

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)

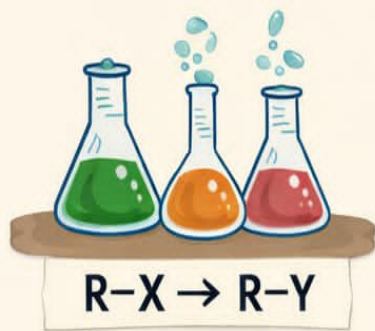
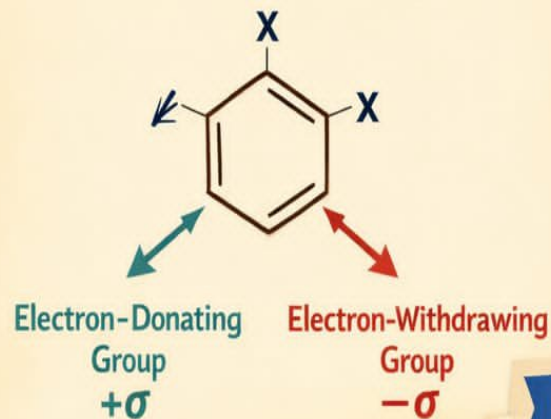
VIII SEM / IV YEAR

TOPIC : HAMMETT CONSTANT

INTRODUCTION TO HAMMETT CONSTANT

What is the Hammett Constant (σ)?

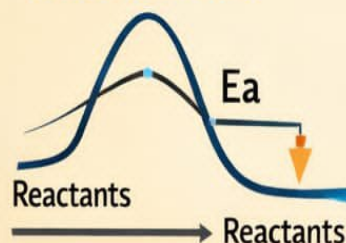
A measure of the electronic effects of substituents on a benzene ring.



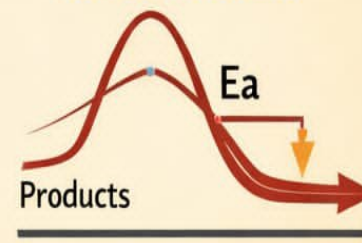
Influence on Reactivity

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

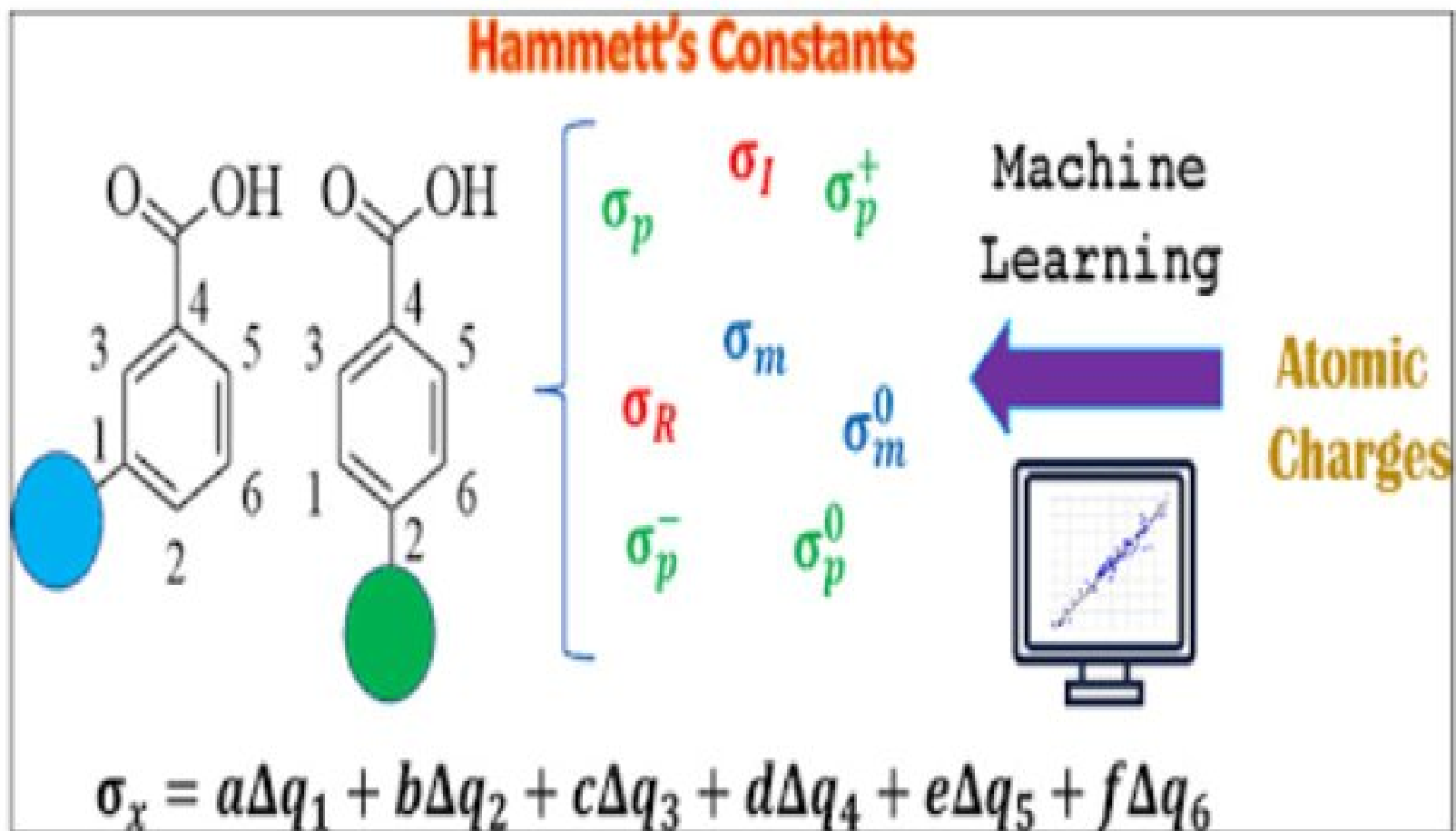
k_X = Rate constant with substituent

k_H = Rate constant for hydrogen

Helps predict reaction behavior!



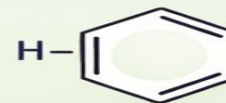
CONT...



TYPES OF HAMMETT CONSTANT

σ^0 Standard Constant

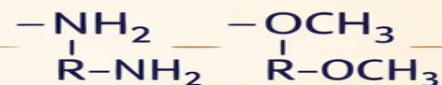
Reference constant for unsubstituted benzene



σ^+ Electron-Donating Constant

For electron-donating groups

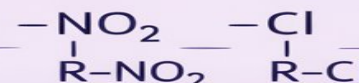
Examples: $-\text{NH}_2$, $-\text{OCH}_3$



σ^- Electron-Withdrawing Constant

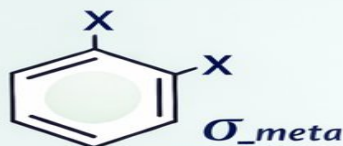
For electron-withdrawing groups

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



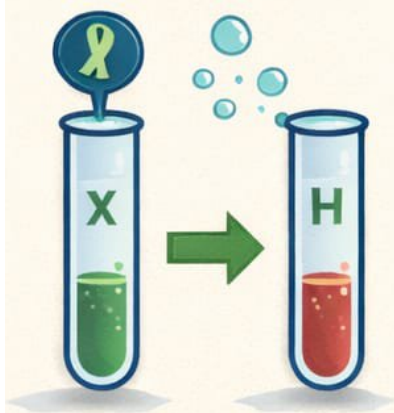
σ_{meta} and σ_{para}

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

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

σ = Hammett Constant

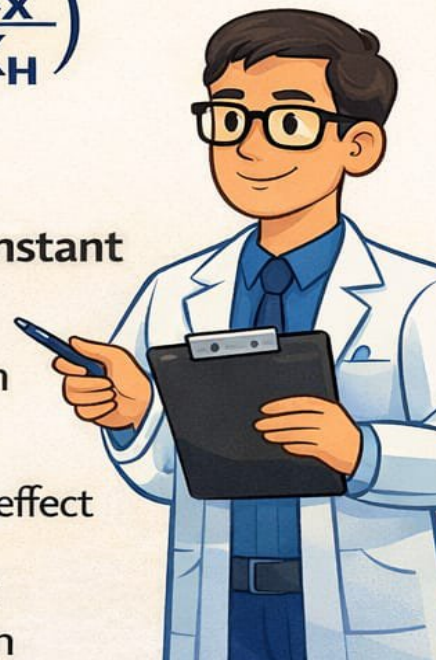
σ_p = Hammett constant
for para substitution

ρ = Reaction constant
indicating substituent effect

σ_m = Hammett constant
for meta substitution

$$\left(\sigma_p + \rho \sigma_m = \rho \right) \log \left(\frac{K_X}{K_H} \right) \\ = 0.42 + 2.30 \log \left(\frac{K_X}{K_H} \right)$$

- 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

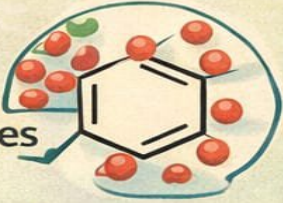
$\uparrow +\sigma$

Increase electron density on the ring

- Stabilize positive charges

Common Examples:

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


 $\text{R}-\text{CH}^+\text{R}$

$\sigma < 0 \rightleftharpoons \sigma > 0$

Electron-Withdrawing Effects

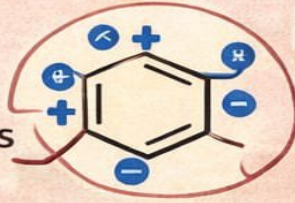
$-\sigma \downarrow$

Decrease electron density on the ring

- Stabilize negative charges

Common Examples:

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


 $\text{R}-\text{C}(=\text{O})\text{N}^+\text{CF}_3$

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

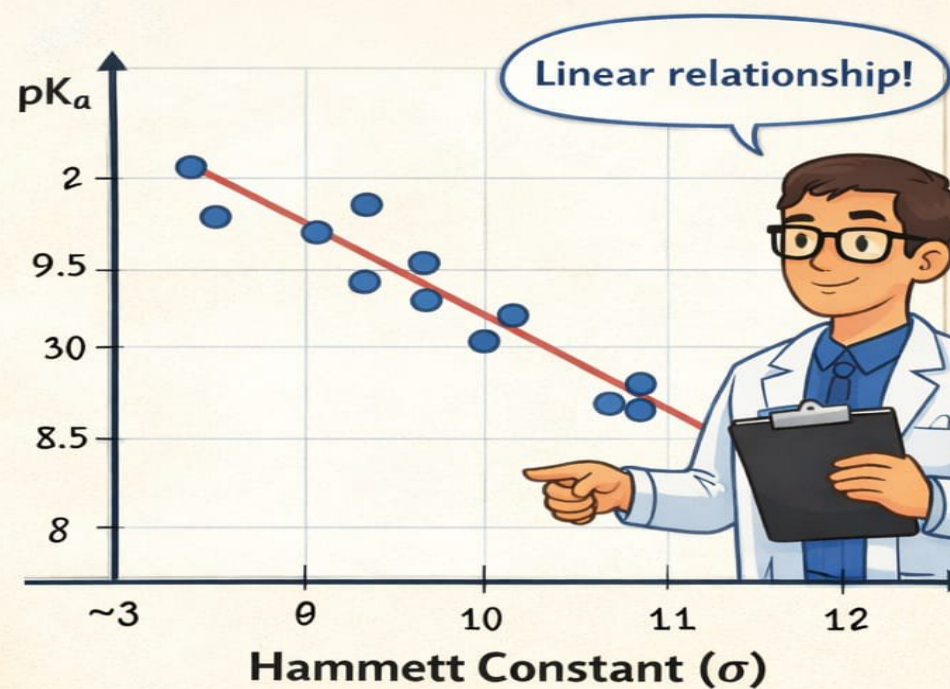
CORRELATION OF HAMMETT CONSTANT WITH pK_a



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

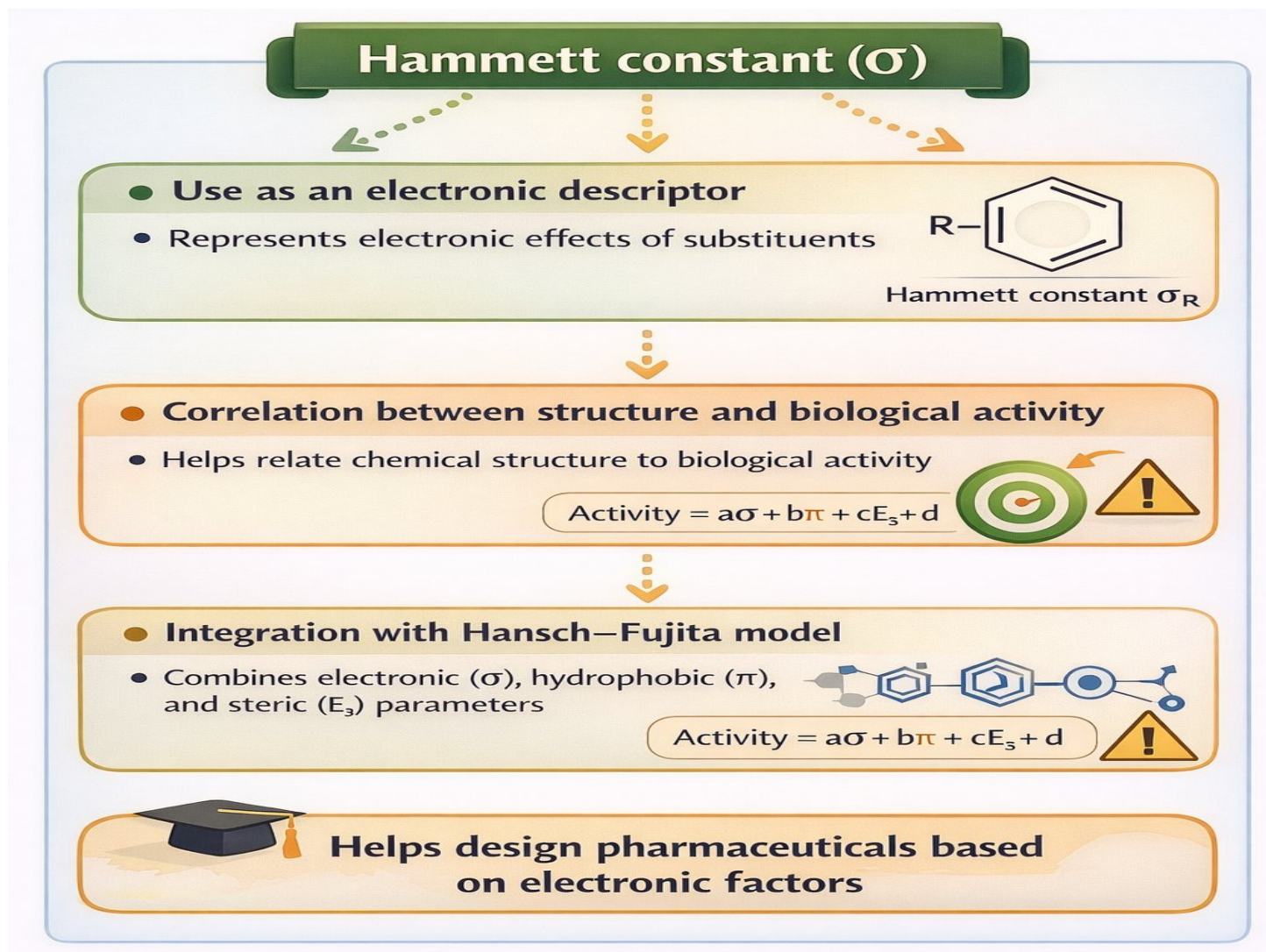
$$pK_a(X) = pK_a(H) + \sigma\rho$$

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



- Benzoic Acid Derivatives
- Trend Line

HAMMETT CONSTANT IN QSAR :



HAMMETT SUBSTITUENTS CONSTANT

Substituent	σ para	σ meta	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



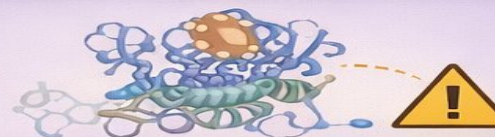
Ignores Steric and Hydrophobic Effects

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



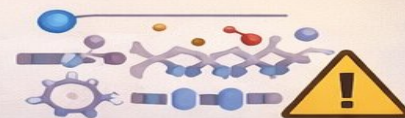
Limited Accuracy for Complex Biological Systems

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

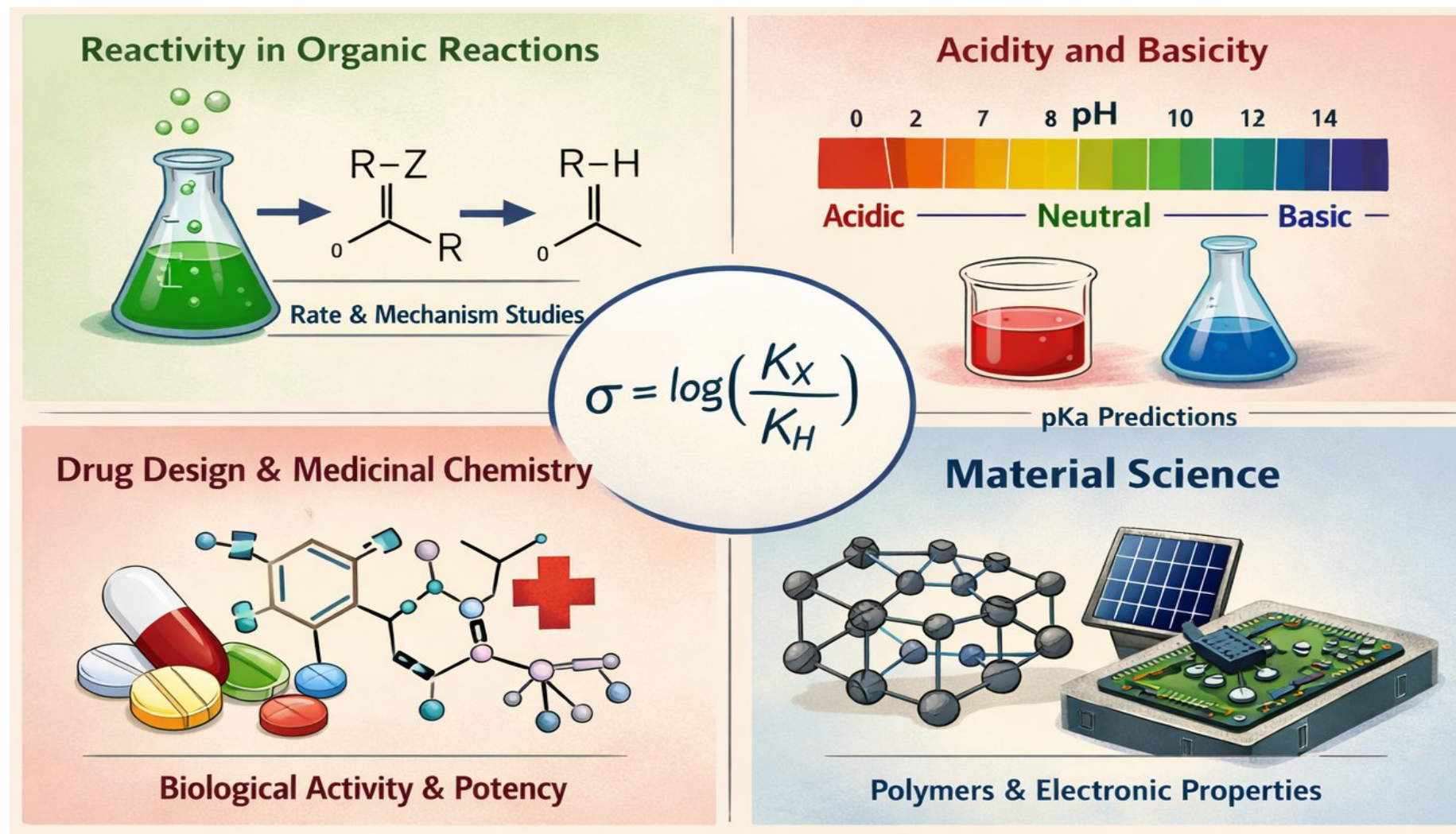


$$\text{Activity} = a\sigma + b\pi + cE_s + d$$

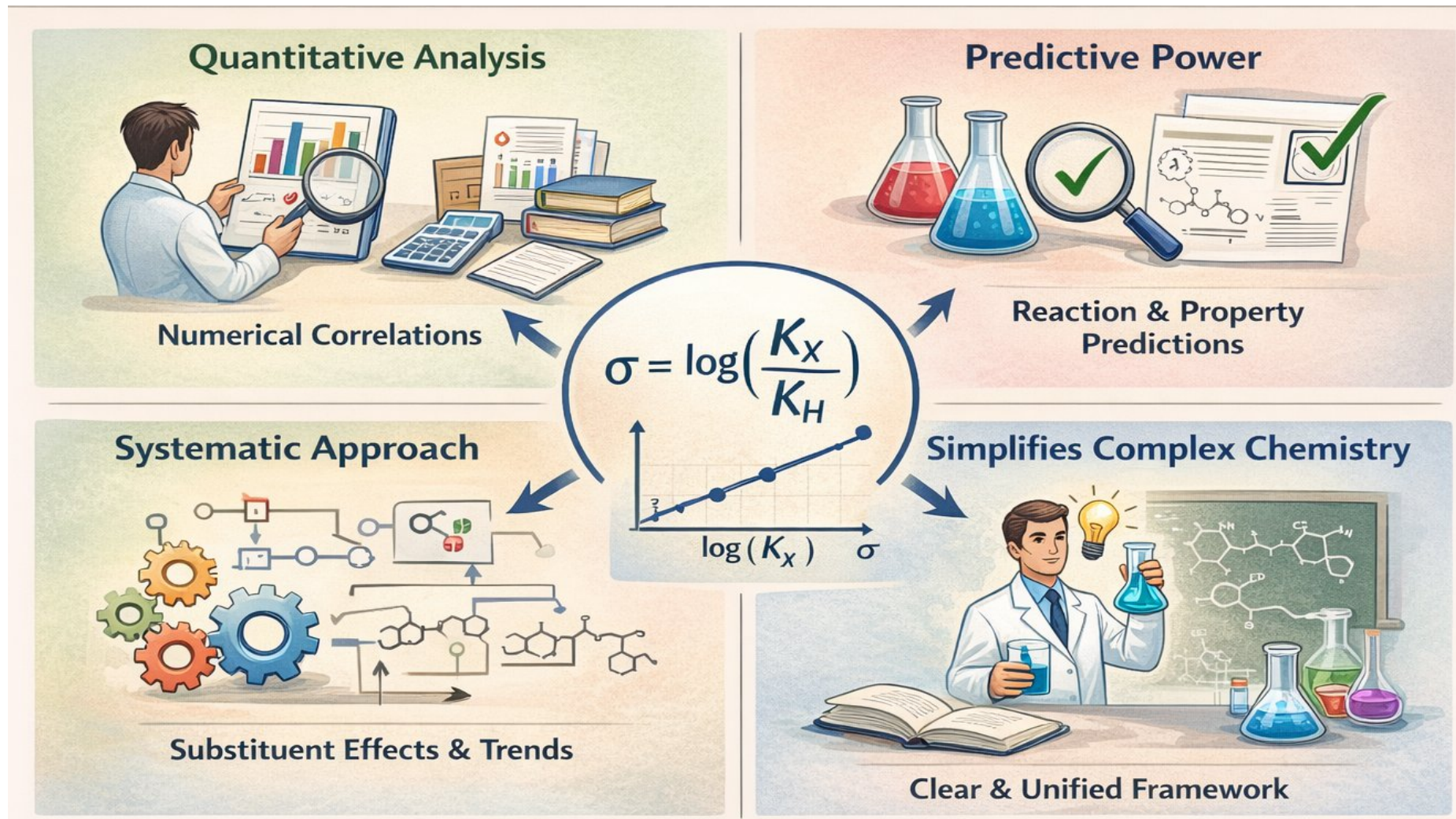
- Biological targets have complex environments
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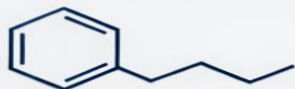
APPLICATIONS OF HAMMETT CONSTANT



ADVANTAGES OF HAMMETT CONSTANT

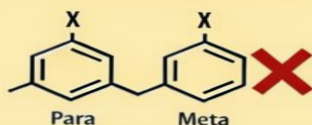


DISADVANTAGES OF HAMMETT CONSTANT



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

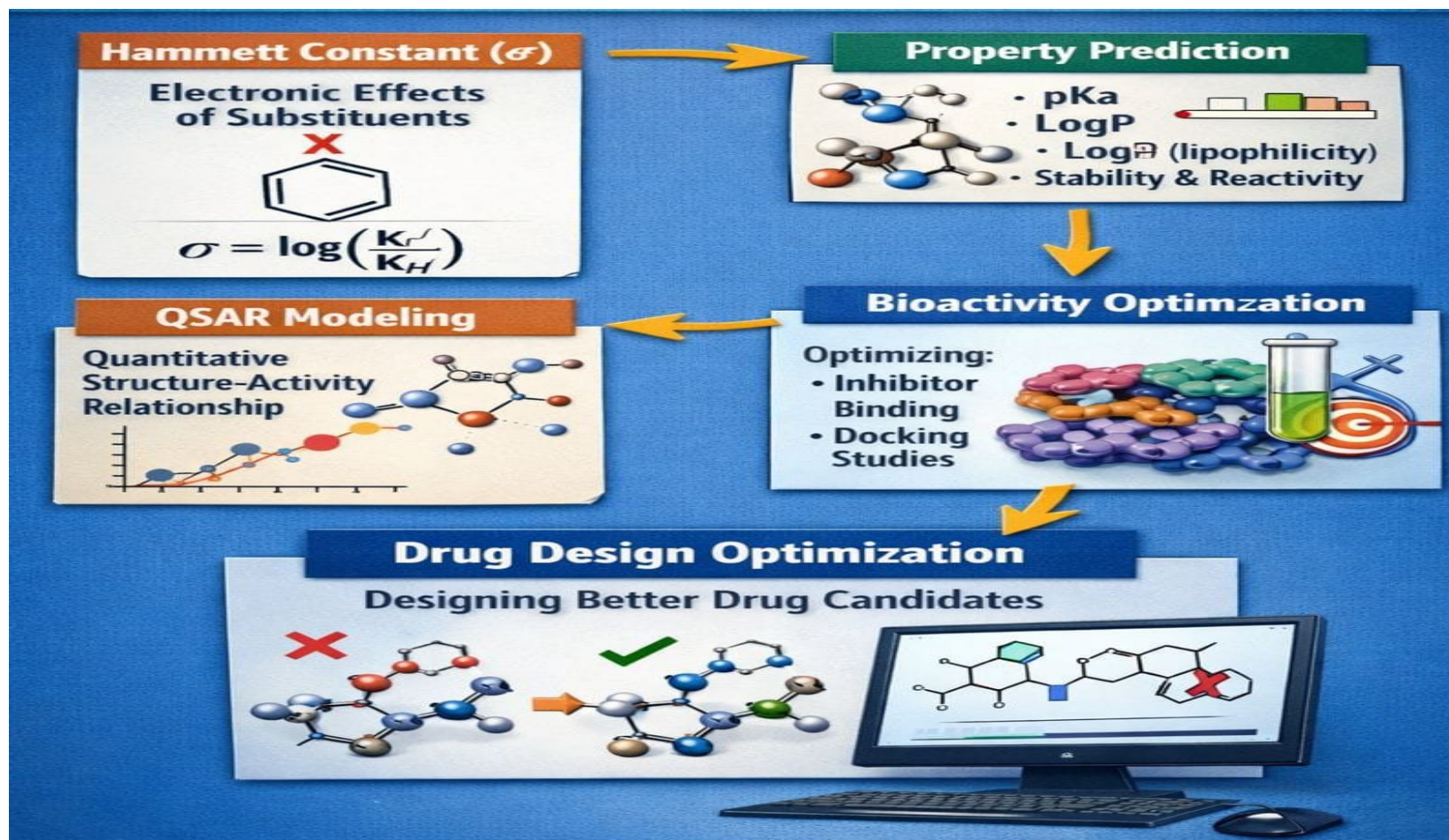
Fails if the reaction mechanism differs.



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:

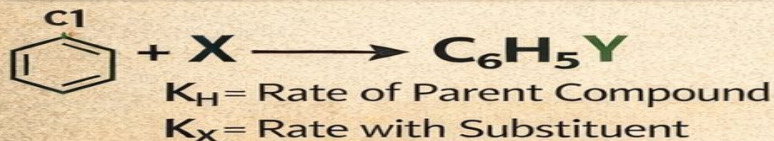
A negative Hammett constant ($\sigma < 0$) indicates an electron-donating substituent



SUMMARY

Definition:

A measure of the electronic effects of substituents on the reactivity of aromatic compounds.



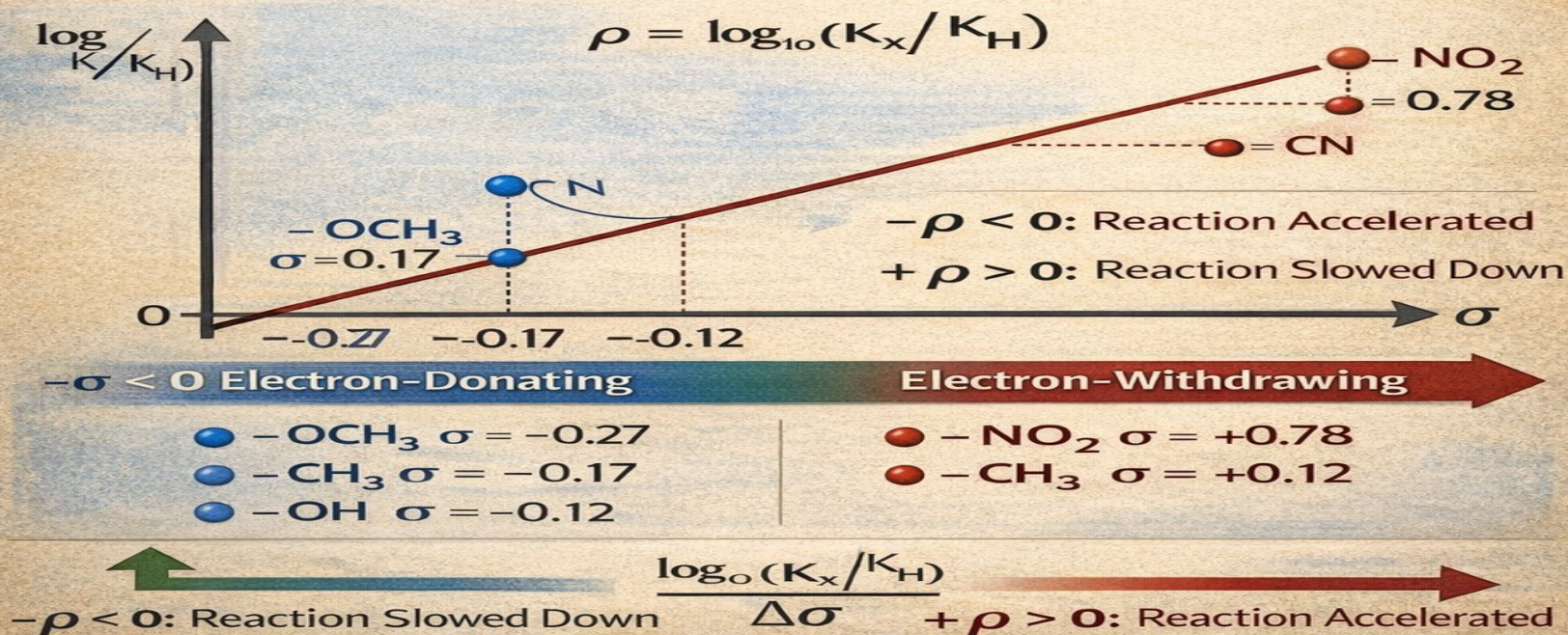
Hammett Equation

$$\sigma = \log \left(\frac{K_X}{K_H} \right)$$

K_X = Rate or equilibrium constant for substituted compound

K_H = Rate or equilibrium constant for the unsubstituted compound

Hammett Plot:



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

