Fonction et réaction organiques II

Fall Semester 2025

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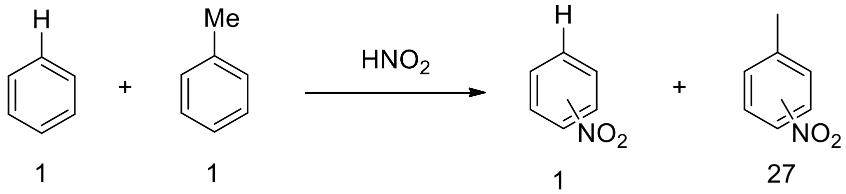
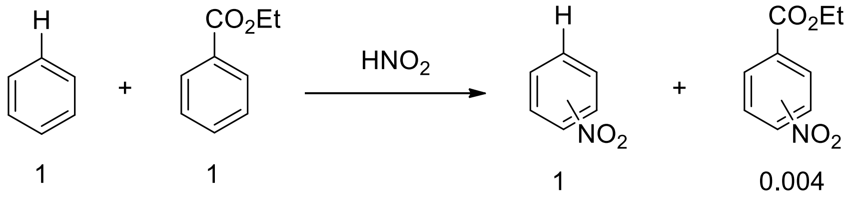
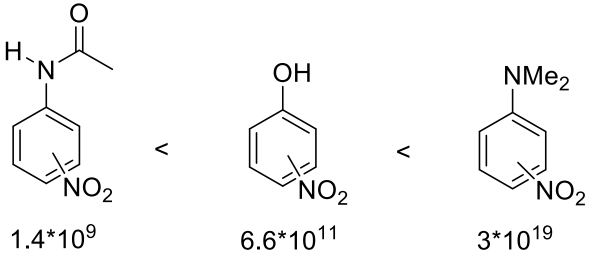
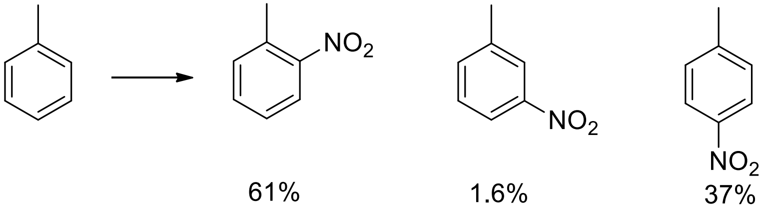
1.2.3. Secondary substitution on the benzene ring

Illustrative examples between EDG and EWG directing groups

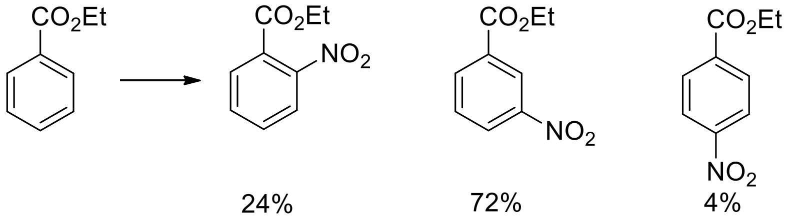








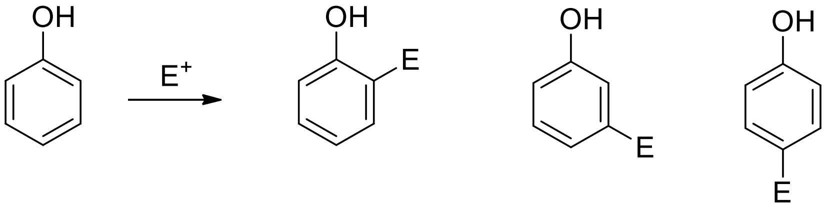
EDG activate all positions. Meta is the least activated one.



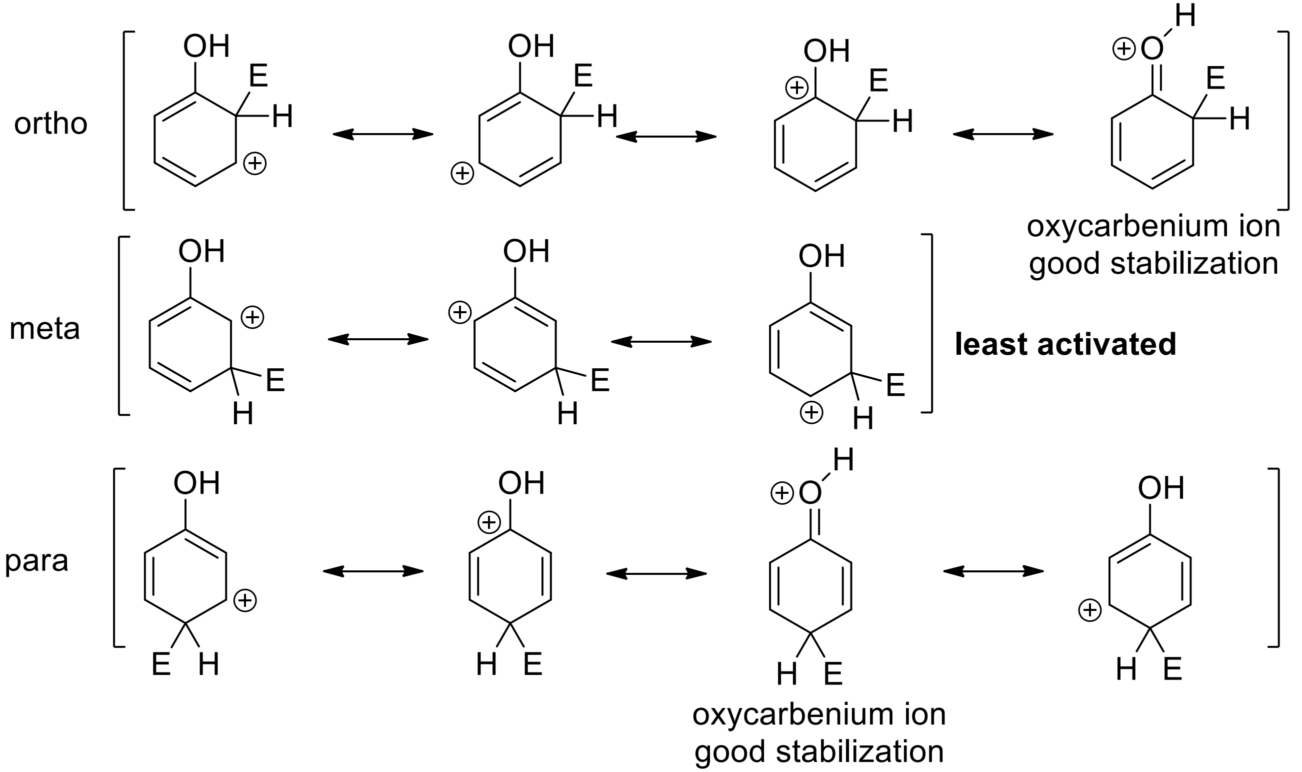
EWG deactivate all positions. Meta is the least deactivated one.

1.2.3. Secondary substitution on the benzene ring

π-donors: all positions are activated as electron density of the ring is increased



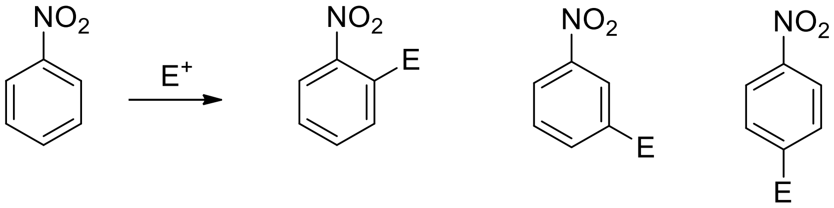
Mesomeric structures of the possible isomers of the σ-complex:



+M: accelerate the reaction and direct ortho and para

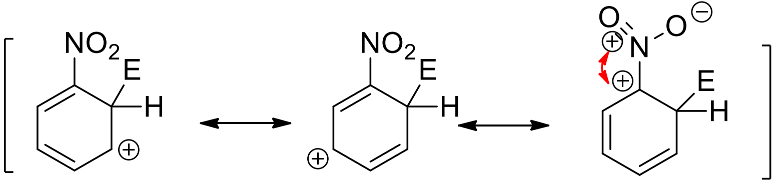
1.2.3. Secondary substitution on the benzene ring

π-acceptors: all positions are deactivated as electron density of the ring is decreased



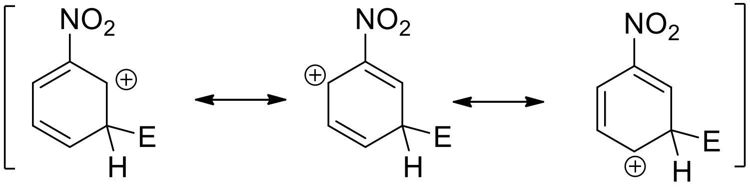
Mesomeric structures of all possible isomers of the σ-complex:

ortho



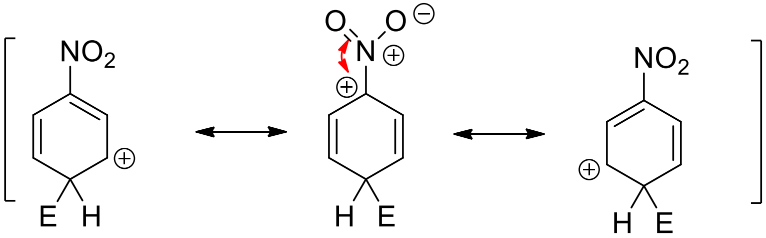
charge repulsion
not a good mesomeric structure

meta



no charge repulsion

para



charge repulsion
not a good mesomeric structure

-M: slows the reaction down and directs meta

1.2.3. Secondary substitution on the benzene ring

- What happen in a formally contradicting case?

(substituent with –I and +M or with +I and –M)

- Generally the M-effect dominates I-effect
- Quantitative assessment with the Hammet equation

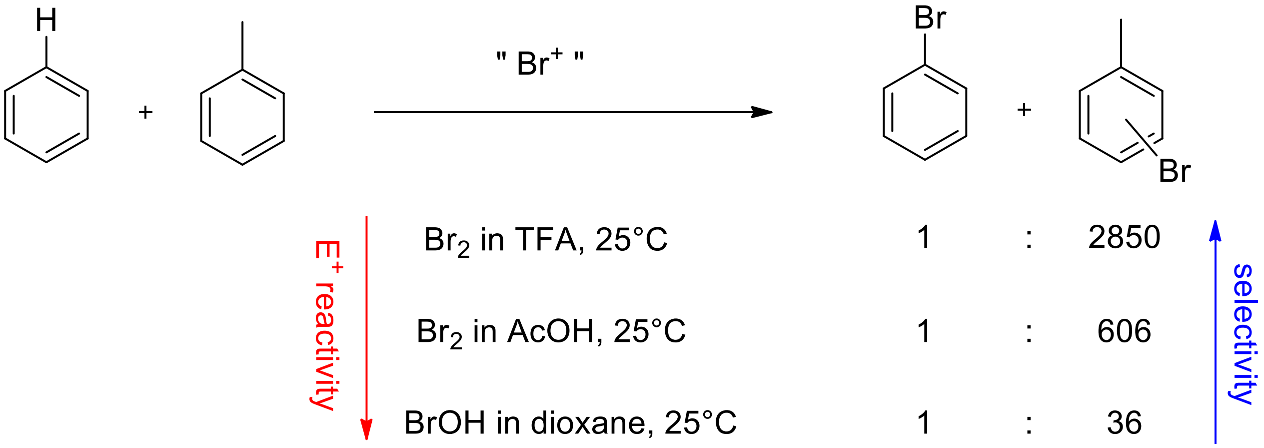
- <u>Special case</u>: halogens –Cl and –Br which have a –I and +M effect

- The reaction rate decrase: -I shows its influence
- ortho and para directing: +M shows its influence

1.2.3. Secondary substitution on the benzene ring

- Selectivity vs reactivity:

For the same substrate combinations, the reaction outcome is influenced by the choice of the reagents:



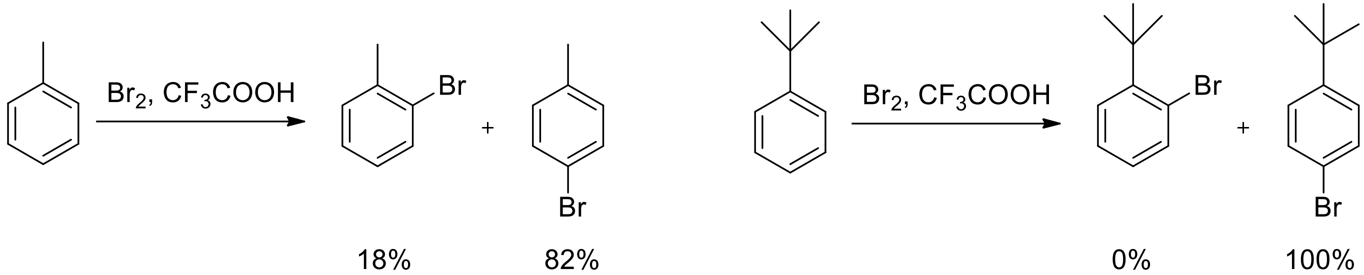
Br_2 in TFA, 25°C	1	:	2850
Br_2 in AcOH, 25°C	1	:	606
BrOH in dioxane, 25°C	1	:	36

Very general principle:
the higher the reactivity of a reagent, the lower its selectivity is.
→ need to adapt it accordingly to the substrate

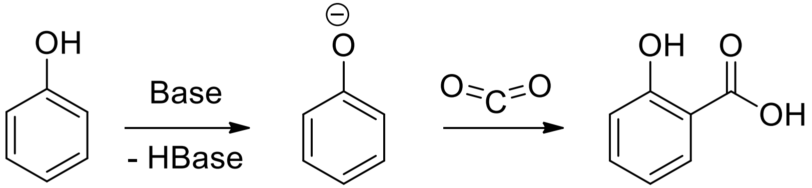
1.2.3. Secondary substitution on the benzene ring

- Ratio of ortho and para products:

1) Ortho is favored by statistics by a factor of 2
2) The para position is often preferred for sterical reasons

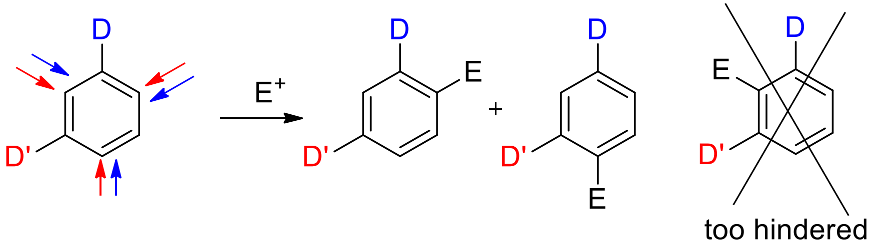


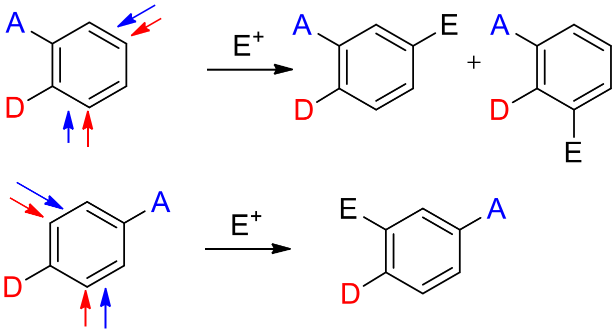
3) Coordination and directing groups can lead to a selective ortho substitution



1.2.4. Introducing a 3rd substituent

- Two substituents enhance their effects if directing in the same sense:



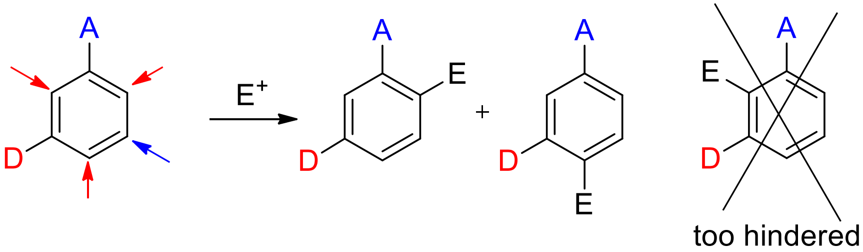


No substitution in bis-ortho position

- Case with EDG and EWG substituents: stronger subtituent wins and decides on the position

M-effects dominate I-effects

Most often activating effects are stronger than deactivating effects (-M)



1.3. Quantitative Substitution Effects

- The Hammett equation: quantitative measurement of substitution effect

$$\boxed{\log \frac{K_X}{K_H} = \rho\,\sigma}$$

K_H: reaction rate for the unsubstituted aromatic compound

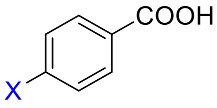
K_X reaction rate for X substituted aromatic compound

σ: substitution parameter (changes with X)

ρ: reaction parameter (changes with the reaction)

–σ-values:

Characteristic for the individual substituent



X = H: $\sigma = 0$

X = EDG: $\sigma < 0$

X = EWG: $\sigma > 0$

Its position is important (different values for a substituent in the o-, m- or p-position)

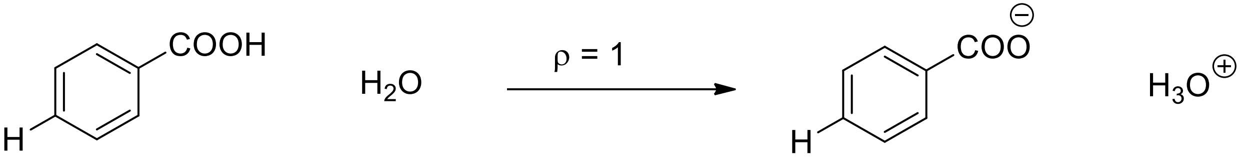
–ρ-values:

$\rho > 0$: a negative charge is developing in the transition state

$\rho = 0$: rare case where the reaction rate is not influenced by substitution

$\rho < 0$: a positive charge is developing in the transition state

-Standardized reaction:



1.3. Quantitative Substitution Effects

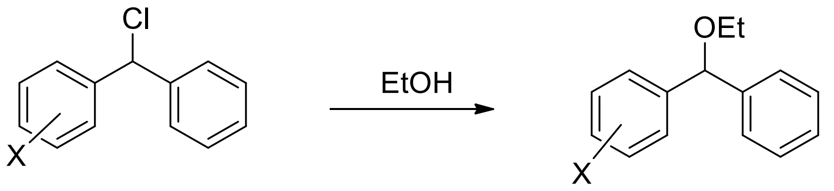
- Valuable information that can be obtained from the Hammett equation:

1) A known reaction (ρ known) can be used to determine the donor or acceptor properties of an unknown substituent X: measure its σ value.

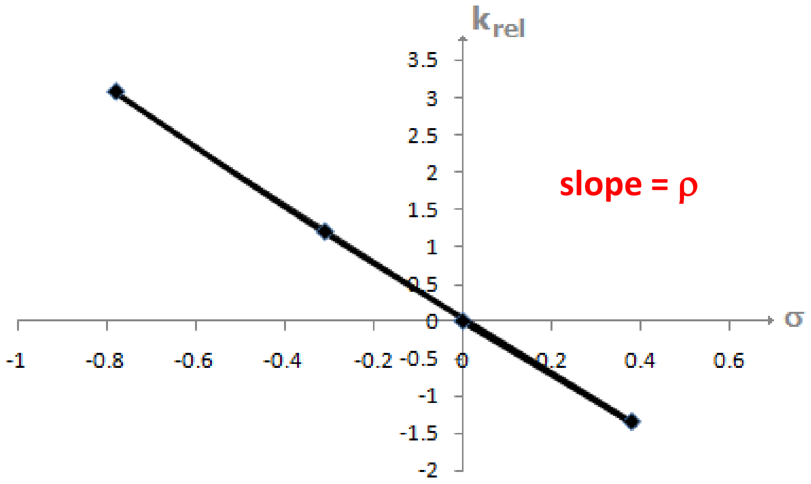
2) Investigate the mechanism of an unknown reaction (ρ unknown): with several known substituents (σ given) measure the ρ value of the reaction and draw conclusion on the charge in the transition state.

1.3. Quantitative Substitution Effects

- Example for the Hammett equation: solvolysis reaction



X	H	p-Cl	p-Me	p-OMe
σ	0	0.38	-0.31	-0.78
K_{rel}	1	0.045	16.2	1200
$\text{Log}(K_{rel})$	0	-1.35	1.2	3.08



slope = ρ

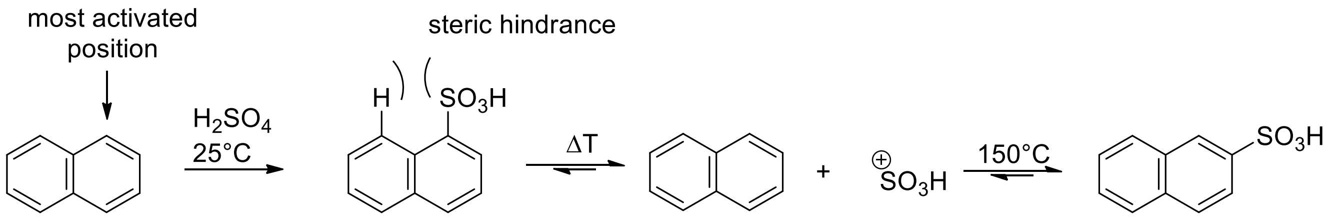
By definition the line goes via origin

Equation give the ρ-value (the slope): $y = -3.828x$

→ a positive charge is developing in the transition state

→ S_N1 reaction

1.4. Reversibility in S_EAr reactions

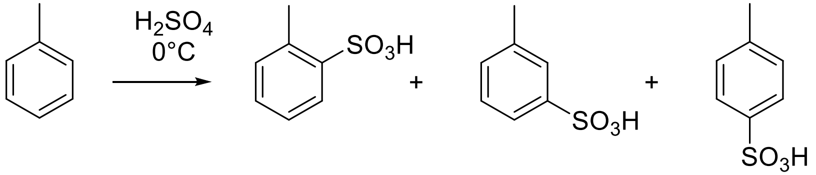


α-Naphthylsulfonic acid
kinetic product has a lower transition state and is formed faster

β-Napthylsulfonic acid
Thermodynamic product, more stable

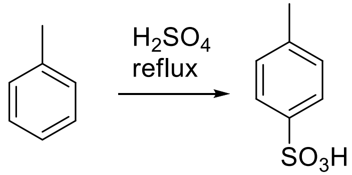
Example:

Kinetic:



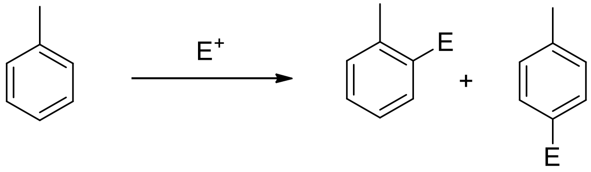
43% 4% 53%

Thermodynamic:

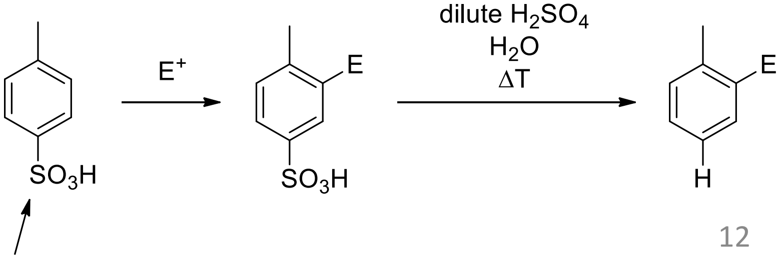


100%

Application: a trick for a removable directing group



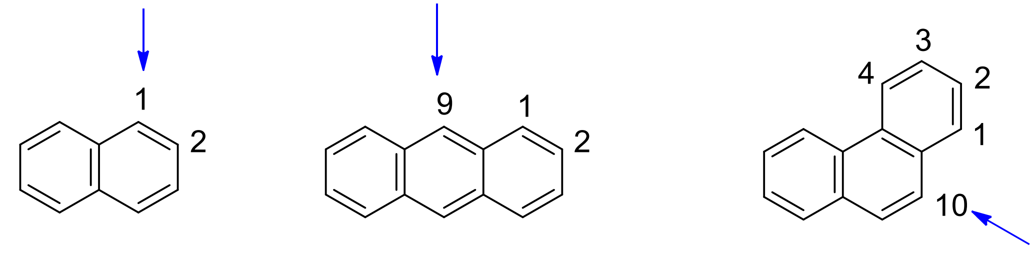
unselective!



Blocks para-position

1.5.1. Reactivity of condensed aromatic substrates

most activated positions



Naphthaline

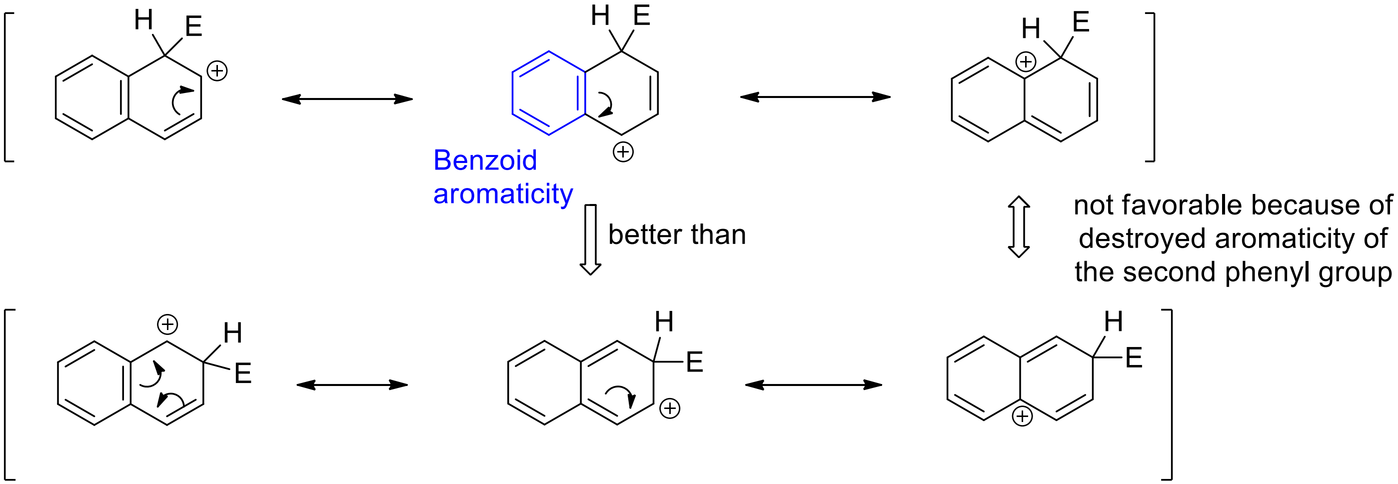
Anthracene

Phenanthrene

Naphthaline: reactivities differences between position 1 and 2 in S_EAr

Position 2:

Position 1:



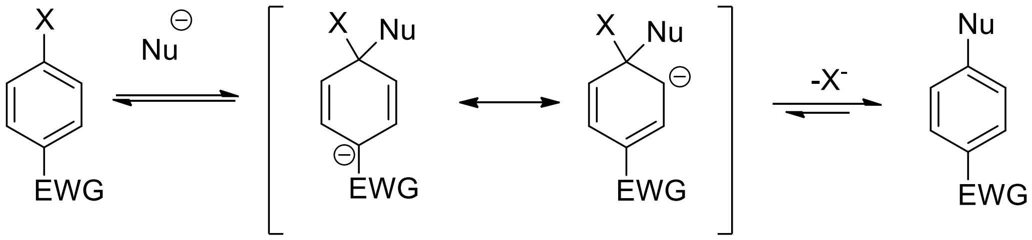
Benzoid aromaticity

better than

not favorable because of destroyed aromaticity of the second phenyl group

quinoid aromaticity is less good

1.6. Nucleophilic Aromatic Substitution S_NAr



Meisenheimer complex

Criteria:

- X must be a leaving group with high electronegativity (F, Cl, OR…)
- EWG group (-NO_2, -CN, …)

→ The reaction proceeds by an addition/elimination mechanism.

→ Obeys second order kinetics

→ EWG substituents must stabilize the negative charge of the Meisenheimer intermediate.

→ Therefore they must be in the ortho- or para- position.