Medicinal chemistry-III
QSAR

DEPARTMENT OF PHARMACY

Topic : Hammett equation

and

Taft’s steric effects on QSAR

Quantitative Structure Activity Relationships

- Identification of new drug molecule to design
- QSAR – Quantify relationship between chemical structure of a drug and its biological activity.

Characteristics of QSAR:

1) Mathematical relationship b/w Biological activity of molecular system & its Geometric and chemical characteristics.
2) Synthesis, Time and tests
3) Billion molecules synthesised around one or more molecule reach clinical trails.
4) Discovery of new Chemical Entity (treatment of various diseases)
5) Biological activity = function (Physiochemical Parameters)

Steps involved in QSAR (bullet points to remember) :

- Selection of biological active series (to check biological activity)
  Eg: Anticancer, Anti inflammatory
- calculation of various physiochemical parameters
- Found correlation b/w physiochemical properties & biological activity by QSAR method.
- Getting Equations with constant values
- Design of compounds based upon QSAR equation
- Predicting the activity of designed compounds
- Synthesis of the compounds.

Physio chemical parameters

1) Lipophilic parameters : partition co-efficient, Π- substitution constant

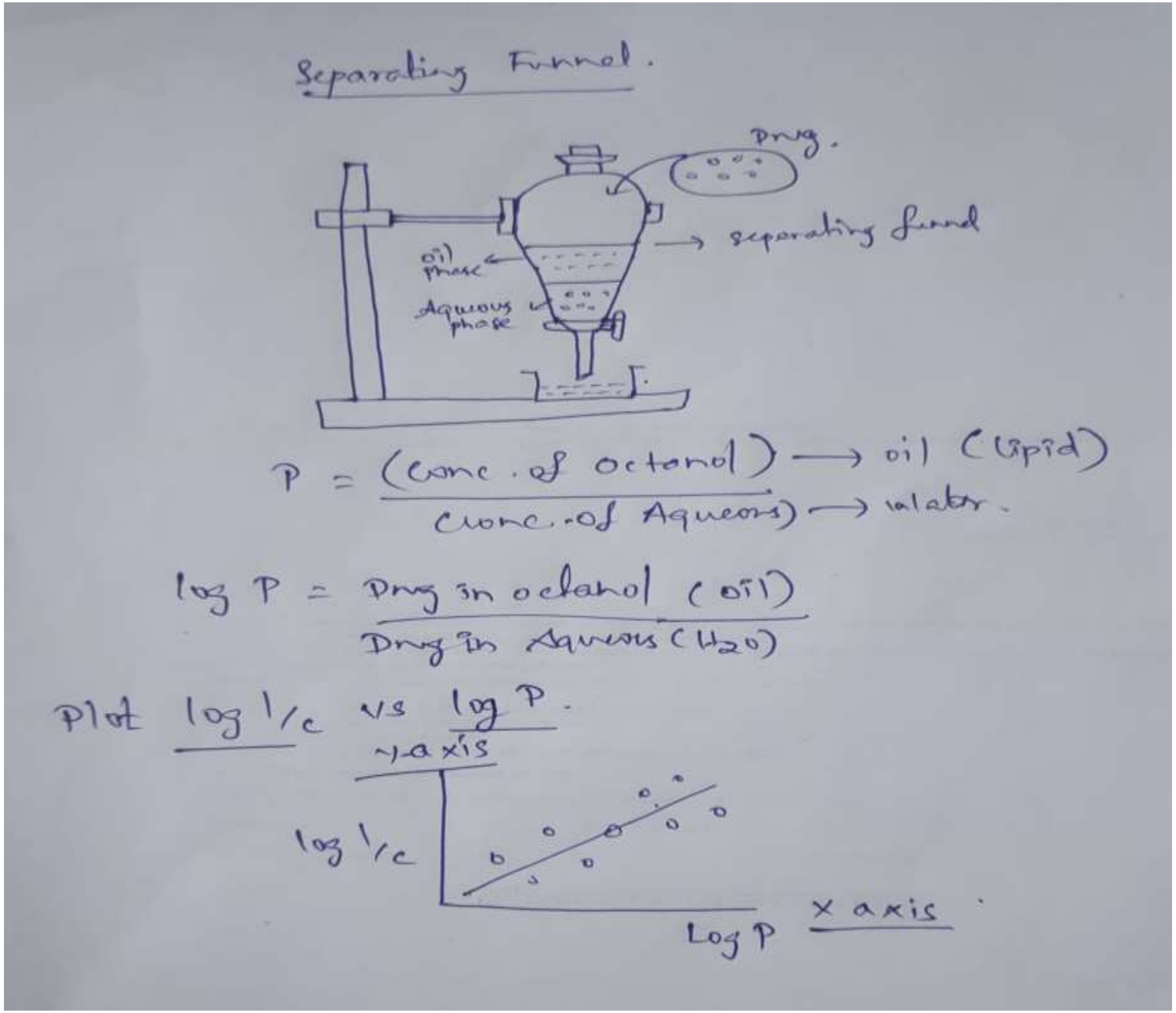
2) Electronic parameters : Hammet constant, Dipole moment

3) Steric parameters : Taft’s constent, Molar reactivity , verloop steric parameter

Physio chemical parameters (relevant to biological activity)

- solubility
- log P
- Protein binding
- Partition co-efficient

Partition co-efficient



Separating Funnel.

$$P = \frac{(\text{Conc. of Octanol})}{(\text{Conc. of Aqueous})}\quad \begin{matrix}\longrightarrow \text{oil (Lipid)}\\ \longrightarrow \text{water.}\end{matrix}$$

$$\log P = \frac{\text{Drug in octanol (oil)}}{\text{Drug in Aqueous } (H_2O)}$$

Plot log 1/c vs log P.

Key Points

Hydrophobicity	Hydrophobic compounds have high P value and Hydrophilic compounds have low P value Hydrophobicity constant (Π)- Positive value- hydrophobic; negative value- hydrophilic
Electronic effects	Hammett substitution constant (σ) Aromatic compounds- electron withdrawing groups- positive Aromatic compounds- electron donating groups- negative Both resonance and inductive effect is considered Cannot be measured for ortho substituents
Steric factors	Taft’s steric factor (E_s) Molar refractivity Verloop steric parameter

Electronic Parameters

- Electronic effects of various substituents will clearly have an effect on a drug's ionization or polarity
- Effect on how easily a drug can pass through cell membranes or how strongly it can bind to a receptor
- Measure used is known as the Hammett substitution constant which is given the symbol σ
- Measure of the electron withdrawing or electron donating ability of a substituent and has been determined by measuring the dissociation of a series of substituted benzoic acids compared to the dissociation of benzoic acid itself

The Hammett Equation

The Substituent Constant, σ

Polar reactions are strongly affected by substituents on the equilibrium constants and rates of reactions of organic molecules and ions.

1937, Louis P. Hammett suggested that the effects of *meta* and *para* substituents on the ionization constants of benzoic acids could be predictors of the electronic influences of substituents in a variety of reactions.

Why?

(1) A large number of substituted benzoic acids are readily available

(2) Ionization constants are easily determined

(3) Substituents on aromatic rings are held at fixed distances from the points of reaction.

The Hammett Equation

The Substituent Constant, σ

Why not *ortho* substituents?

They might influence reactions by steric inhibition of access to the reaction center, or by steric inhibition of resonance, or by hydrogen bonding effects.

Definition of a substituent constant, σ

$$\sigma = \log (K/K_H) \quad \text{in } H_2O \text{ at } 25\ ^{o}C$$

K = acidity constant of substituted benzoic acid

K_H = acidity constant of benzoic acid

$$\sigma = \log K - \log K_H = pK_H - pK$$

The Hammett Equation

The Substituent Constant, σ

σ meta and σ para values indicates that they represent a measure of the electron-donating and electron-attracting powers of the substituents.

(1) Strongly electron-attracting groups such as N_2^+, NO_2, and CF_3 groups have large positive σ values
- increase of the acidity constants of benzoic acids

(2) Strongly electron-donating groups such as NH_2 and OH groups have large negative σ values
- decrease of the acidity constants of benzoic acids

The Hammett Equation

The Substituent Constant, σ

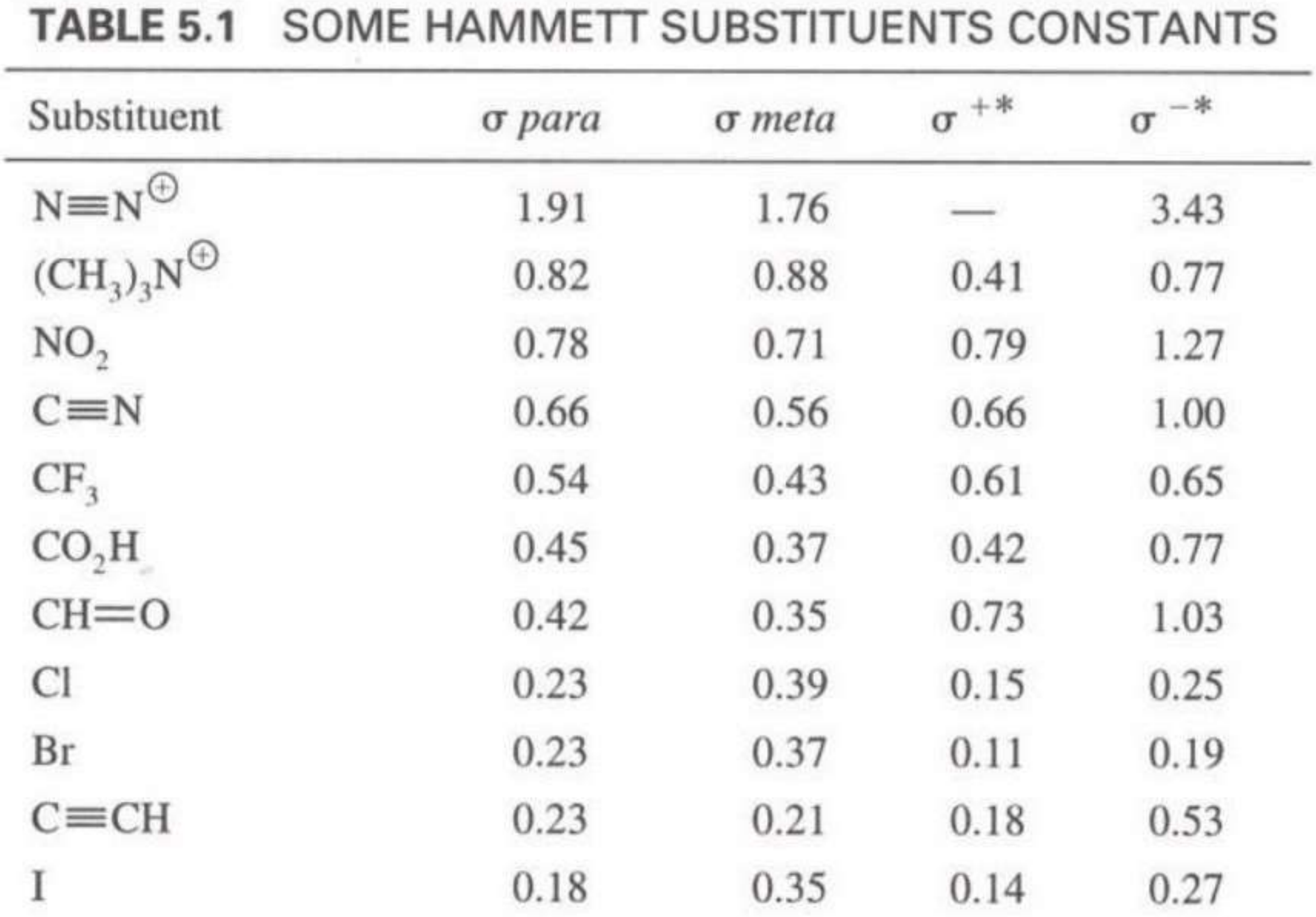
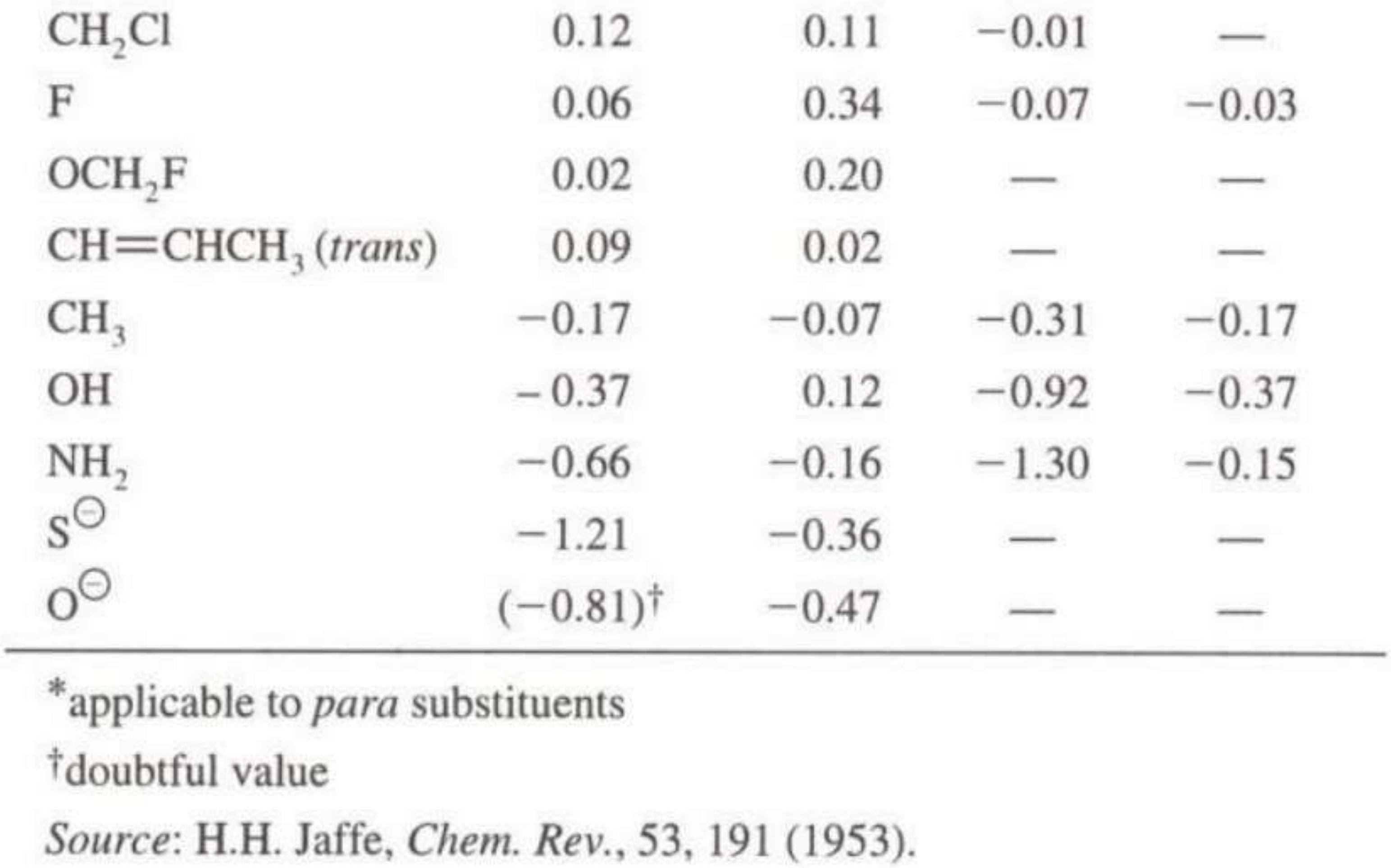


TABLE 5.1 SOME HAMMETT SUBSTITUENTS CONSTANTS

Substituent	σ *para*	σ *meta*	σ^{+*}	σ^{-*}
$N\equiv N^{\oplus}$	1.91	1.76	—	3.43
$(CH_3)_3N^{\oplus}$	0.82	0.88	0.41	0.77
NO_2	0.78	0.71	0.79	1.27
$C\equiv N$	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
$CH{=}O$	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
$C\equiv CH$	0.23	0.21	0.18	0.53
I	0.18	0.35	0.14	0.27

The Hammett Equation

The Substituent Constant, σ



CH_2Cl	0.12	0.11	−0.01	—
F	0.06	0.34	−0.07	−0.03
OCH_2F	0.02	0.20	—	—
$CH{=}CHCH_3$ (*trans*)	0.09	0.02	—	—
CH_3	−0.17	−0.07	−0.31	−0.17
OH	−0.37	0.12	−0.92	−0.37
NH_2	−0.66	−0.16	−1.30	−0.15
$S^{\ominus}$	−1.21	−0.36	—	—
$O^{\ominus}$	(−0.81)[†]	−0.47	—	—

[*] applicable to *para* substituents

[†] doubtful value

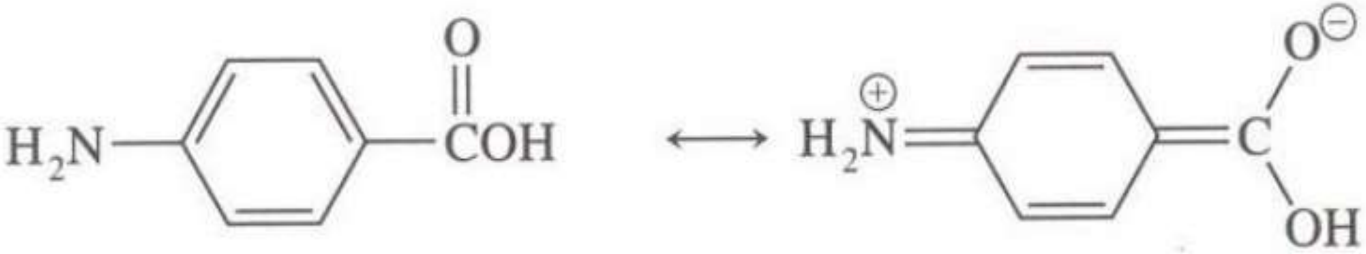
Source: H.H. Jaffe, *Chem. Rev.*, 53, 191 (1953).

The Hammett Equation

The Substituent Constant, σ

Comparison of the effects of the same substituents in *meta* and *para* positions. In the case of NH_2 group, the absolute value of σ_{para} is much larger than that of σ_{meta}.

- Electron-donating ability of the amino group is largely due to resonance effects.
- The para position can directly distribute electrons into the carboxyl group of benzoic acid.
- Carboxyl group is more difficult to become a negatively charged carboxylate anion.
- Low acidity constant



Resonance structures for *p*-aminobenzoic acid

The Hammett Equation

The Substituent Constant, σ

For a few substituents such as the OH and OCH_3 groups, σ_{meta} and σ_{para} have opposite signs.

Why? Two different factors
(1) Inductive effect
(2) Resonance effect

For the OH and OCH_3 groups, the two types of electronic effects work in opposite directions.
para substituents: resonance effect > the inductive effect
meta substituents: resonance effect < the inductive effect

Halogen atoms are poorer electron donors than oxygen atoms and thus σ values have positive signs, but the values are larger in *meta* position than in *para* position.

The Hammett Equation

The Substituent Constant, σ

For σ values for substituents in polysubstitued aromatic Molecules are approximately additive.

(Example)

3-methyl-5-nitrobenzoic acid

$\sigma = (-0.07) + (0.71) = 0.64$

The Hammett Equation

The Reaction Constant, ρ

Hammett diagrams

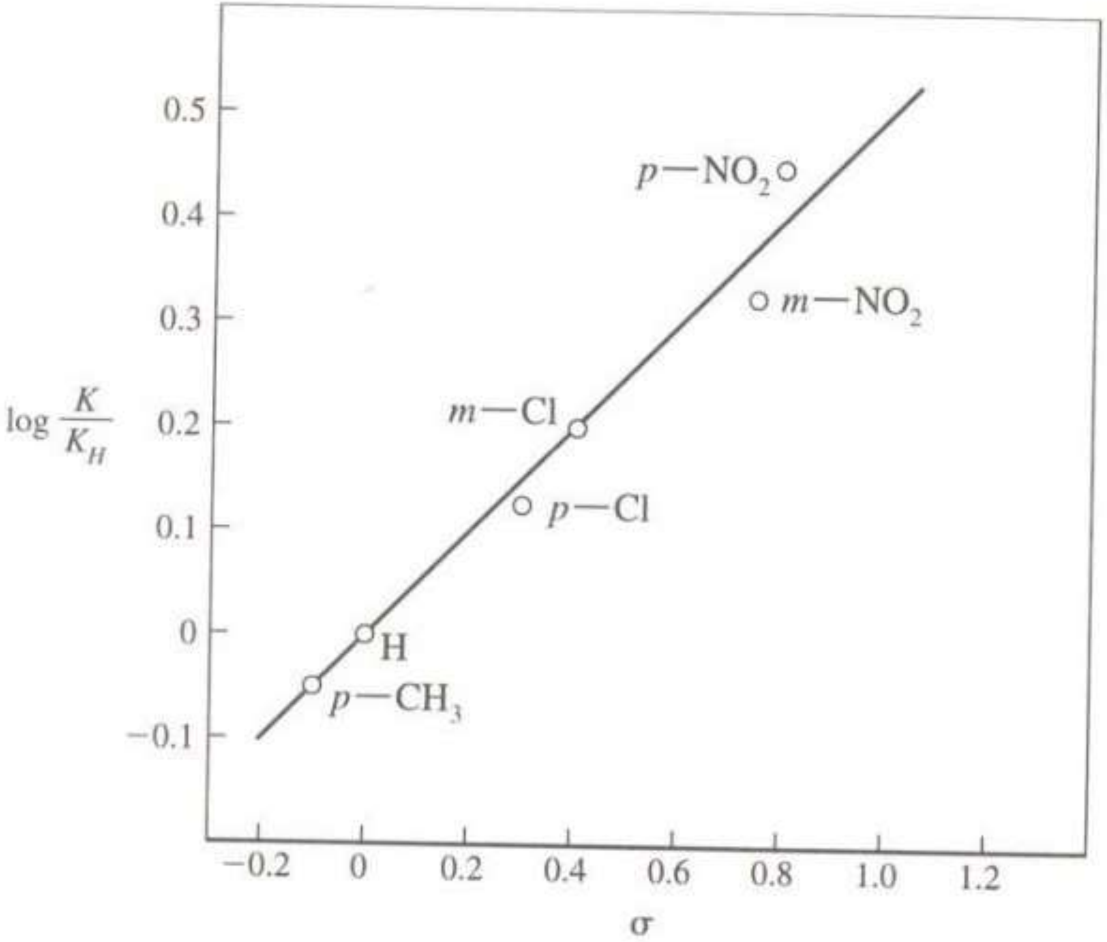


FIGURE 5.1 A Hammett plot for the dissociation constants of phenylacetic acids.

$\log K/K_H$ for phenylacetic acids

Hammett equation

$\log K/K_H = \rho\sigma$

$\log K - \log K_H = \rho\sigma$

ρ = slope of the line (the reaction constant)

The Hammett Equation

The Reaction Constant, ρ

The significance of ρ values

- A reaction with a positive ρ value is assisted by electron-attracting substituents.
- A reaction with a negative ρ value is assisted by electron-donating substituents

(Example)

Ionization of carboxylic acids have positive values of ρ
In contrast, the basicities of carboxylate anions would have negative ρ values

The Hammett Equation

The Reaction Constant, ρ

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The Hammett Equation

The Reaction Constant, ρ

Reaction mechanism and the Hammett equation

It can offer important information about the mechanism of chemical reactions. The sign and magnitude of ρ can be of particular significance.

(Example) The hydrolysis of benzoyl chlorides in water

Several mechanisms can be proposed.

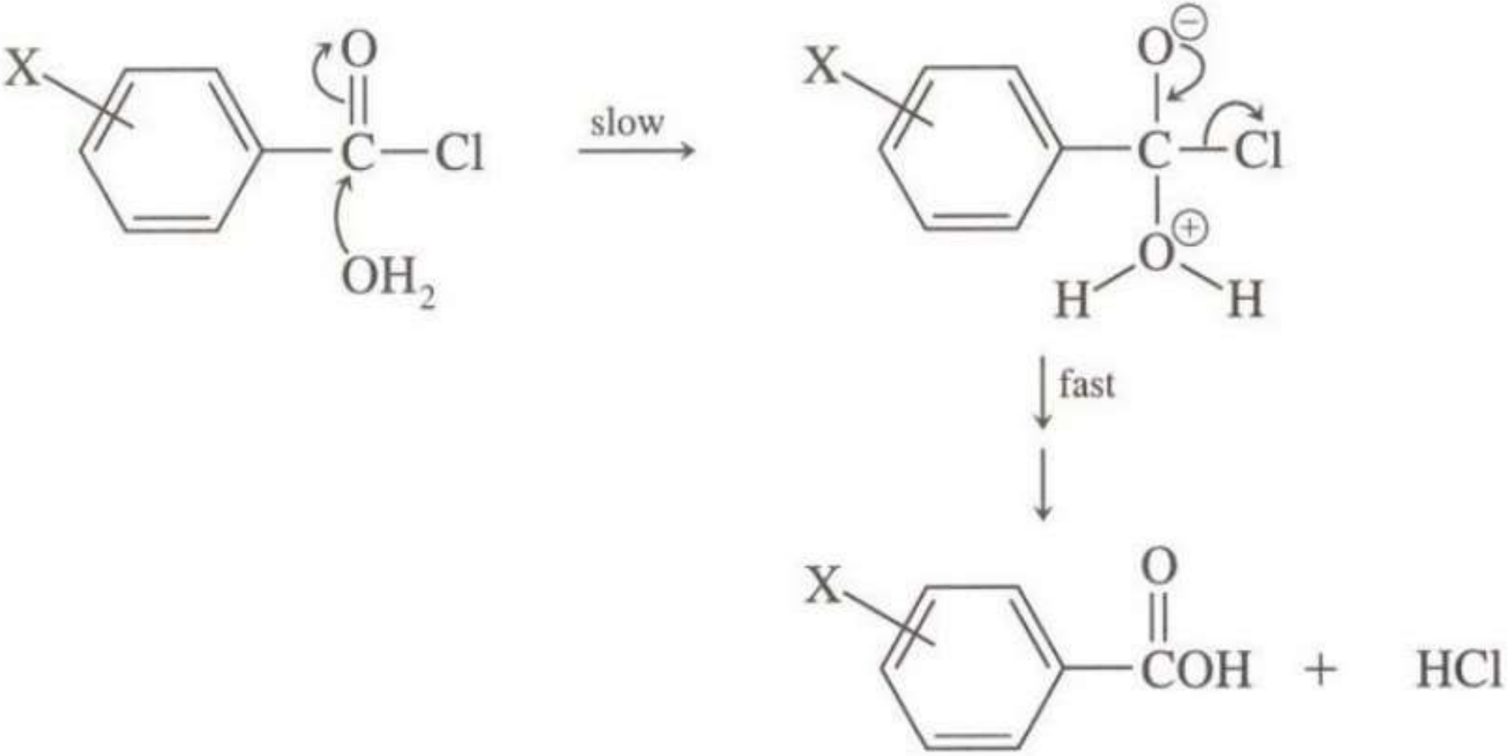
The Hammett Equation

The Reaction Constant, ρ

Reaction mechanism and the Hammett equation

- Proposed mechanism (1)

Water molecule might add to the carbonyl groups to form tetrahedral intermediates in slow, rate-limiting step.



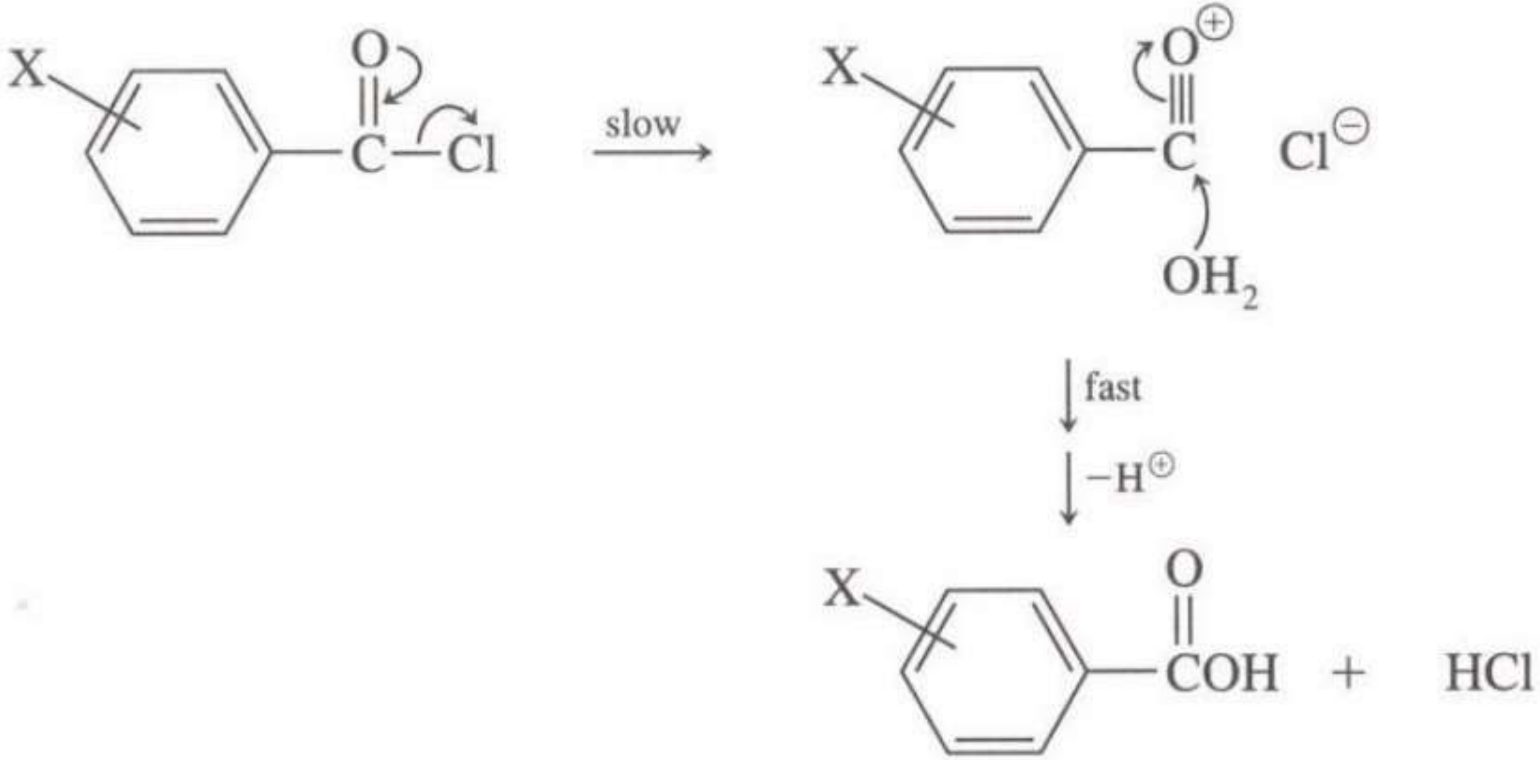
The Hammett Equation

The Reaction Constant, ρ

Reaction mechanism and the Hammett equation

- Proposed mechanism (2)

Carbon-chlorine bonds might dissociate in slow, rate-limiting steps.



The Hammett Equation

The Reaction Constant, ρ

Reaction mechanism and the Hammett equation

- The dissociation of benzoyl chlorides to form carbocations would be assisted by EDG, but the addition of water to the carboxyl groups should be fastest in benzoyl chlorides with EWG.

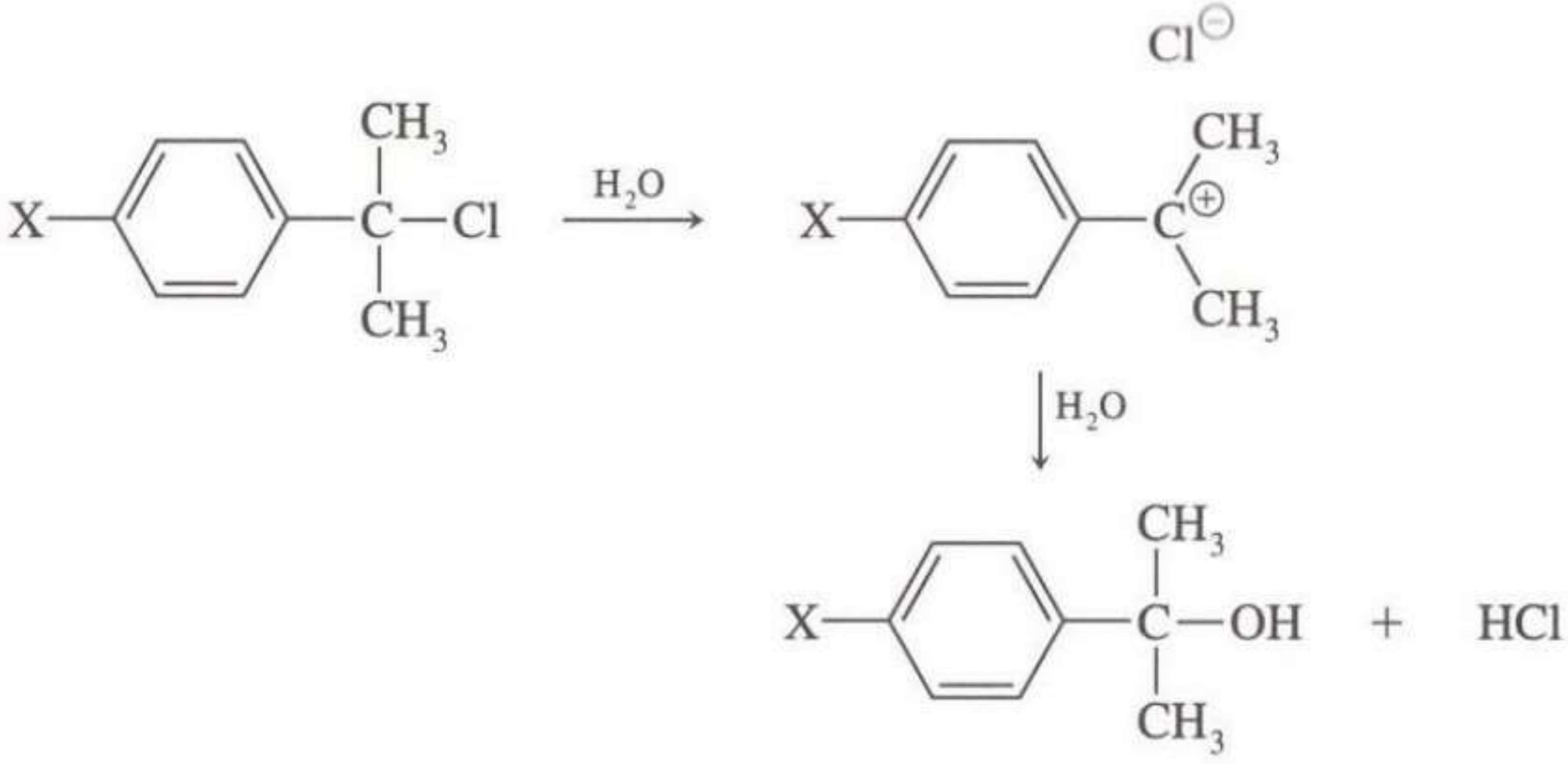
- Hammett plot for this reaction has a positive value of ρ is consistent with mechanism (1).

The Hammett Equation

σ^+ and σ^- Constants

In some reactions strongly EDG in *para* positions accelerate the reaction rates far more than would be predicted from their σ values.

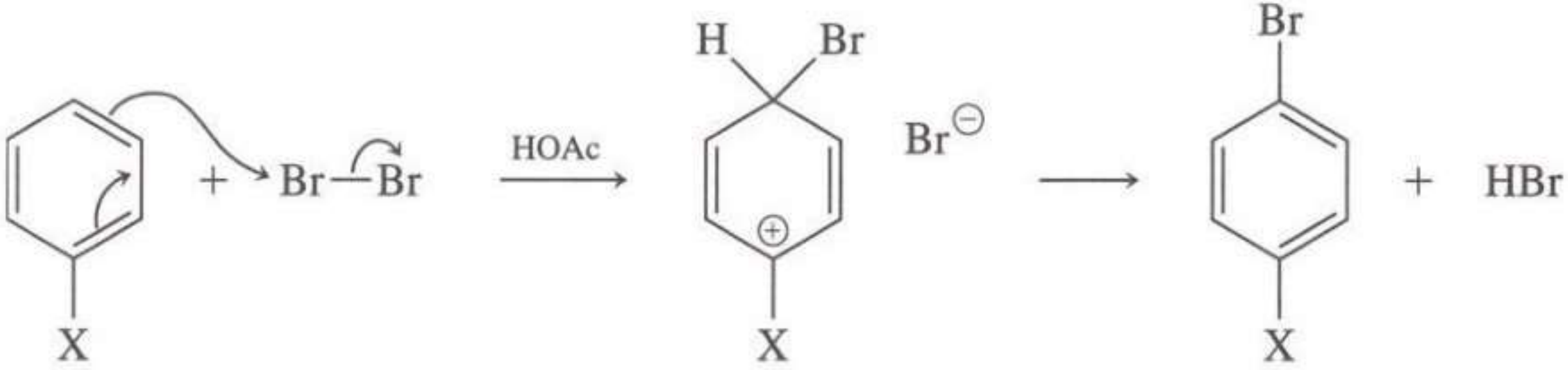
(Examples) S_N1 reactions of *t*-cumyl chlorides



The Hammett Equation

σ^+ and σ^- Constants

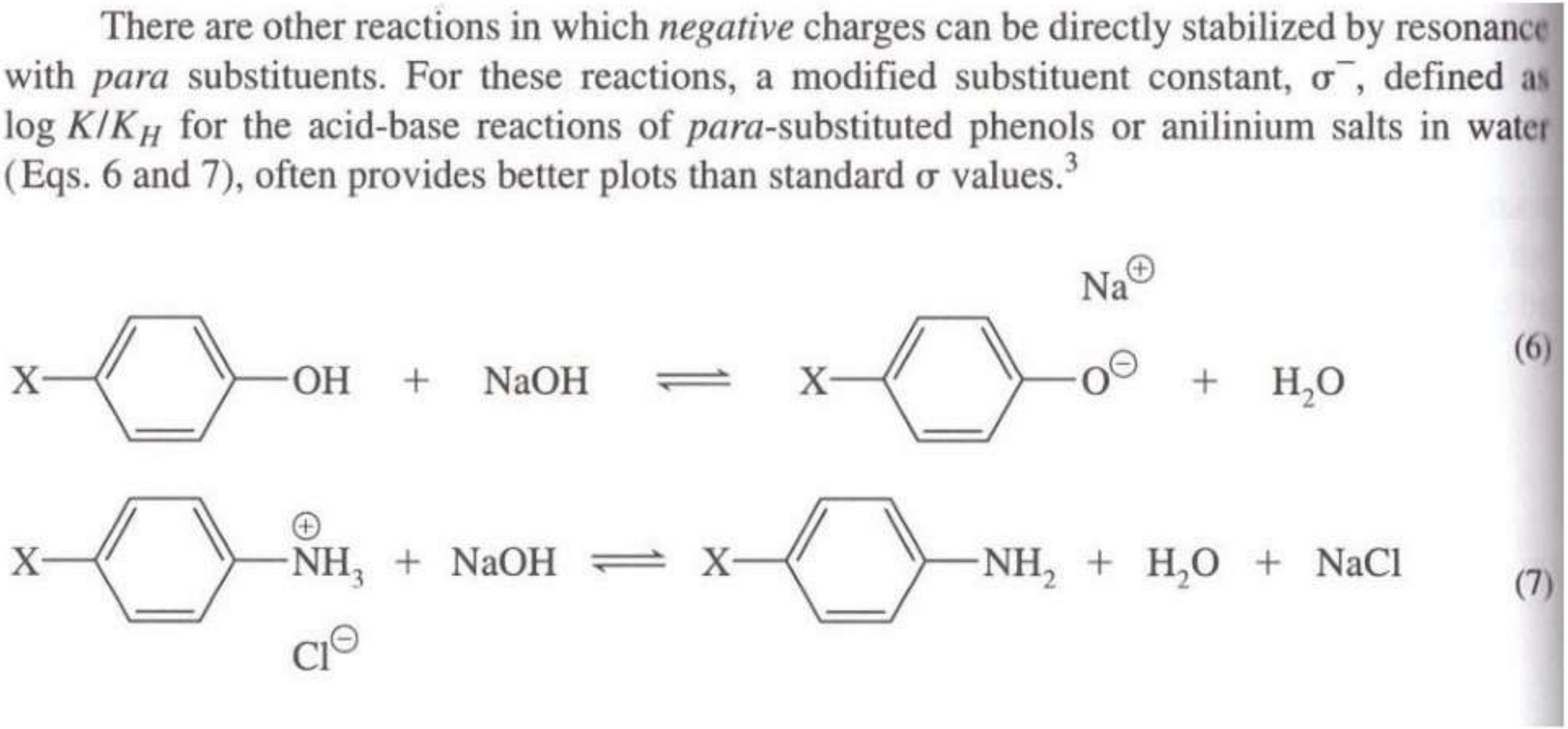
(Examples) S_E reactions of aromatic rings



In two reactions direct conjugation may exist between the *para* substituents and empty orbitals in TS.
In these cases, modified para-substituent constants, σ^+ are often useful.

The Hammett Equation

σ^+ and σ^- Constants



There are other reactions in which *negative* charges can be directly stabilized by resonance with *para* substituents. For these reactions, a modified substituent constant, σ^-, defined as $\log K/K_H$ for the acid-base reactions of *para*-substituted phenols or anilinium salts in water (Eqs. 6 and 7), often provides better plots than standard σ values.[3]

The Hammett Equation

Curved Hammett Plots

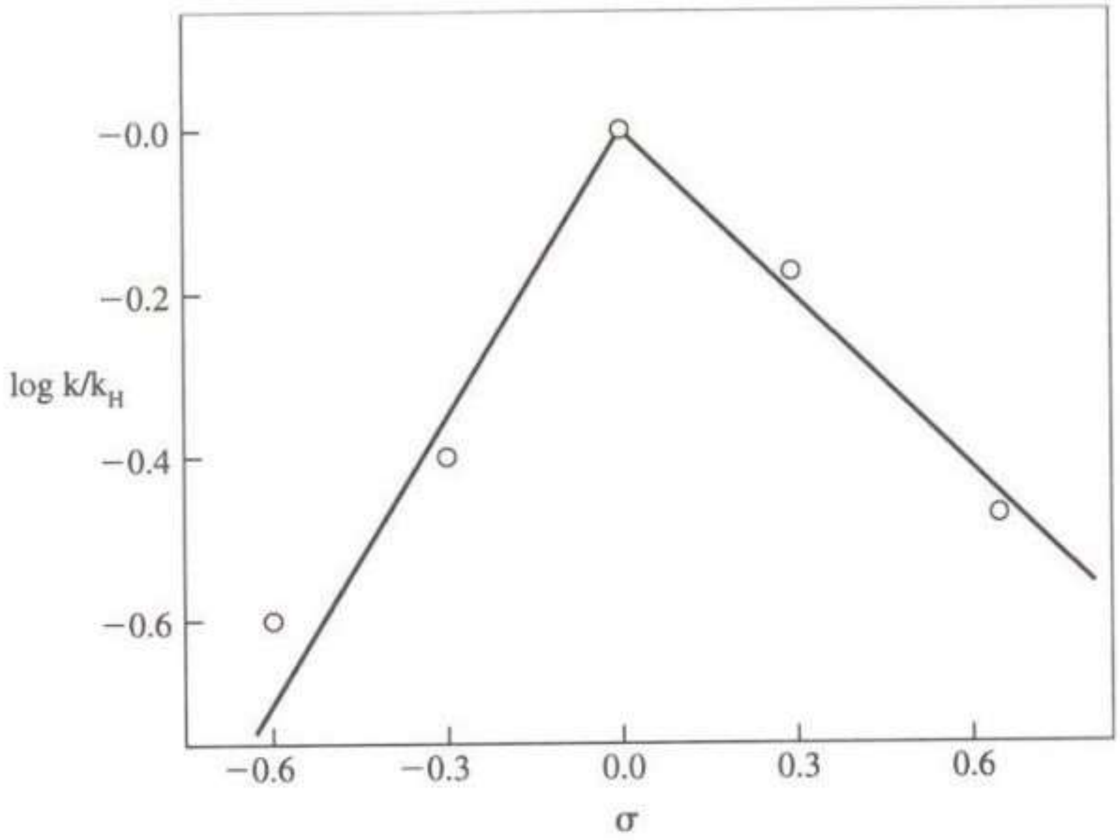
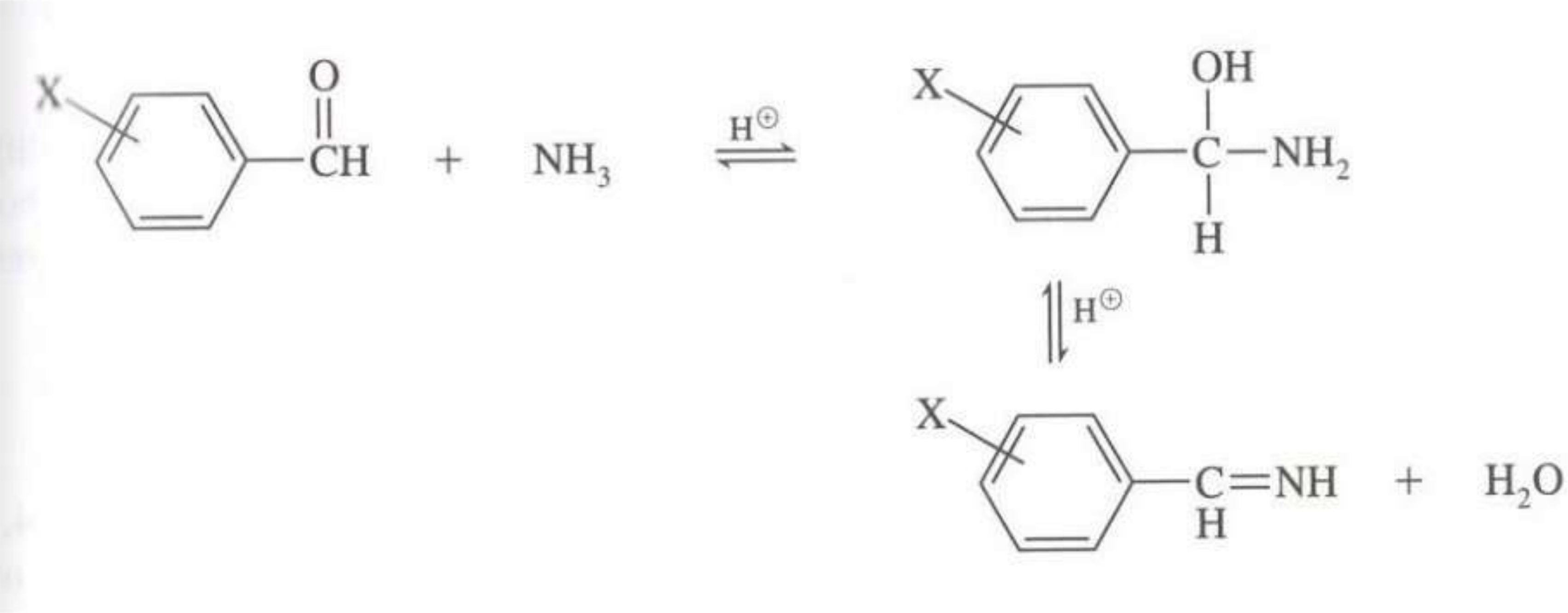


FIGURE 5.2 The reaction of aromatic aldehydes with ammonia.

The reaction has undergoes a change in mechanism as the electronic effects of the substituents changed.

The Hammett Equation

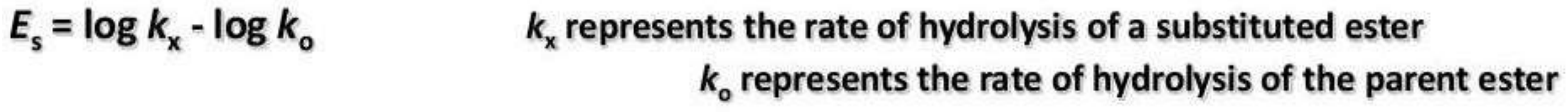
Curved Hammett Plots



Taft’s Steric factors

- For a drug to interact with an enzyme or a receptor, it has to approach, then bind to a binding site
- Bulk, size, and shape of the drug have an influence on this process
- Bulky substituent may act like a shield and hinder the ideal interaction between drug and receptor
- Alternatively, a bulky substituent may help to orientate a drug properly for maximum receptor binding and increase activity
- Quantifying steric properties is more difficult than quantifying hydrophobic or electronic properties

- Highly unlikely that a drug's biological activity will be affected by steric factors alone
- Attempts have been made to quantify the steric features of substituents by using Taft's steric factor
- Number of substituents which can be studied by this method is restricted
- Can be calculated similar to Electronic effects



$$E_s = \log k_x - \log k_o$$

k_x represents the rate of hydrolysis of a substituted ester

k_o represents the rate of hydrolysis of the parent ester

Separation of polar, Resonance, and Steric Effects

The Taft Equation

Effect of substituents on the rates of reactions of a series of esters, XCO_2R.

- If R is constant, the rates of reactions depend on the inductive, resonance, and steric effects of group X.
- If X is saturated carbon, there could be no direct resonance interaction between X and the carboxyl group.

Rates of basic hydrolysis could be defined by the following equation.

$$\log\left[\frac{k}{k_H}\right]_{\text{in base}} = \rho^*\sigma^* + E_s$$

Separation of polar, Resonance, and Steric Effects

The Taft Equation

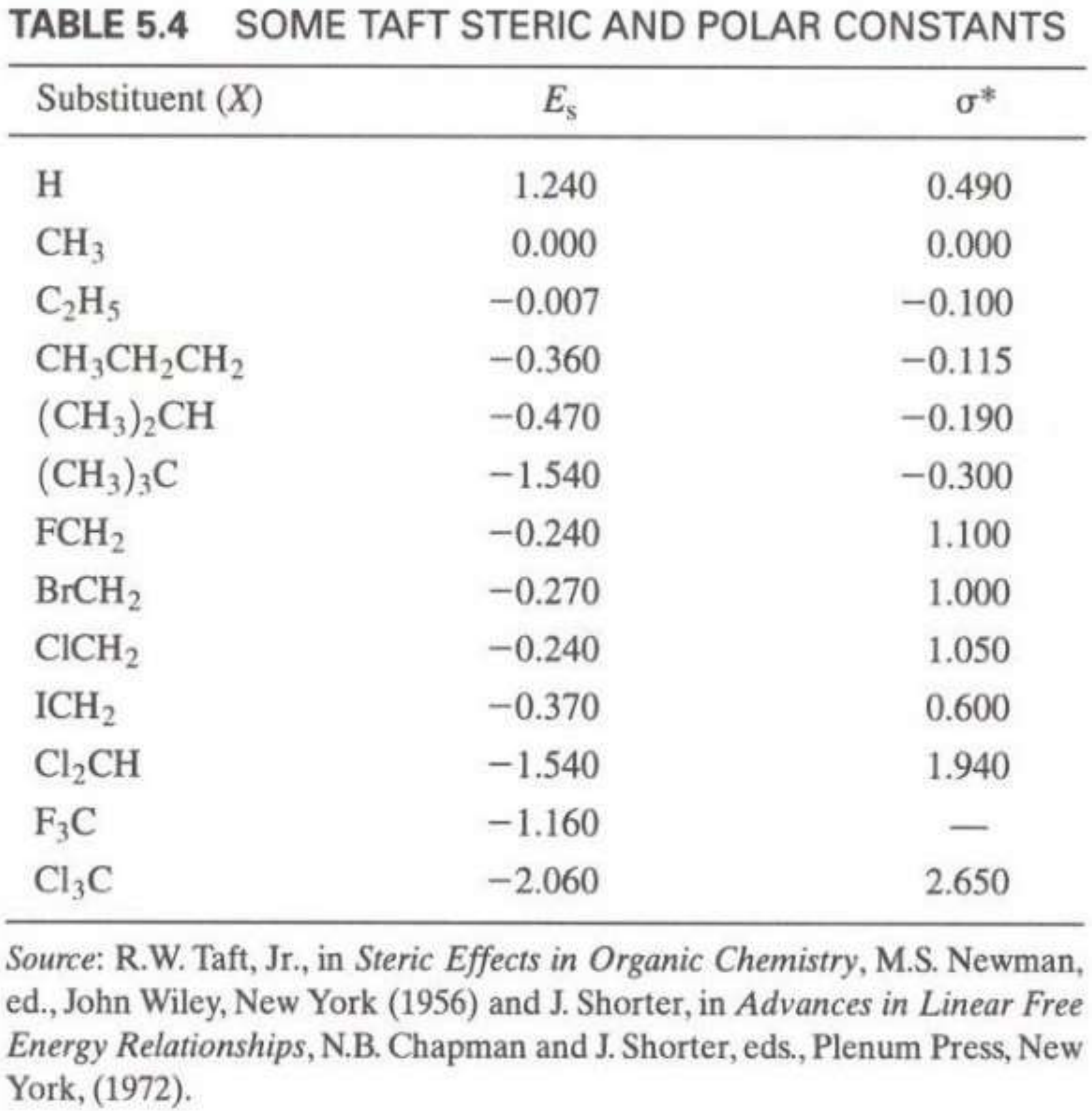


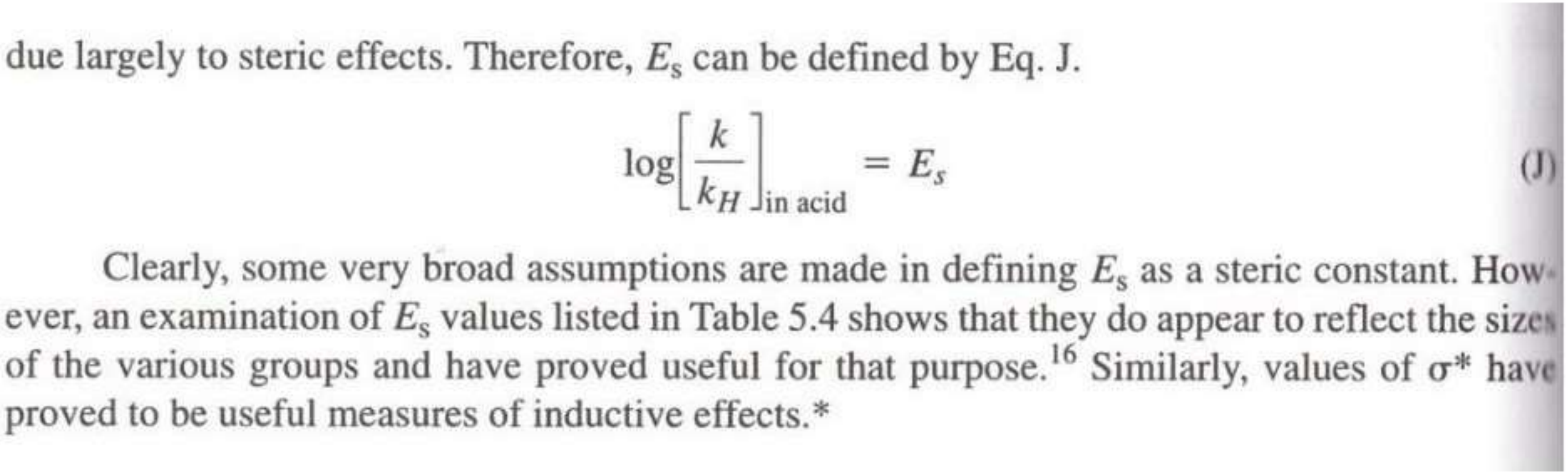
TABLE 5.4 SOME TAFT STERIC AND POLAR CONSTANTS

Substituent (*X*)	E_s	σ^*
H	1.240	0.490
CH_3	0.000	0.000
C_2H_5	−0.007	−0.100
$CH_3CH_2CH_2$	−0.360	−0.115
$(CH_3)_2CH$	−0.470	−0.190
$(CH_3)_3C$	−1.540	−0.300
FCH_2	−0.240	1.100
$BrCH_2$	−0.270	1.000
$ClCH_2$	−0.240	1.050
ICH_2	−0.370	0.600
Cl_2CH	−1.540	1.940
F_3C	−1.160	—
Cl_3C	−2.060	2.650

Source: R.W. Taft, Jr., in *Steric Effects in Organic Chemistry*, M.S. Newman, ed., John Wiley, New York (1956) and J. Shorter, in *Advances in Linear Free Energy Relationships*, N.B. Chapman and J. Shorter, eds., Plenum Press, New York, (1972).

Separation of polar, Resonance, and Steric Effects

The Taft Equation



due largely to steric effects. Therefore, E_s can be defined by Eq. J.

$$\log\left[\frac{k}{k_H}\right]_{\text{in acid}} = E_s \qquad \text{(J)}$$

Clearly, some very broad assumptions are made in defining E_s as a steric constant. However, an examination of E_s values listed in Table 5.4 shows that they do appear to reflect the sizes of the various groups and have proved useful for that purpose.[16] Similarly, values of σ^* have proved to be useful measures of inductive effects.*

Thank
You