

SNS COLLEGE OF PHARMACY AND HEALTH SCIENCES

Affiliated To The Tamil Nadu Dr. MGR Medical University, Chennai

Approved by Pharmacy Council of India, New Delhi.

Coimbatore -641035



COURSE NAME : COMPUTER AIDED DRUG DESIGN(BP 807 ET)

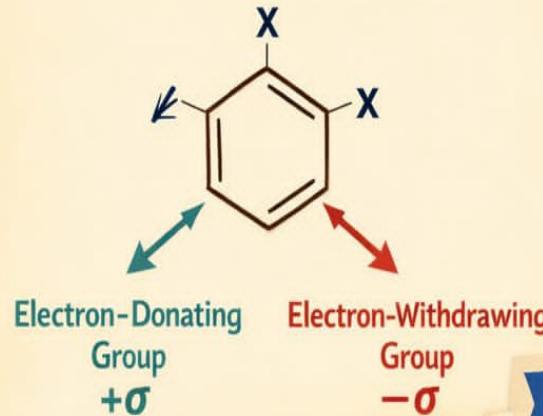
VIII SEM / IV YEAR

TOPIC : HAMMETT CONSTANT

INTRODUCTION TO HAMMETT CONSTANT

What is the Hammett Constant (σ)?

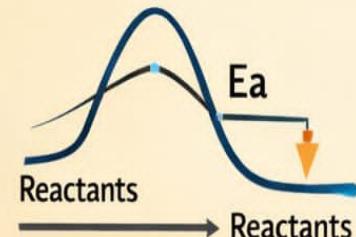
A measure of the electronic effects of substituents on a benzene ring.



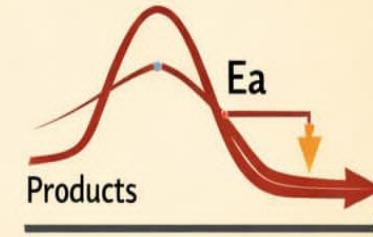
Influence on Reactivity

Affects the rate of reaction and equilibrium.

Faster Reaction



Slower Reaction



Hammett Equation

$$\sigma = \log\left(\frac{k_x}{k_h}\right)$$

σ = Hammett Constant

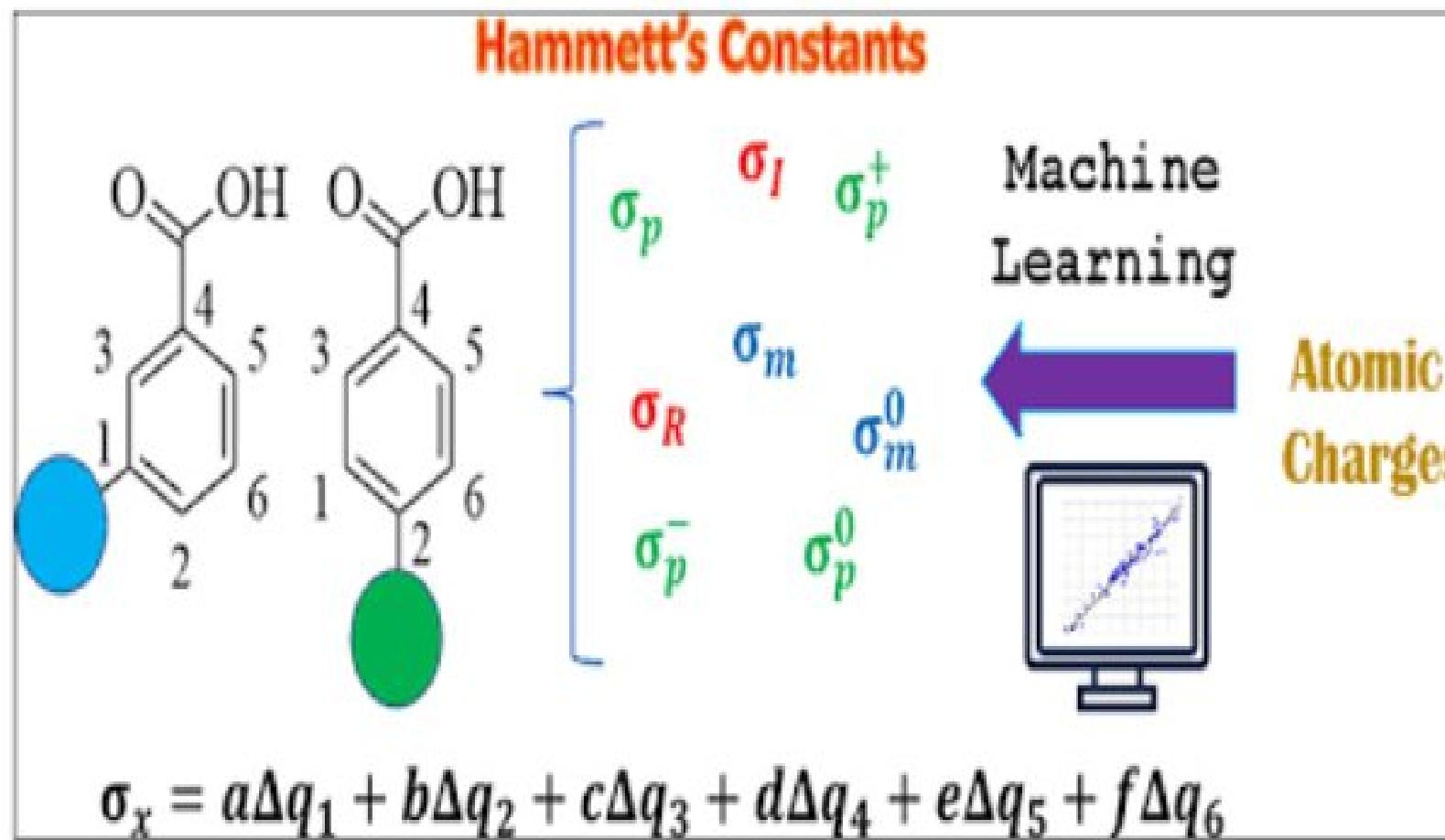
k_x = Rate constant with substituent

k_h = Rate constant for hydrogen

Helps predict reaction behavior!



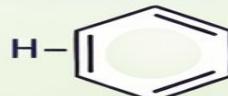
CONT...



TYPES OF HAMMETT CONSTANT

σ^0 Standard Constant

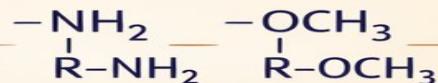
Reference constant for unsubstituted benzene



σ^+ Electron-Donating Constant

For electron-donating groups

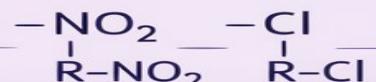
Examples: $-\text{NH}_2$, $-\text{OCH}_3$



σ^- Electron-Withdrawing Constant

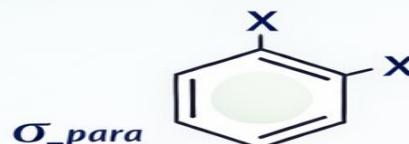
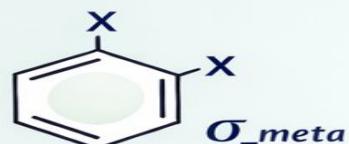
For electron-withdrawing groups

Examples: $-\text{NO}_2$, $-\text{Cl}$



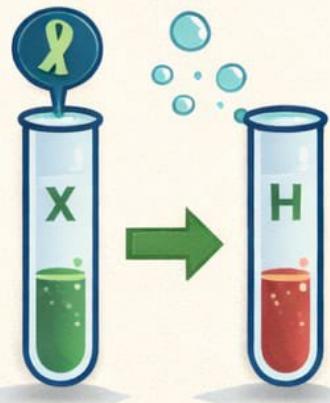
σ_{meta} and σ_{para}

Constants for meta and para positions



HAMMETT EQUATION

$$\sigma = \log \left(\frac{k_x}{k_H} \right)$$



σ = Hammett Constant

k_x = Rate constant with substituent

k_H = Rate constant for hydrogen



MODIFIED HAMMETT EQUATION

$$\sigma = \sigma_p + \rho \sigma_m = \log \left(\frac{K_x}{K_H} \right)$$

σ = Hammett Constant

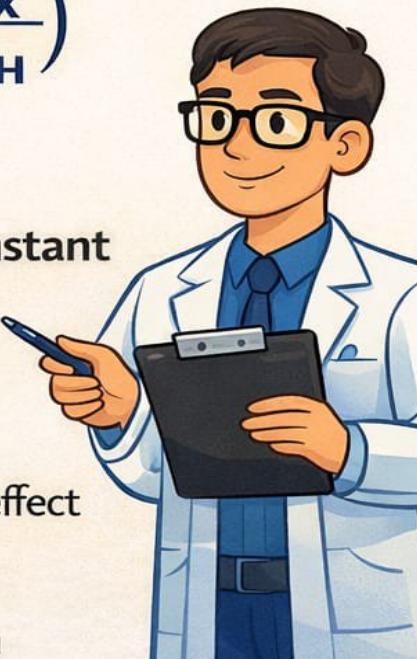
σ_p = Hammett constant
for para substitution

ρ = Reaction constant
indicating substituent effect

σ_m = Hammett constant
for meta substitution

$$\begin{aligned}
 \sigma &= \sigma_p + \rho \sigma_m = \log \left(\frac{K_x}{K_H} \right) \\
 &= 0.42 + 2.30 \log \left(\frac{K_x}{K_H} \right)
 \end{aligned}$$

- **σ** = Total Hammett Constant
- **σ_p** = Hammett constant
for para substitution
- **ρ** = Reaction constant
indicating substituent effect
- **σ_m** = Hammett constant
for meta substitution



ELECTRONIC EFFECT REPRESENT OF HAMMETT CONSTANT

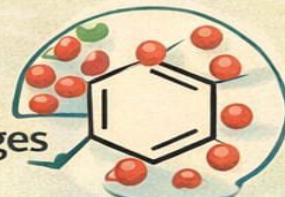
Hammett Constant (σ) measures the electronic effects of substituents on a benzene ring.

Electron-Donating Effects



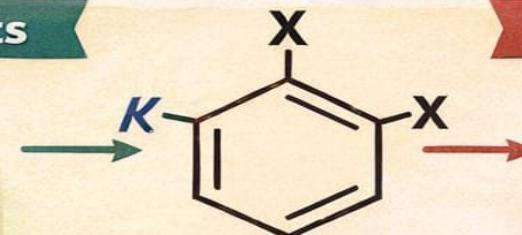
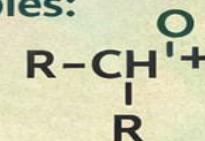
Increase electron density on the ring

- Stabilize positive charges



Common Examples:

- $-\text{CH}_3$
- $-\text{OCH}_3$
- $-\text{NH}_2$

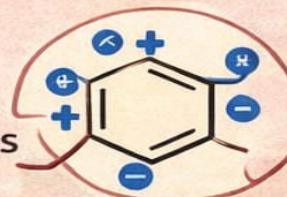


Electron-Withdrawing Effects



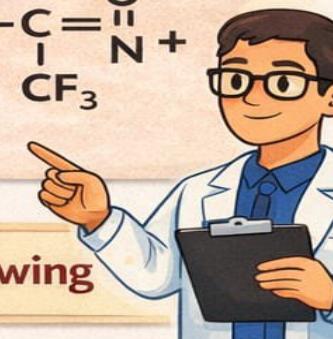
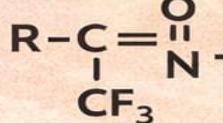
Decrease electron density on the ring

- Stabilize negative charges



Common Examples:

- $-\text{NO}_2$
- $-\text{CN}$
- $-\text{CF}_3$



$\uparrow \sigma$ for Electron-Donating Groups $\sigma < 0 \leftrightarrow \sigma > 0$ for Electron-Withdrawing

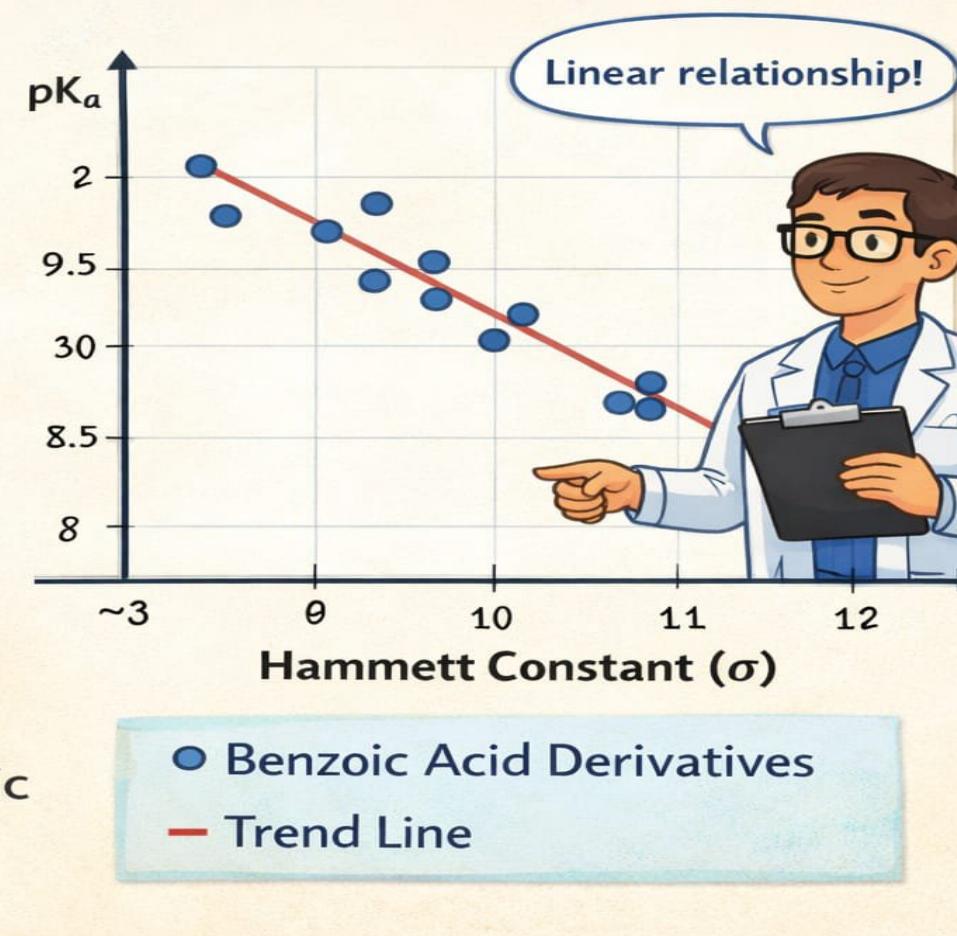
CORRELATION OF HAMMETT CONSTANT WITH pK_a



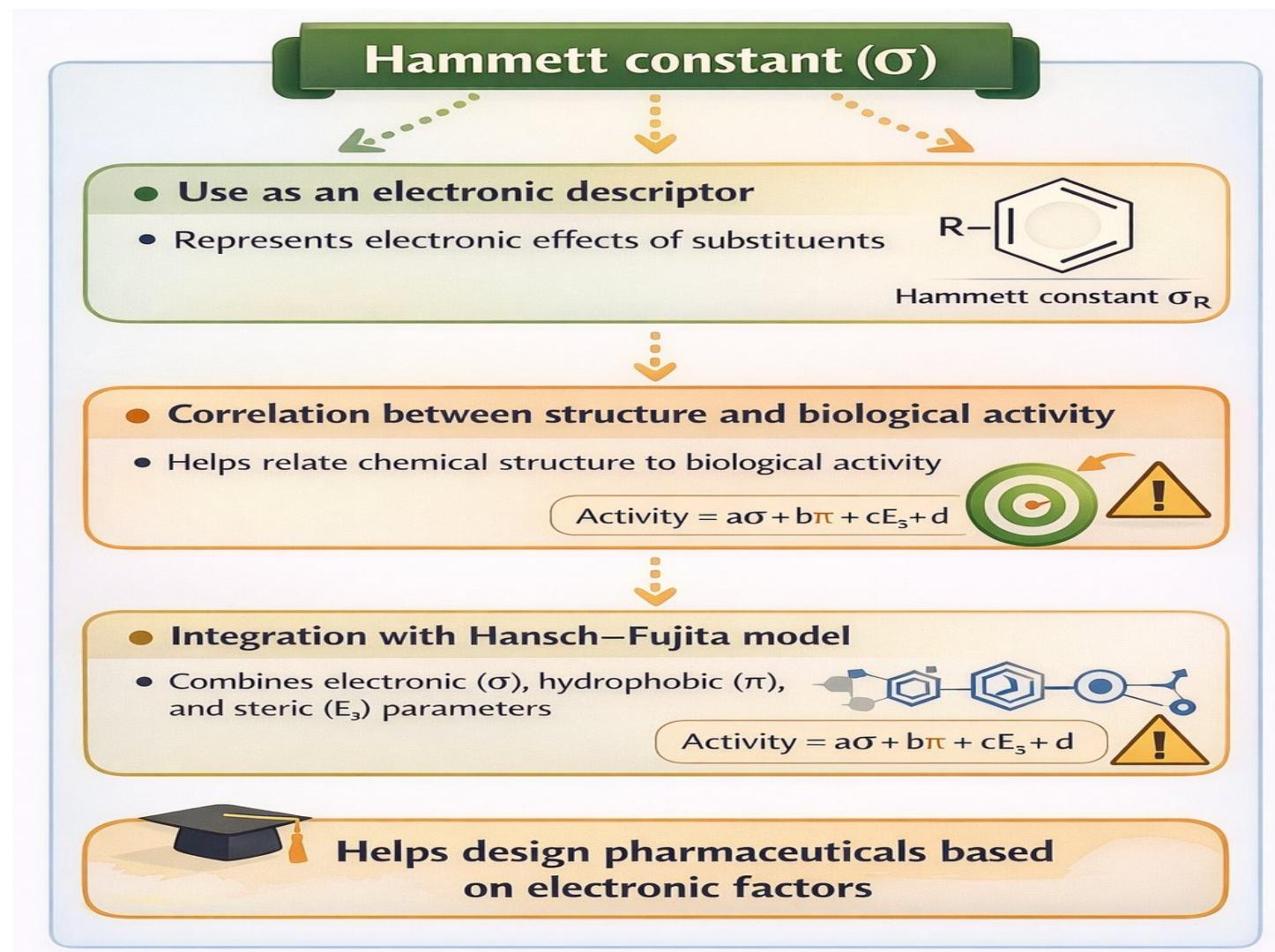
Hammett Constant (σ) relates to the acid dissociation constant (pK_a) of substituted benzoic acids.

$$pK_a(X) = pK_a(H) + \sigma \rho$$

- $pK_a(X) = pK_a$ of substituted benzoic acid
- $pK_a(H) = pK_a$ of unsubstituted benzoic acid
- ρ = sensitivity constant of the reaction



HAMMETT CONSTANT IN QSAR :



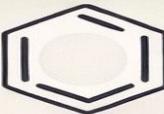
HAMMETT SUBSTITUENTS CONSTANT

Substituent	σ <i>para</i>	σ <i>meta</i>	σ ⁺ *	σ ⁻ *
$\text{N}\equiv\text{N}^{\oplus}$	1.91	1.76	—	3.43
$(\text{CH}_3)_3\text{N}^{\oplus}$	0.82	0.88	0.41	0.77
NO_2	0.78	0.71	0.79	1.27
$\text{C}\equiv\text{N}$	0.66	0.56	0.66	1.00
CF_3	0.54	0.43	0.61	0.65
CO_2H	0.45	0.37	0.42	0.77
$\text{CH}=\text{O}$	0.42	0.35	0.73	1.03
Cl	0.23	0.39	0.15	0.25
Br	0.23	0.37	0.11	0.19
$\text{C}\equiv\text{CH}$	0.23	0.21	0.18	0.53
I	0.18	0.35	0.14	0.27

LIMITATIONS OF HAMMETT CONSTANT

Limited to Aromatic Systems

- Mainly applicable to aromatic compounds
- Not suitable for aliphatic or non-aromatic molecules



Hammett constant σ_R

Ignores Steric and Hydrophobic Effects

- Does not account for steric hindrance of bulky groups
- Overlooks hydrophobic (lipophilic) interactions



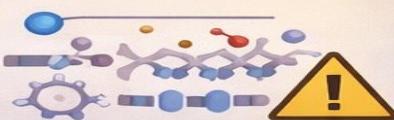
Limited Accuracy for Complex Biological Systems

- Biological targets have complex environments
- σ alone may not predict real-world biological activity

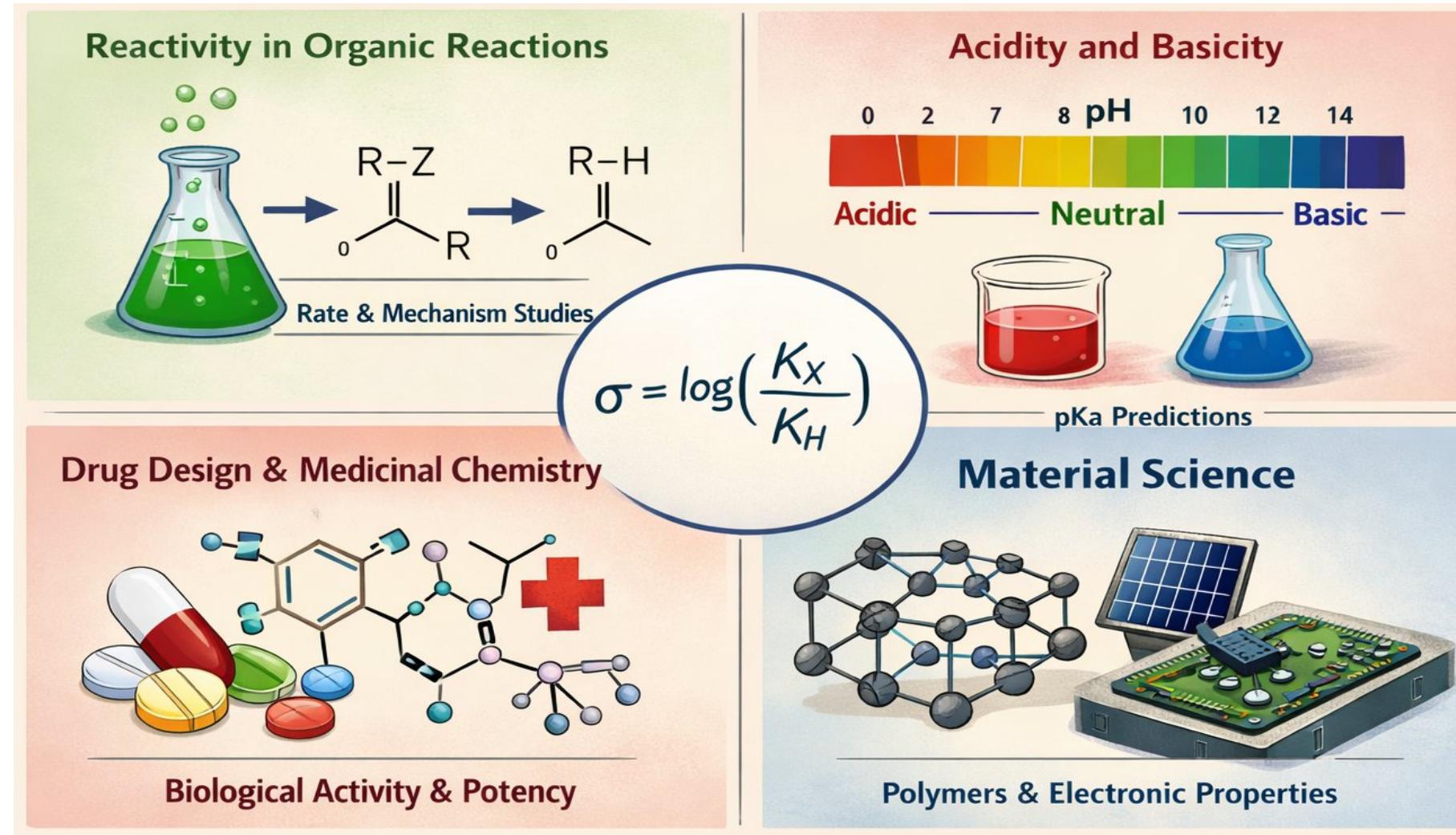


- Biological targets have complex environments
- σ alone may not predict real-world biological activity

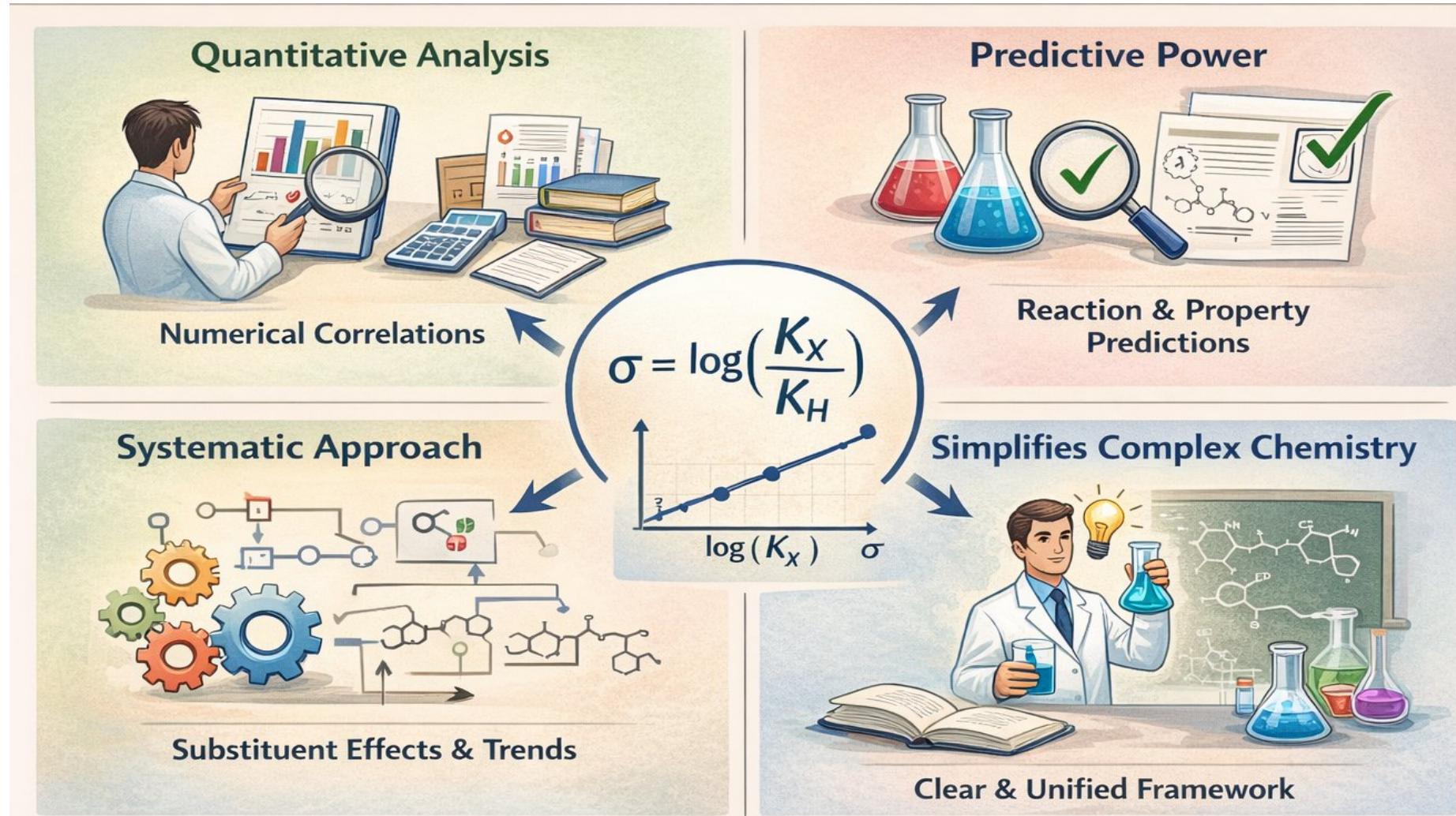
$$\text{Activity} = a\sigma + b\pi + cE_3 + d$$



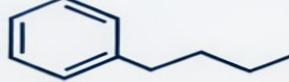
APPLICATIONS OF HAMMETT CONSTANT

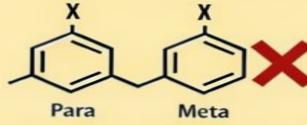


ADVANTAGES OF HAMMETT CONSTANT



DISADVANTAGES OF HAMMETT CONSTANT

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Applicable Mainly to Aromatic Systems
Not reliable for aliphatic or non-aromatic systems.
- 

Limited to Para and Meta Positions
Fails for ortho substituents.
- 

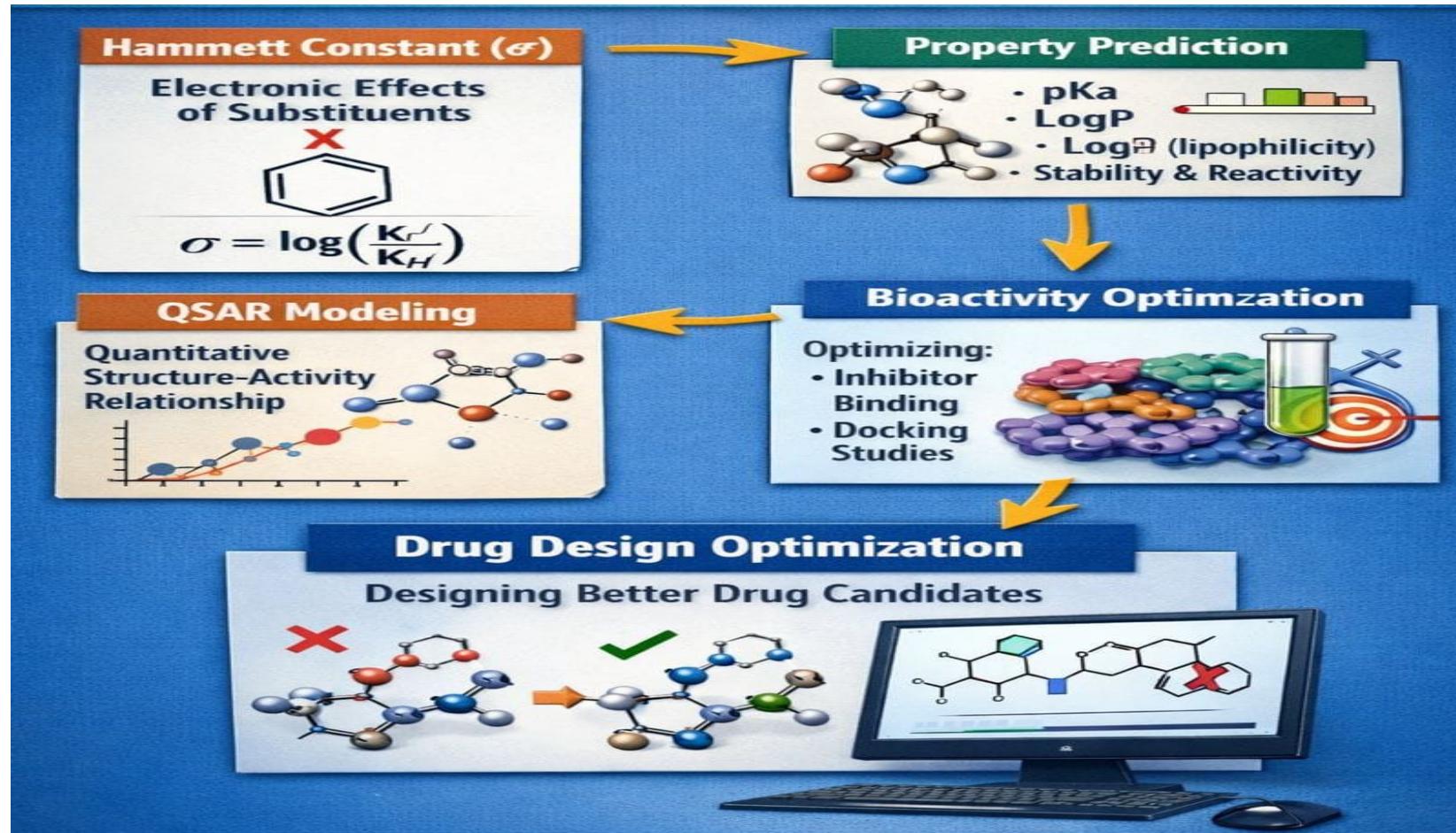
Ignores Steric Effects
Doesn't consider steric hindrance.
- 

Solvent Dependence
Results vary with solvent changes.
- 

Not Suitable for All Mechanisms
Fails if the reaction mechanism differs.
- 

Poor Applicability to Biological Systems
Doesn't work well in complex biological environments.

ROLE OF HAMMETT CONSTANT IN CADD



ASSESSMENTS

1) Which of the following is a correct form of the Hammett equation?

- A) $\log(k/k_0) = \rho\sigma$
- B) $pK_a = \log(C)$
- C) $\Delta G = -RT \ln K$
- D) $\log P = \Sigma \pi$

2) In drug design, the Hammett constant is often correlated with:

- A) Drug solubility only
- B) Drug reactivity, metabolism, or binding affinity
- C) Molecular weight
- D) Drug color

3) A substituent with a positive σ value is generally:

- A) Electron-donating
- B) Electron-withdrawing
- C) Neutral
- D) Non-polar

4) The Hammett constant (σ) is primarily used to describe:

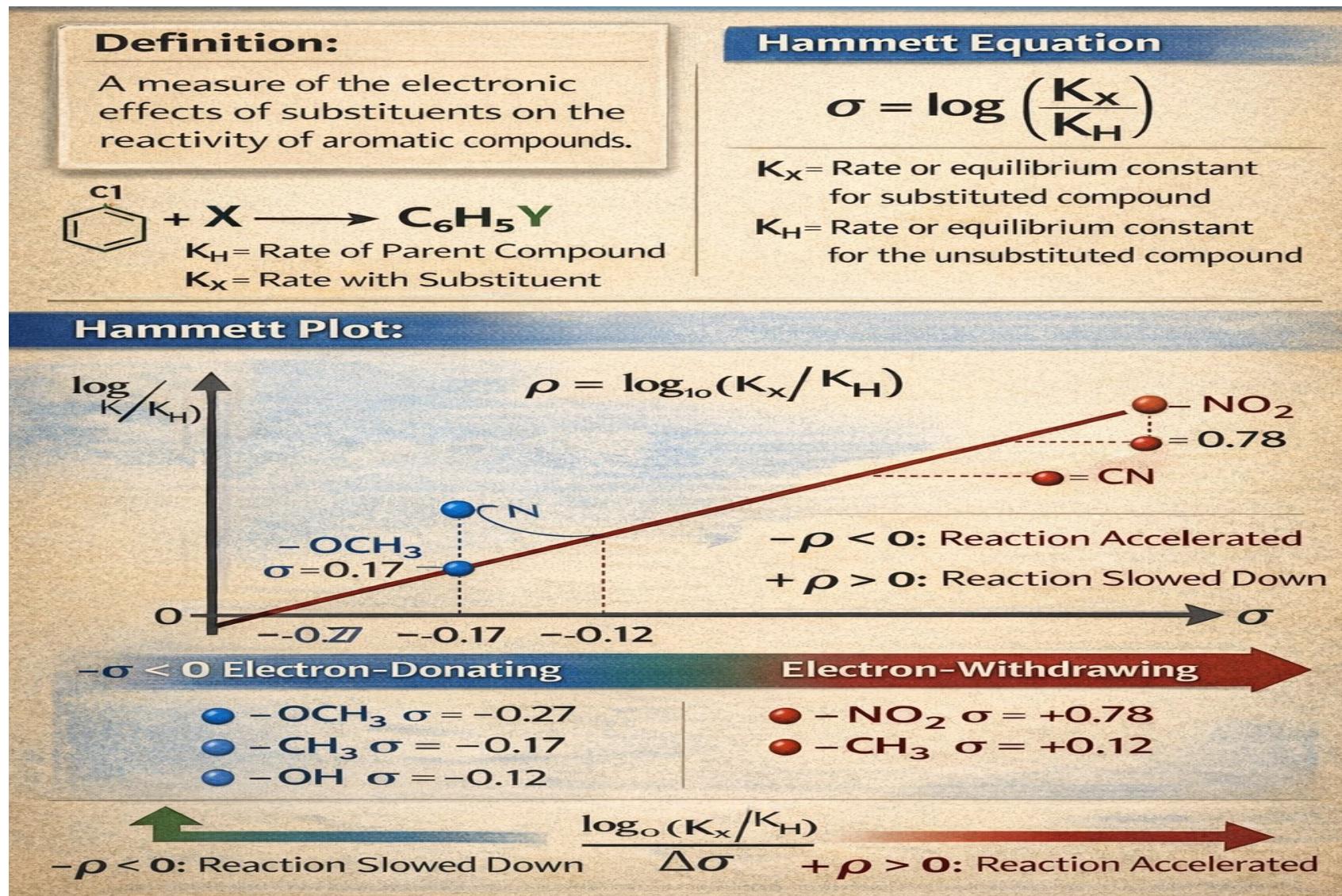
- A) Lipophilicity of a molecule
- B) Electronic effects of substituents on aromatic rings
- C) Molecular weight
- D) Hydrogen bonding potential

5) True / False:

A negative Hammett constant ($\sigma < 0$) indicates an electron-donating substitu



SUMMARY



REFERENCE

- 1)** Hansch, C. & Leo, A. — Substituent Constants for Correlation Analysis in Chemistry and Biology
- 2)** Hansch, C. (1971). “Quantitative Structure-Activity Relationships in Drug Design” — in Drug Design, Volume 1 (E.J. Ariëns, Ed.)
- 3)** Martin, Y.C. — Quantitative Drug Design: A Critical Introduction

