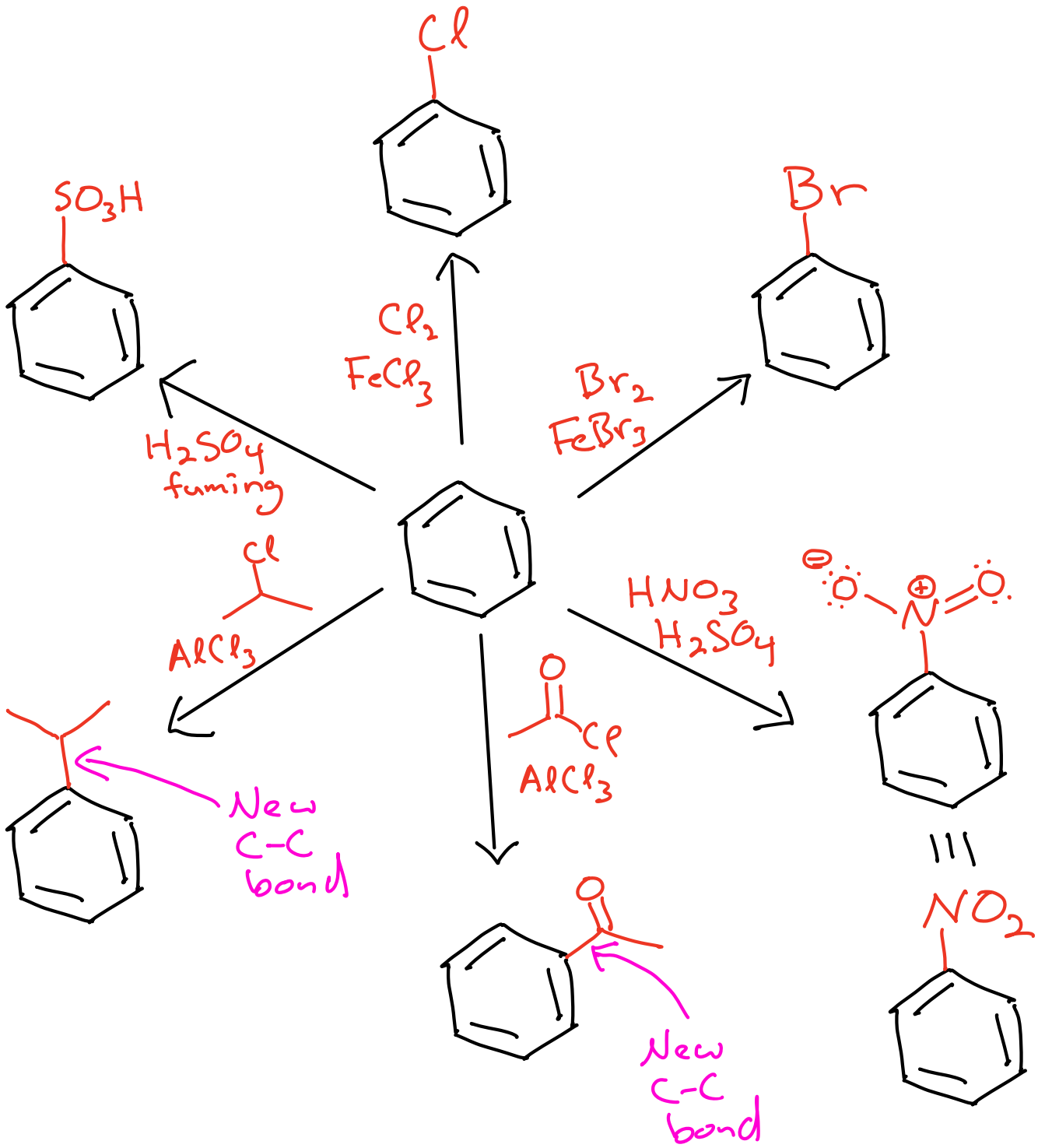
Friedel-Crafts Acylation **RCOCl, $AlCl_3$**



Acylium ion

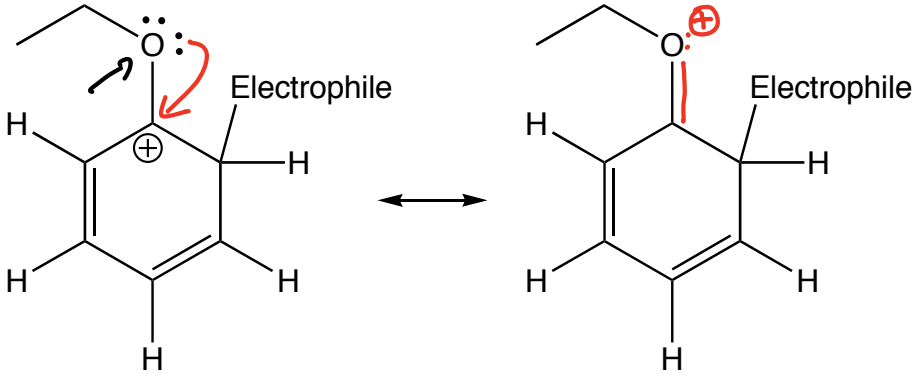


Other notes: 1) It is hard to stop the Friedel-Crafts alkylation after one alkyl group adds (because alkyl groups are "good", that is, activating), but it can be done. 2) Neither Friedel-Crafts reaction works if there is already an electron withdrawing (bad) group on the ring.


Cl
SO3H
Br
Cl2
FeCl3
Br2
FeBr3
H2SO4
fuming
Cl
AlCl3
HNO3
H2SO4
O
Cl
AlCl3
New
C-C
bond
NO2
New
C-C
bond

Arenium ion ***stabilizing*** interactions ← GOOD

A) **Pi donation**, a resonance effect for atoms with lone pairs attached to the ring

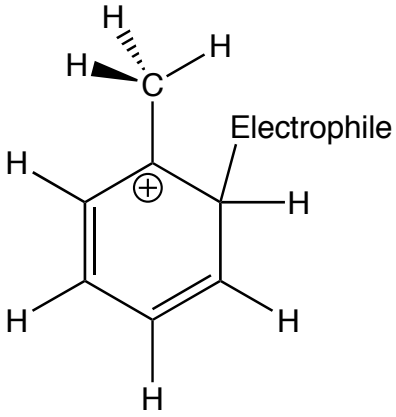


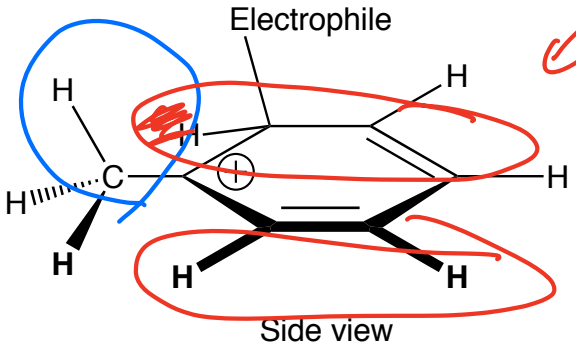
← "pi-pi"

The "Greek interactions"

"sigma-pi"

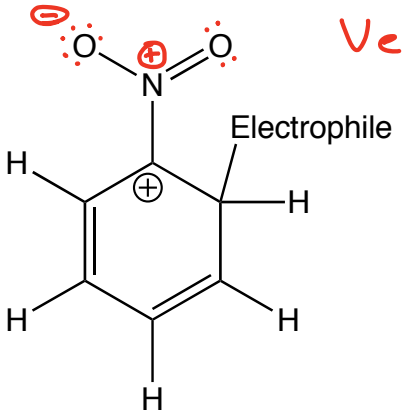
B) **Hyperconjugation** for alkyl groups attached to the ring



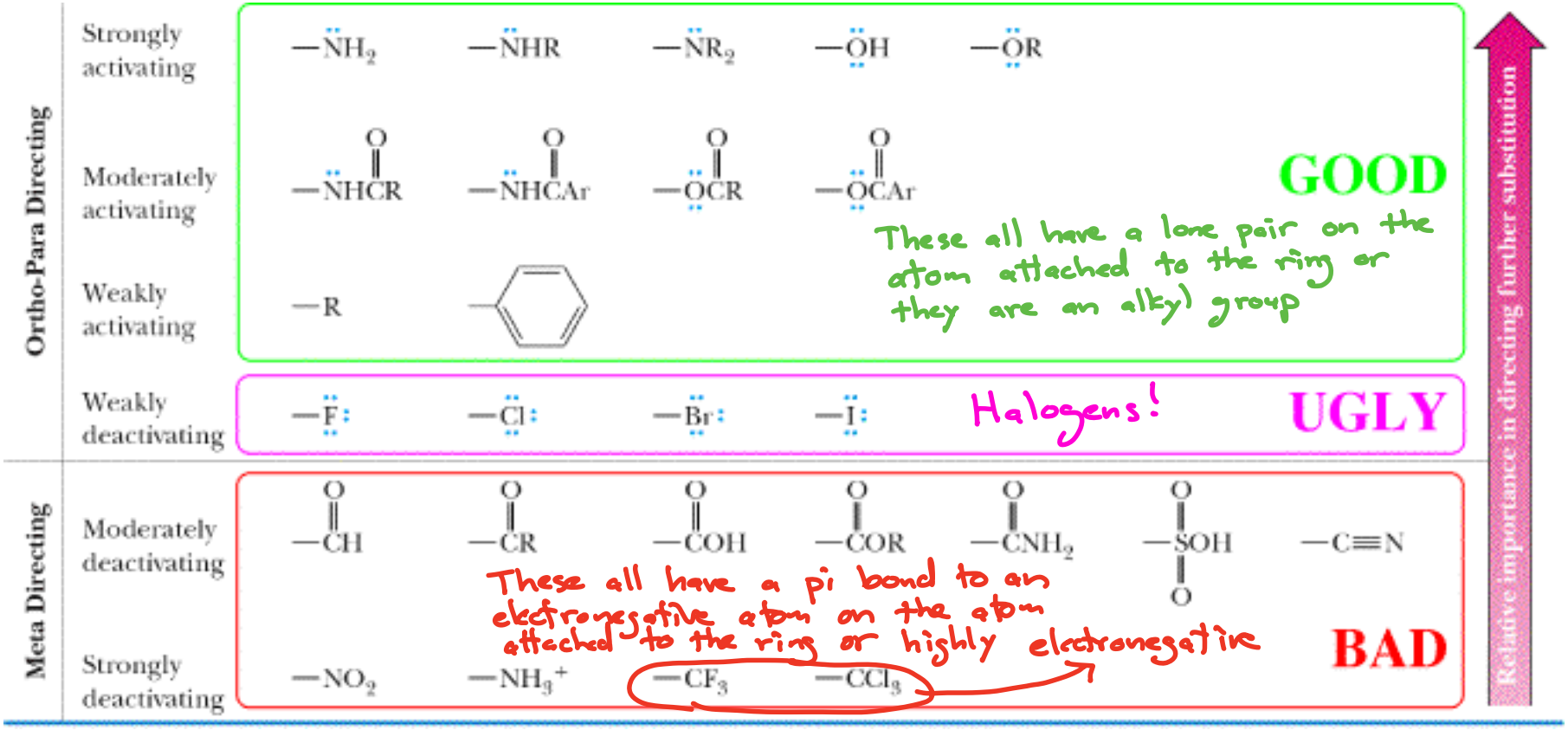


Arenium ion ***destabilizing*** interaction ← BAD

A) **Inductive effect** of electronegative atoms or groups attached to the ring

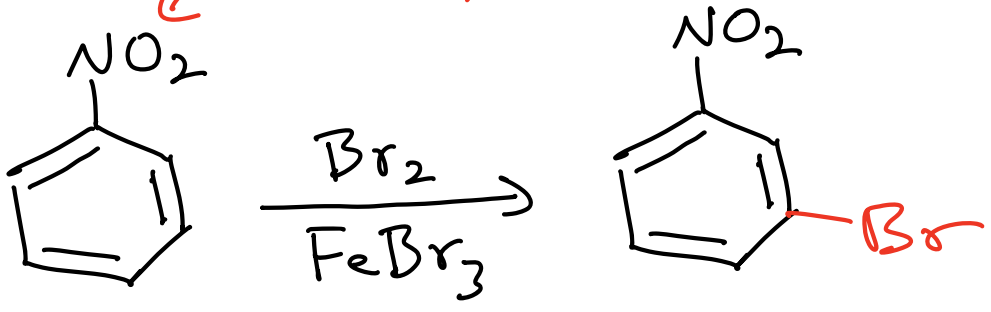


Very electron withdrawing

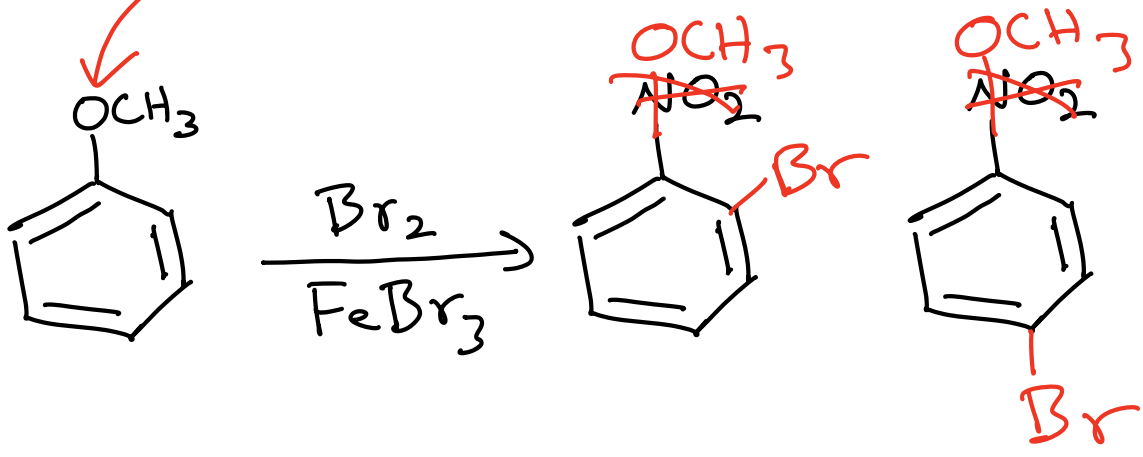

Ortho-Para Directing
Strongly activating
—NH2
—NHR
—NR2
—OH
—OR
Moderately activating
—NHCR
—NHCAr
—OCR
—OCAr
Weakly activating
—R
GOOD
These all have a lone pair on the atom attached to the ring or they are an alkyl group
Weakly deactivating
—F:
—Cl:
—Br:
—I:
Halogens!
UGLY
Meta Directing
Moderately deactivating
—CH
—CR
—COH
—COR
—CNH2
—SOH
—C≡N
These all have a pi bond to an electronegative atom on the atom attached to the ring or highly electronegative
Strongly deactivating
—NO2
—NH3+
—CF3
—CCl3
BAD
Relative importance in directing further substitution

Examples

BAD, meta directing



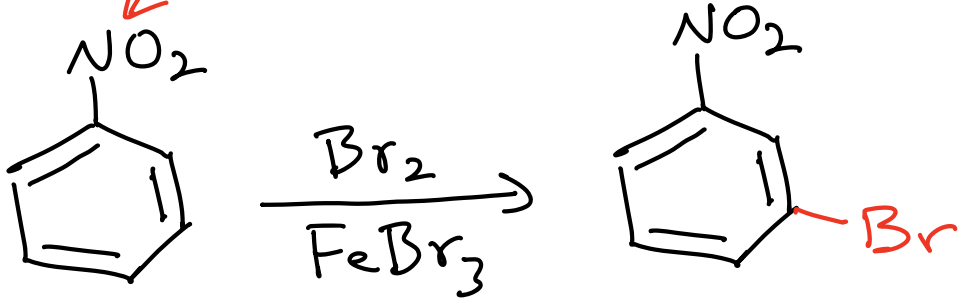
GOOD, ortho, para directing



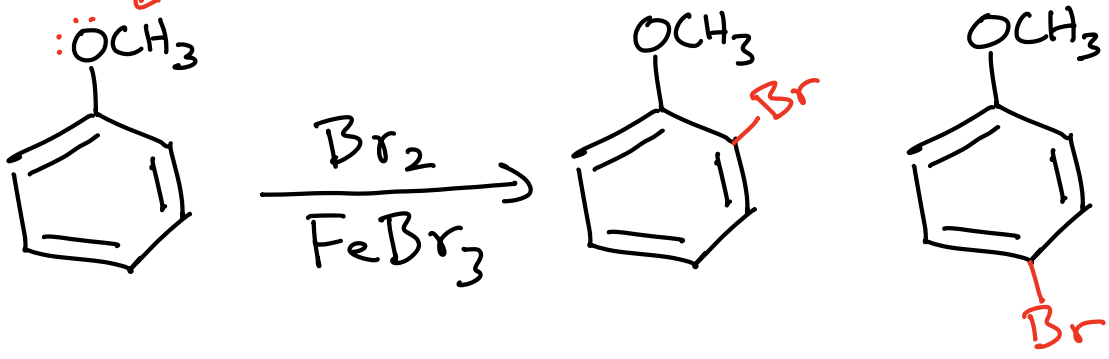
OOPS! In class I did not notice an error in the notes → The notes incorrectly had an $-NO_2$ group on the two product rings. Shoud be $-OCH_3$. Below it is drawn correctly.

Examples

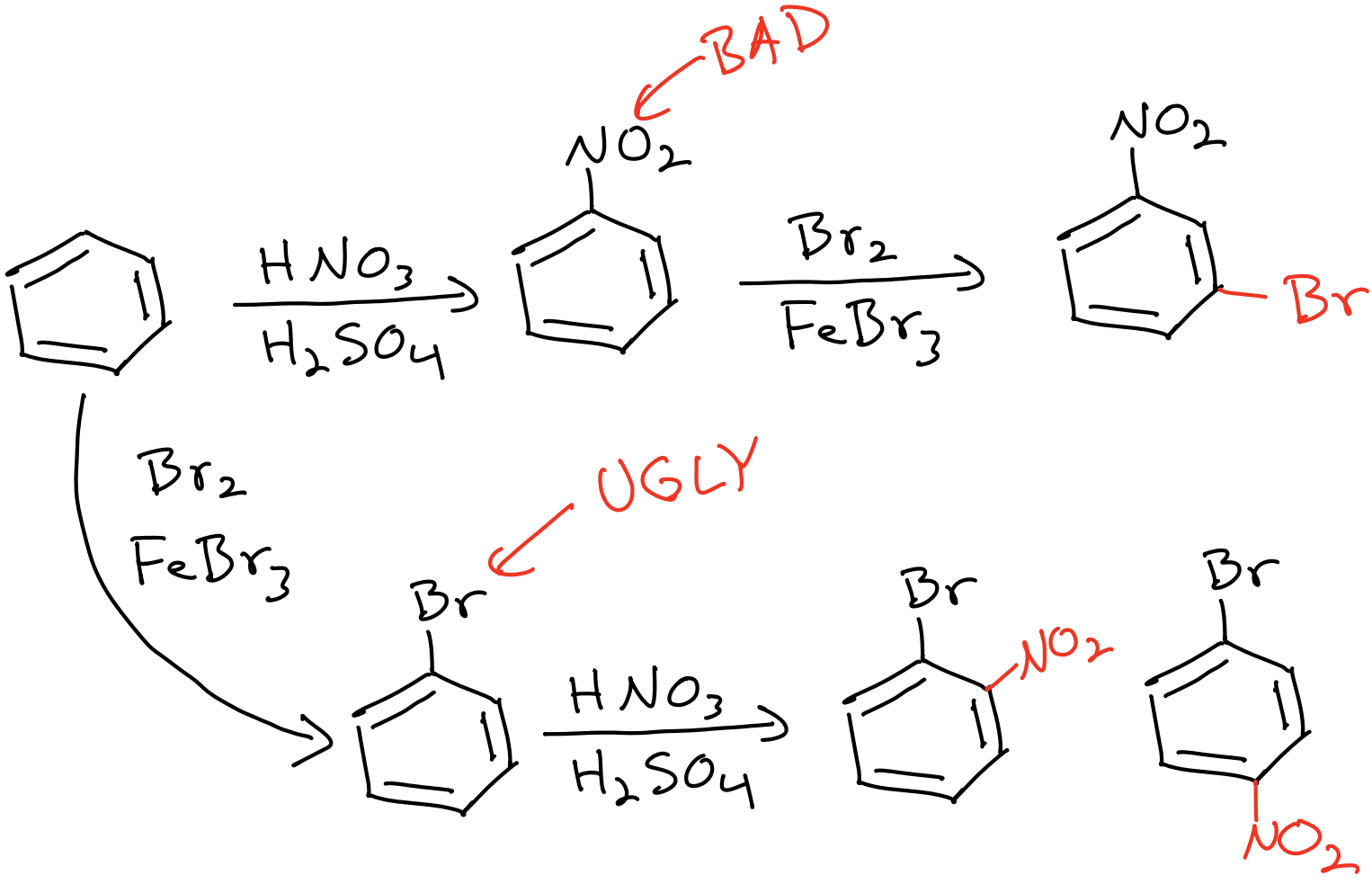
BAD → Meta directing



GOOD → Ortho, Para directing



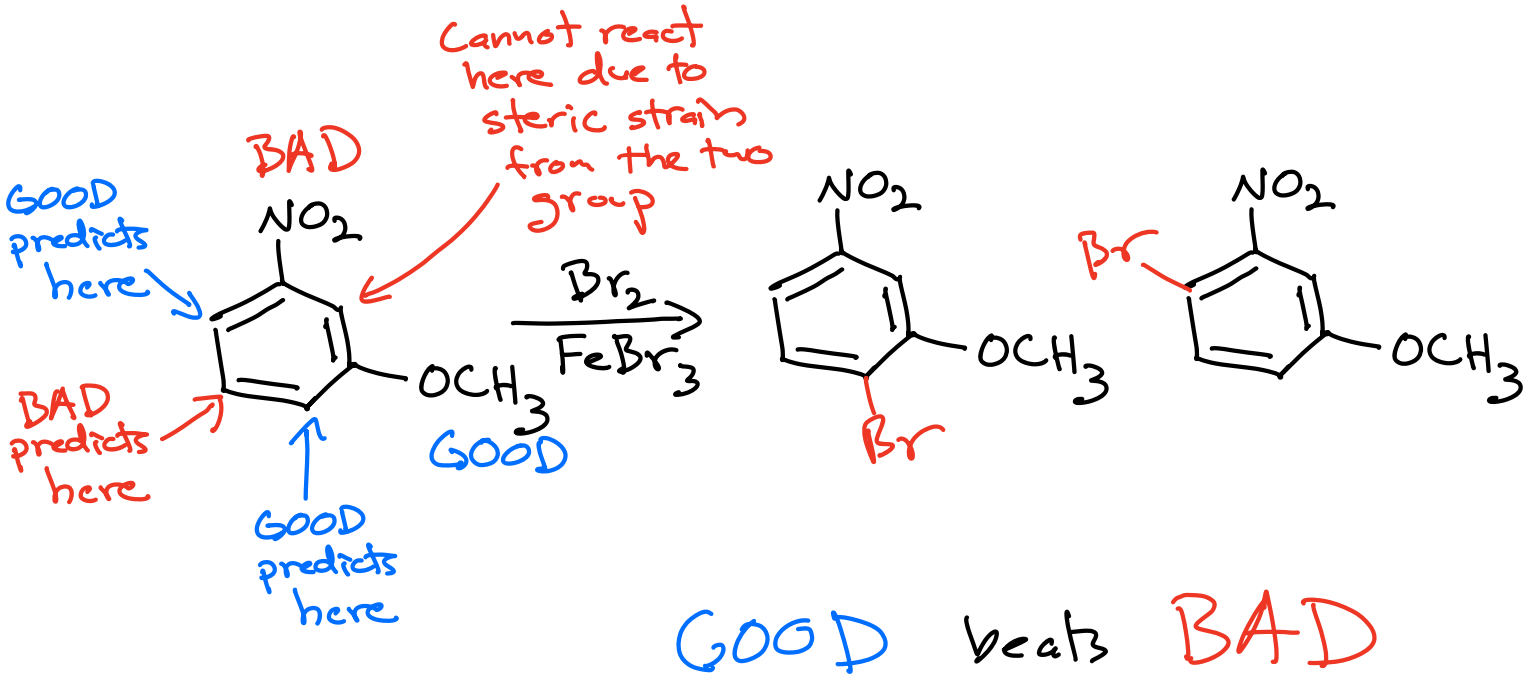
The order in which you add groups matters!



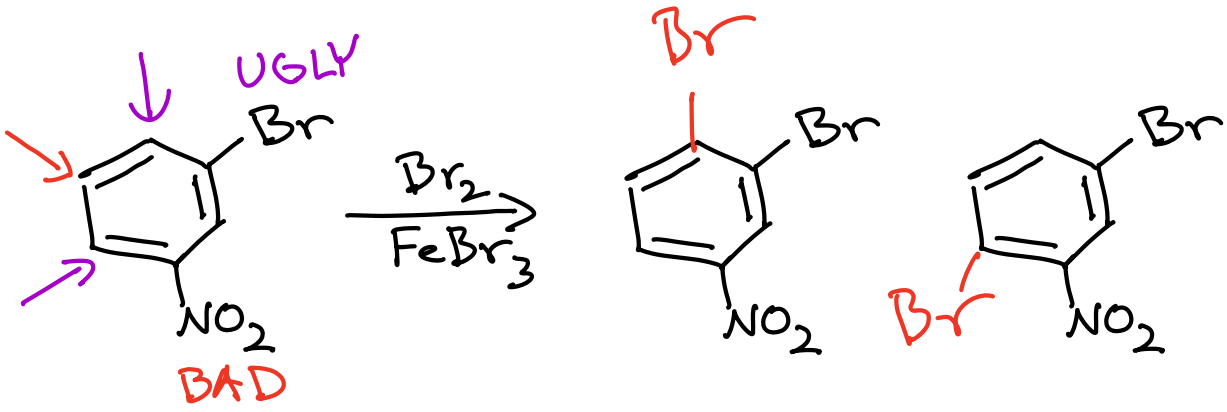
THE GOOD, THE BAD AND THE UGLY (1966)

What if there are two groups already on the ring and they predict different products? It is a duel → the movie got it right!

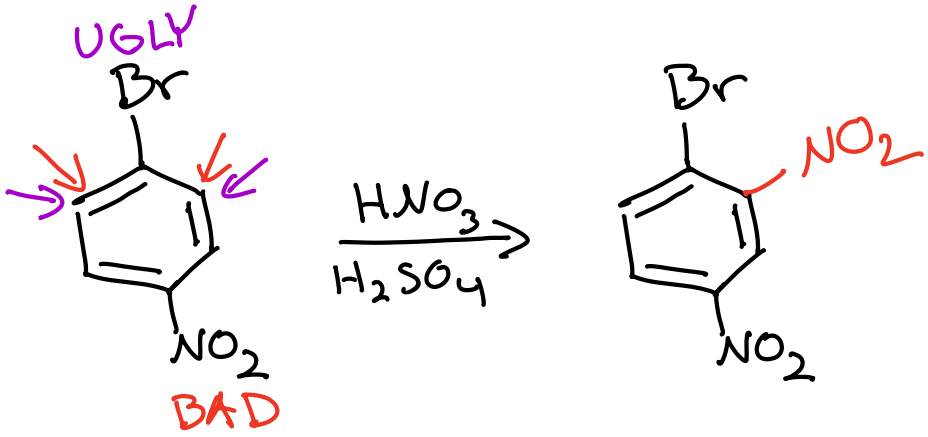
Just like in the movie: GOOD beats BAD and UGLY, UGLY beats BAD!



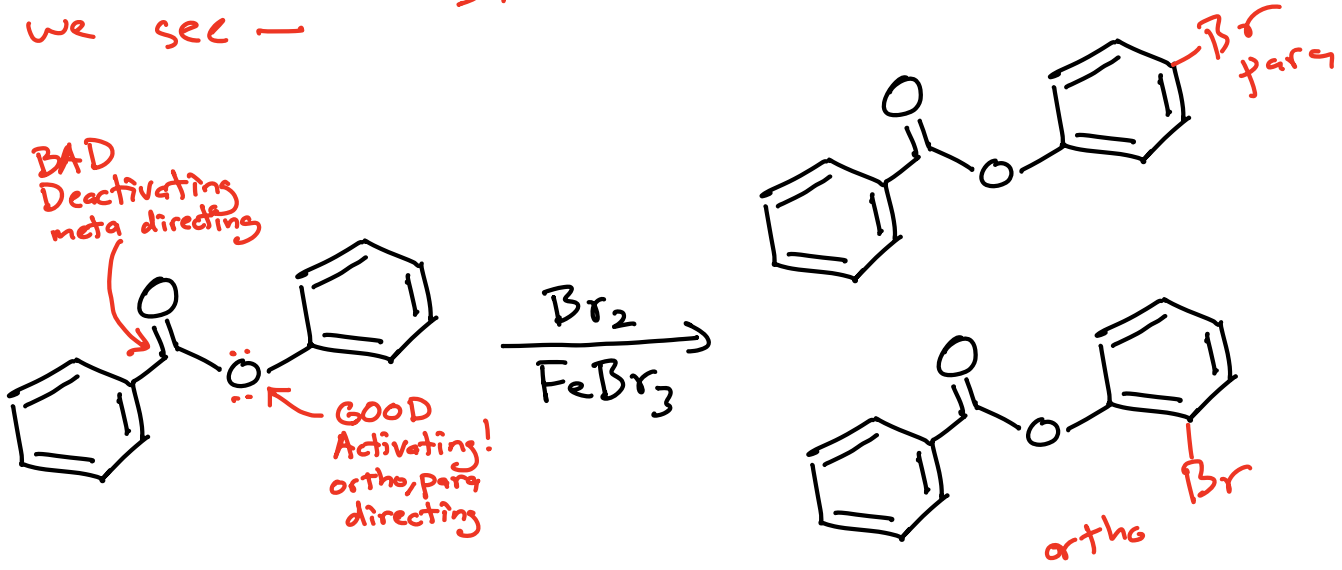
GOOD beats BAD



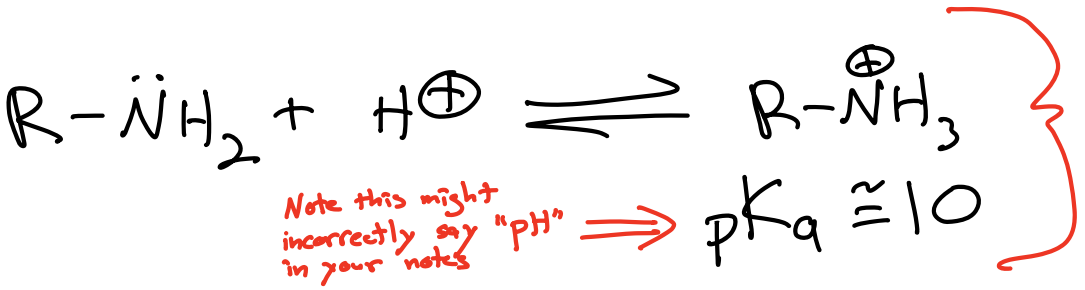
Sometimes two groups will predict the same outcome



Classic Question → As you can see in the energy diagrams, the ring with the GOOD group has a lower energy barrier so that product is what we see —



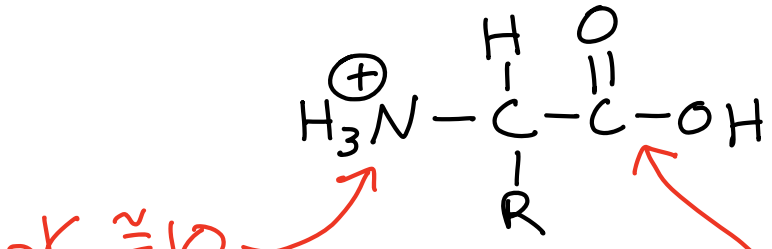
Amines → Relatively strong bases and relatively strong nucleophiles



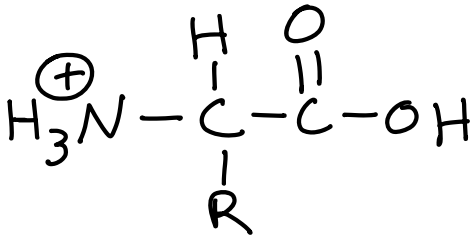
Major form present at neutral pH (pH ≅ 7)

Amines are protonated and positively-charged at neutral pH ⇒ Very important in biochemistry!

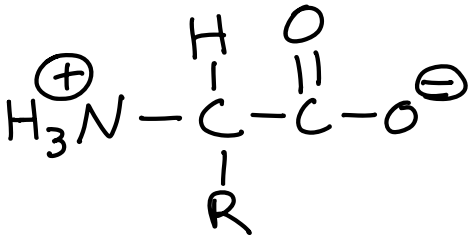
Amino Acids



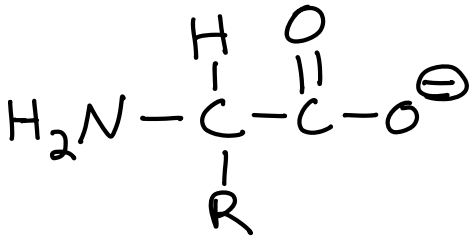
pH 1.0



pH 7.0

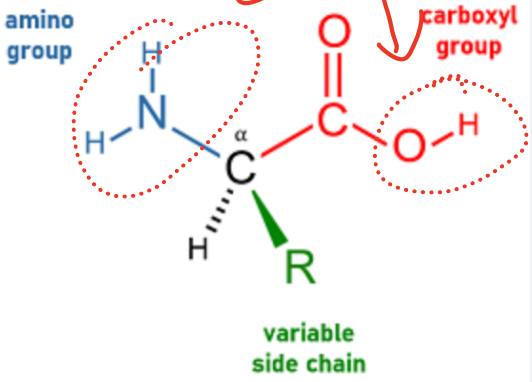


pH 11.0



These are the only possible different forms of an amino acid! (No other forms are possible because of the pKa values!)

Wikipedia

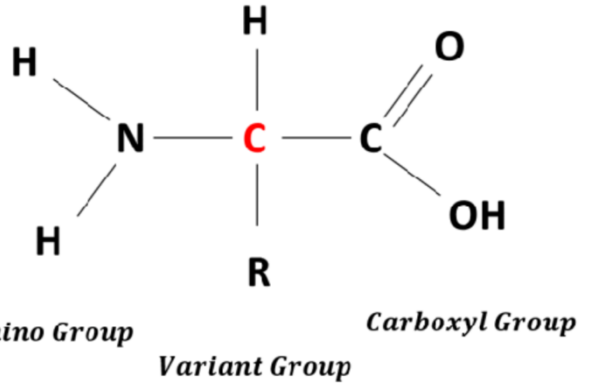


File:Amino acid generic structure.png - Wikipedia

Visit >

These are all wrong! There is no pH possible in which the carboxylic acid is protonated but the amine is not!!

ResearchGate



amino acid structure | Download Scientific Diagram

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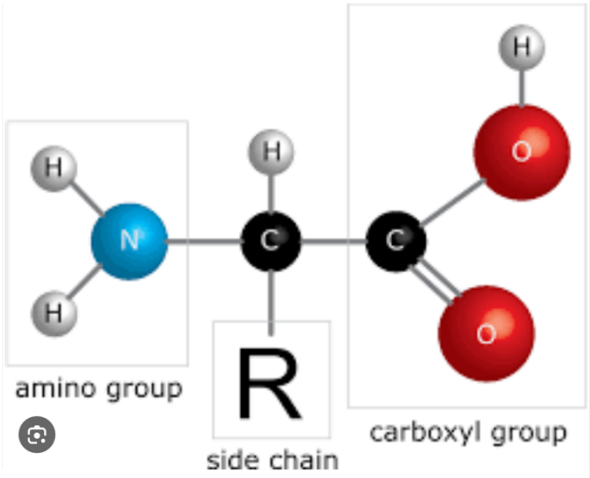

Protein > Amino Acids

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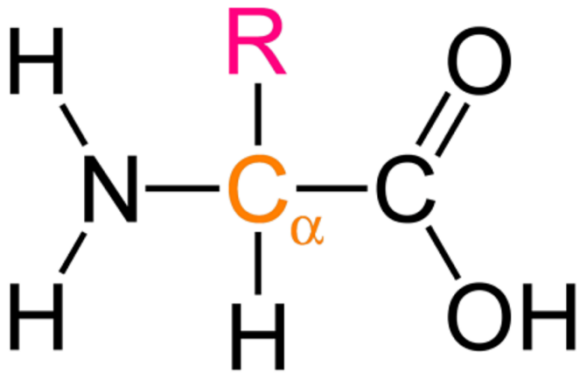

Proteins & Amino Acids | Formation, Structures & Sources - Lesson | Study.com

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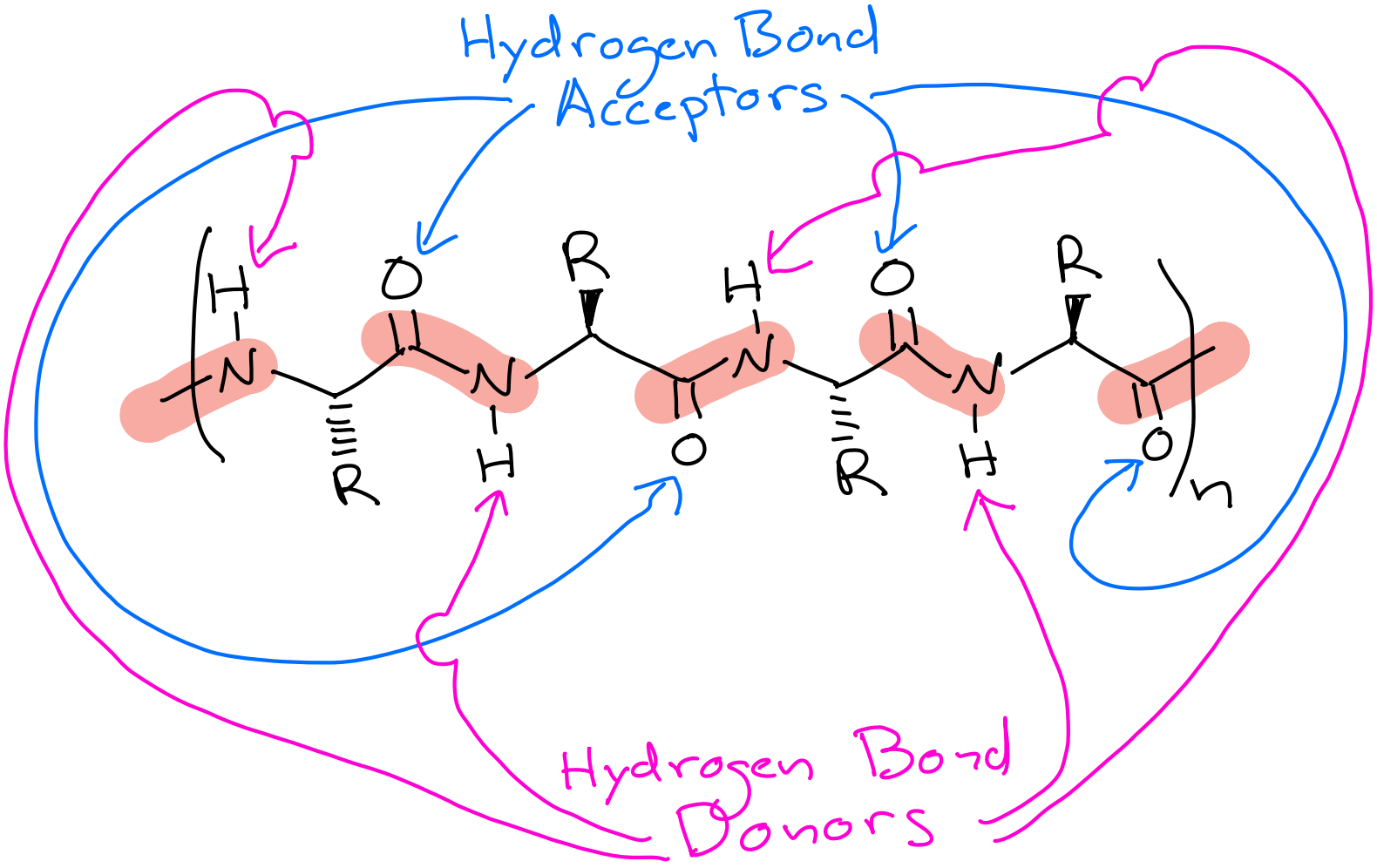
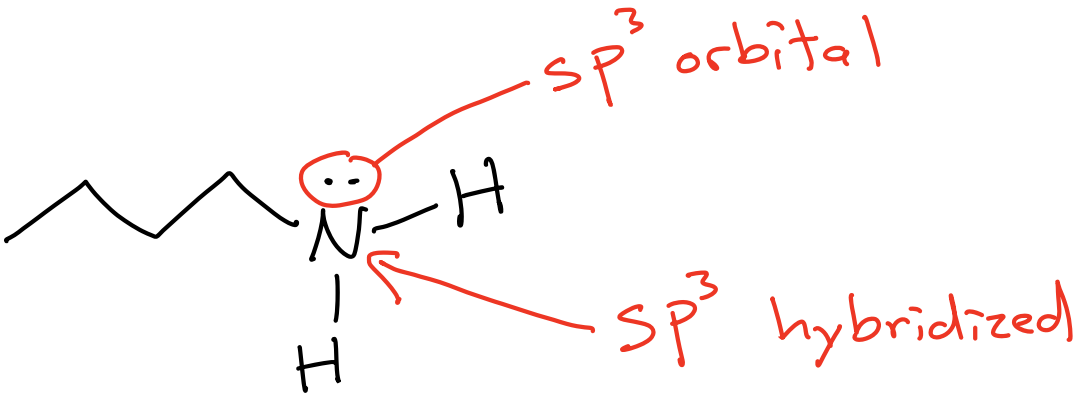
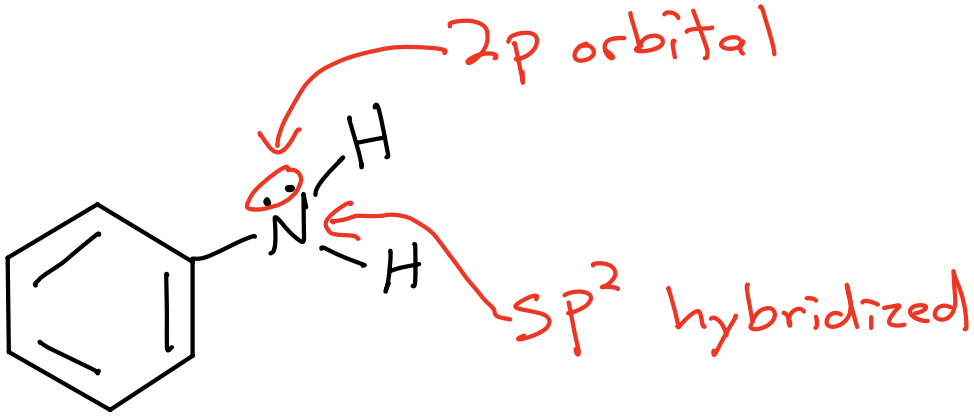
What does this means for amides:

1) The amide group can make strong hydrogen bonds

2) The C–N bond does not rotate at room temperature



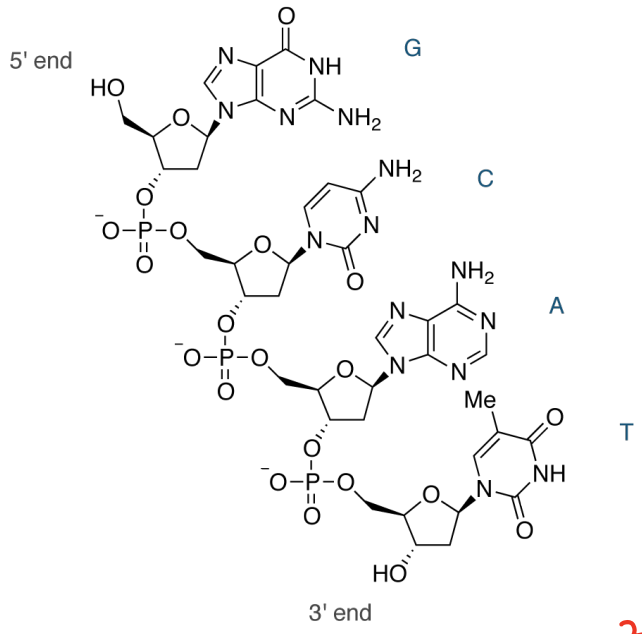


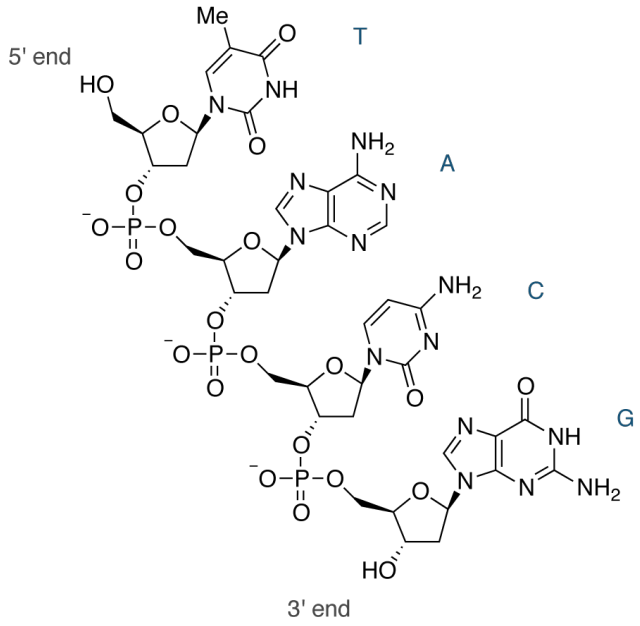


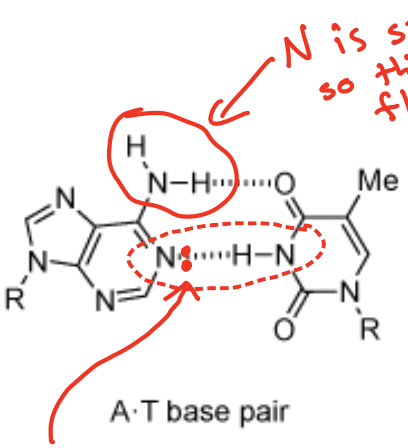
Golden rule: π electrons are more stable when delocalized

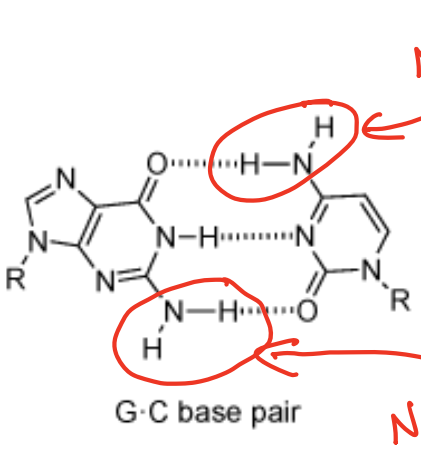
The lone pair is delocalized into the aromatic π system! The lone pair needs to be is a 2p orbital so N must sp^2 hybridized

This is critical to DNA and RNA structure: DNA bases are aromatic and the $-NH_2$ groups on the bases are sp^2 and flat



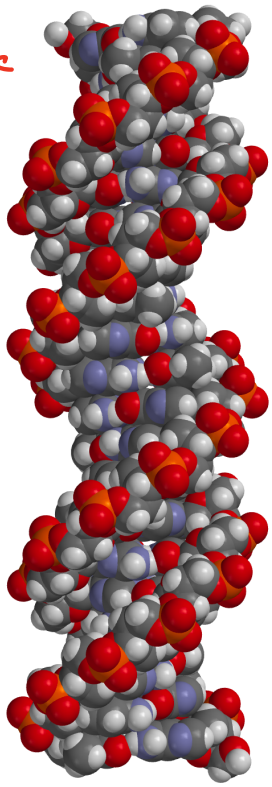


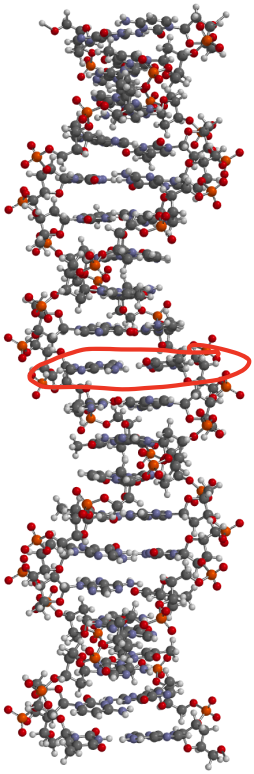




Analogous to pyridine

Lone pair is in an sp^2 orbital and available to make a strong hydrogen bond



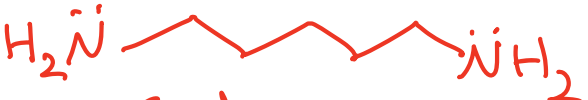


base pairs are flat because N atoms are sp^2

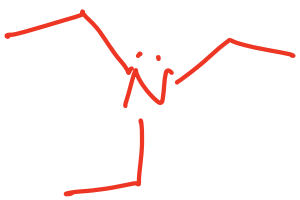
Our sense of smell is highly sensitive to certain molecules that are the result of decomposition of mammal and fish flesh among other things. Not only can we detect very small amounts of these "signal" molecules, we are hard wired to be highly nauseated when we smell them → evolutionary protection to keep us from eating what might look OK, yet would make us sick.

Putrescine

Rotten Mammal



Cadaverine



Rotten Fish

Triethylamine

H_2S

Rotten Eggs

Hydrogen sulfide

Barf

Butyric acid