1.

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* QSAR - (Quantitative Structure - Activity Relationship) - Corwin Hensch - early 1960s

- It is defined as mathematical relationship in the form of an equation between the biological activity and measurable physicochemical parameters.

(M. Eq.)

- QSAR attempts to identify and quantify the P'chemical Properties of drug and to see whether any of those property has an effect on the drugs biological activity. By using a

P Meter

- QSAR is a measure of the potential Contribution of its group to a particular property of the parent drug.

* Activity is expressed as $\log(1/c)$

c = is the minimum Concentration required to Cause a defined biological response.

- Physicochemical Properties as log P

[LES]

* Physicochemical Parameters: Various Parameters used in QSAR studies are:

1. Lipophillic Parameters: Partition Coefficient
   π - Substitution Constant.

2. Electronic Parameters: Hammet Constant
   dipole moment

3. Steric Parameters: Taft's Constant
   molar refractivity, Verloop steric parameter

value ⊕ - hydrophilic - water lover
⊖ hydrophobic - no intraction with water

2.

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1. Lipophilic Parameters: Partition Coefficient - Lipophilicity is Partitioning of the compound between an aqueous and non-aqueous phase.

#1 Partition Coefficient: Solubility of drug in aqueous and non-aqueous Solvent.

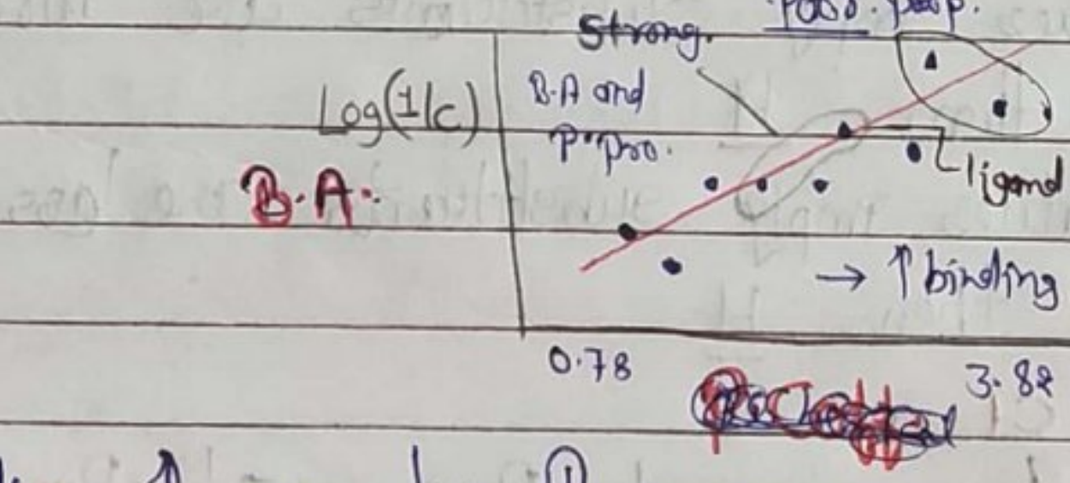
$$P = \frac{\text{drug in octanol}}{\text{drug in water}}$$

→ because it has polar head, similar to fatty acid (long Hydroc chain)

High P (lead) = High hydrophobicity → ↑ diffusion Rate (Lipo. ↑ character)
Low P = Low Hydrophobicity (High Hydrophilic)

(i) Linear Relationship b/w log P and Log 1/C =
- Activity of drug as often related to P
  eg. binding of drugs to Serum albumin (blood protein)

[Procedure is known as linear regression analysis by least square method]
- (Straight line - limited range of log P)

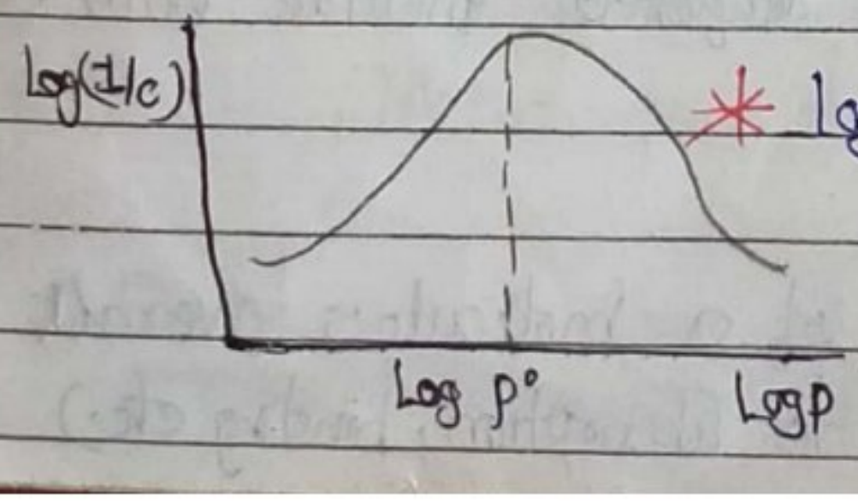


$$\log(1/c) = k_1 \log P + k_2$$

where k_1, k_2 - Constant

- Binding ↑ as log P increases.
- Binding is greater for hydrophobic drugs.
  Lipophilic

(ii) Non-linear relationship b/w log P and Log 1/C
General anesthetic activity of ethers.
- (Parabolic Curve - large range of log P values)



* $\log(1/c) = -k_1 (\log P)^2 + k_2 \log P + k^3$

* Optimum value of log P for anesthetic activity = log P°

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*2. π - Substituents Constant or hydrophobic Substituents Constants:

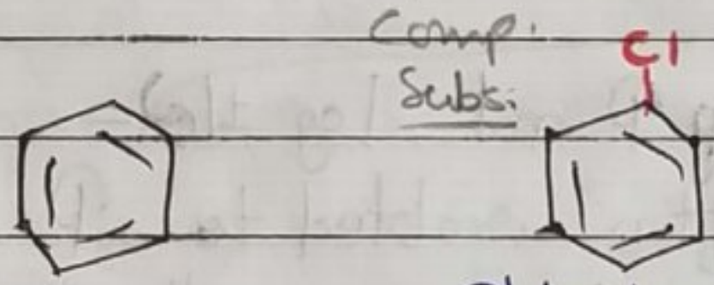
* The π-Substituents Constants defined by Hansch and Co-workers also Called Hansch Analysis.

* Measure of how hydrophobic a substituent is, relative to H

$$\pi X = \log P_X - \log P_H$$

where - π = Hydrophobic Subs. Constant

Comp: Subst:



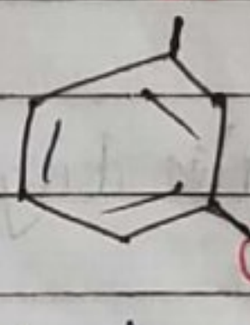
Benzene — Chlorobenzene — Benzamide

Log P = 2.13 — Log P = 2.84 — Log P = 0.64

$\pi_{Cl} = 0.71$ — $\pi_{CONH_2} = -1.49$

- Positive values imply substituents are more hydrophobic than H (benzene)
- Negative values imply substituents are less hydrophobic then H

Examples



(meta-chlorobenzamide)

$\log P_{(theory)} = \log P_{(benzene)} + \pi_{Cl} + \pi_{CONH_2}$

$= 2.13 + 0.71 - 1.49$

$= 1.35$

$\log P_{(observed)} = 1.51$

- A QSAR equation may include both. P and p

P = measures the importance of a molecules overall hydrophobicity (relevent to absorption, binding etc.)

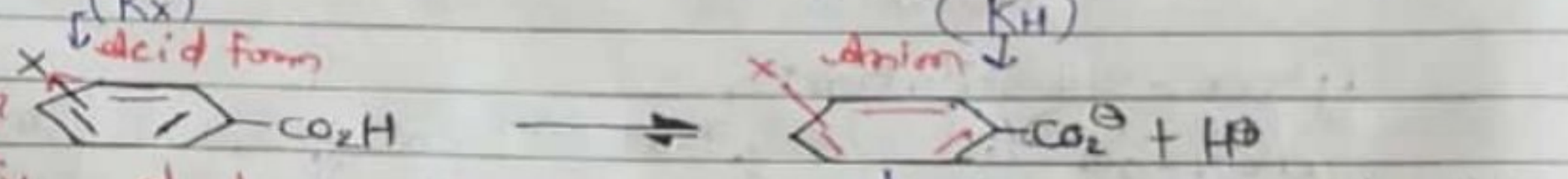
P = identifies specific regions of the molecule which might interact with hydrophobic regions in the binding site.

2. Electronic Parameters: Electron distribution in a drug molecules affects the drug's distribution and activity. the non-polar- and polar drugs are readily transported through membrane when in their unionised form than in their ionised form. When the drug reaches to its target site, the electron distribution in its structure control the type of bond it will form with the target : The bond formed influences the drug's biological activity.

4

Hammet Substitution Constant (σ) is a measure of a substituents (i.e. functional moiety) ability to either withdraw or donate electrons.
it may be determined by measuring the dissociation of a series of benzoic acid substituted derivatives in relation to the dissociation of pure benzoic acid itself.

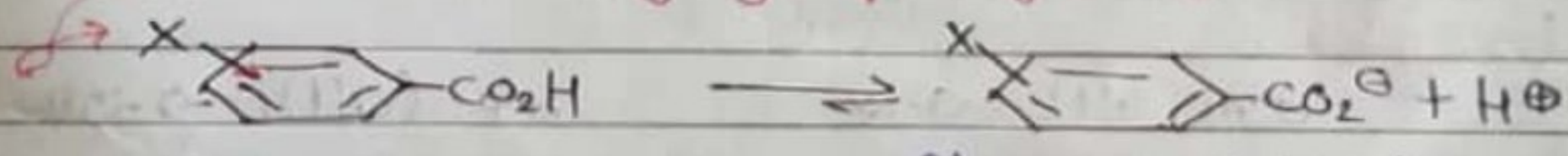
- Hammett Substituent Constants (σ)
- Exc- X = electron withdrawing group (eg. NO_2)



1. X = electron withdrawing group
↳ Charge is stabilised by X- equilibrium shift to Right. $Kx > KH$

$$\sigma_x = \log \frac{Kx}{KH} = \log Kx - \log KH$$ (positive Value)

2. X = electron donating group (eg. CH_3)



- Charge destabilised, equilibrium shift to left $Kx < KH$

σ = Values depends on inductive and resonance effects.
σ = Values depends on whether the substituents is Meta or Para (inductive effect)

5.

The Hammett substituent Constant (σx) for a particular substituent (x) is defined by the following equation.

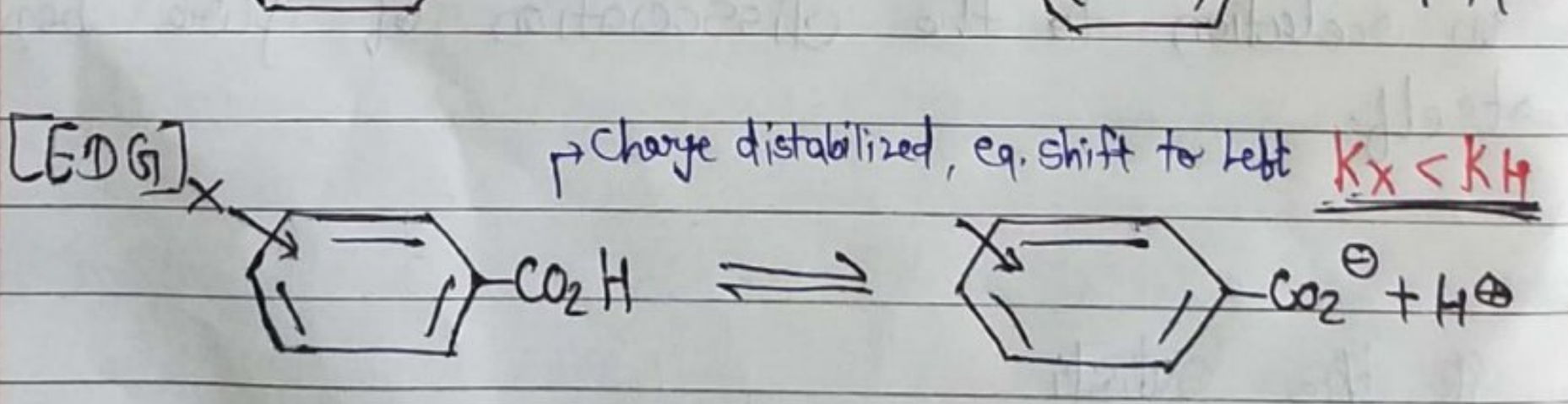
$$\sigma x = \log \frac{Kx}{KH} = \log Kx - \log KH$$

EWGs = $-NO_2$, $-CN$, $-COOH$, $-CHO$, $-NO$, $-SO_2R$ etc.

- Benzoic acid containing $e^{\ominus}$ withdrawing substituents will have larger Kx values than benzoic acid itself. → therefore, the value of σx is positive.

- Benzoic acid containing EDGs will have smaller Kx values than benzoic acid → therefore, the value of σx is negative.

EDGs - F, Cl, Br, I, $-OR$, $-OH$, $-NH_2$, etc.



* Position of equilibrium dependent on substituent group X.

6.

Limitation- One of the limitation of Hammett Constant is that it does not hold for ORTHO substituents. This characteristic is known as the ortho-effect.

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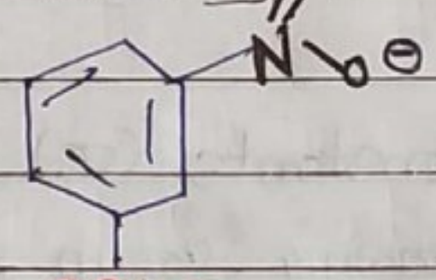
Hammett Substituent Constant (s)

1. Examples:

$\sigma_p (NO_2) = 0.78$ $\sigma_m (NO_2) = 0.71$

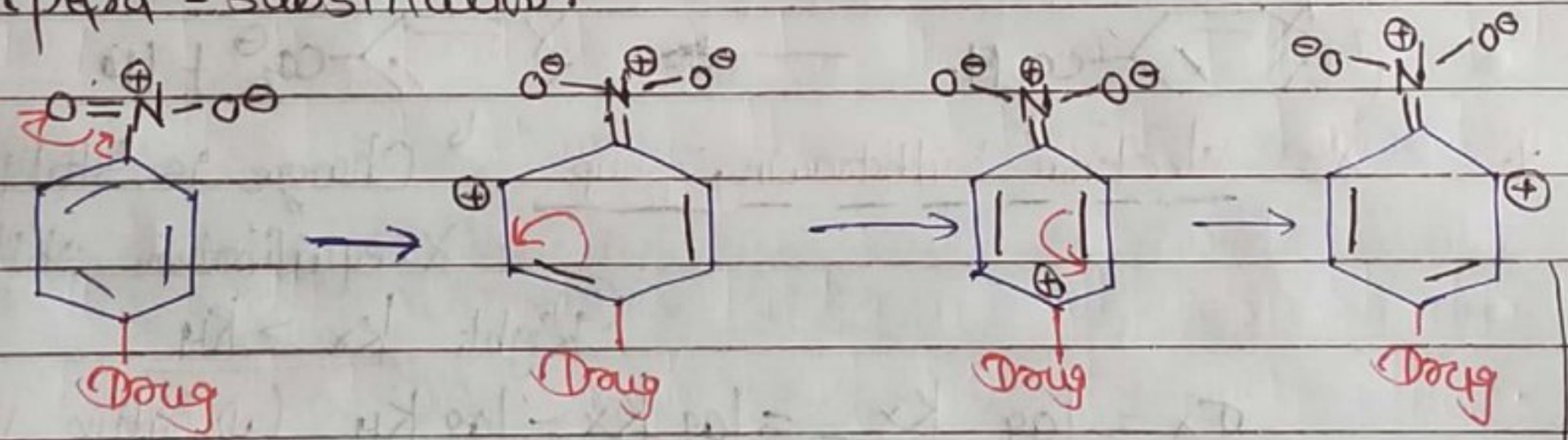
* meta-substitution:



DRUG

e-withdrawing (inductive effect only)

Para-substitution:

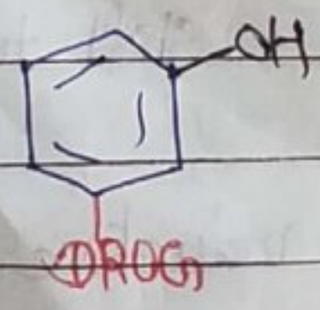


e-withdrawing (induction + resonance effect)

2. Examples:

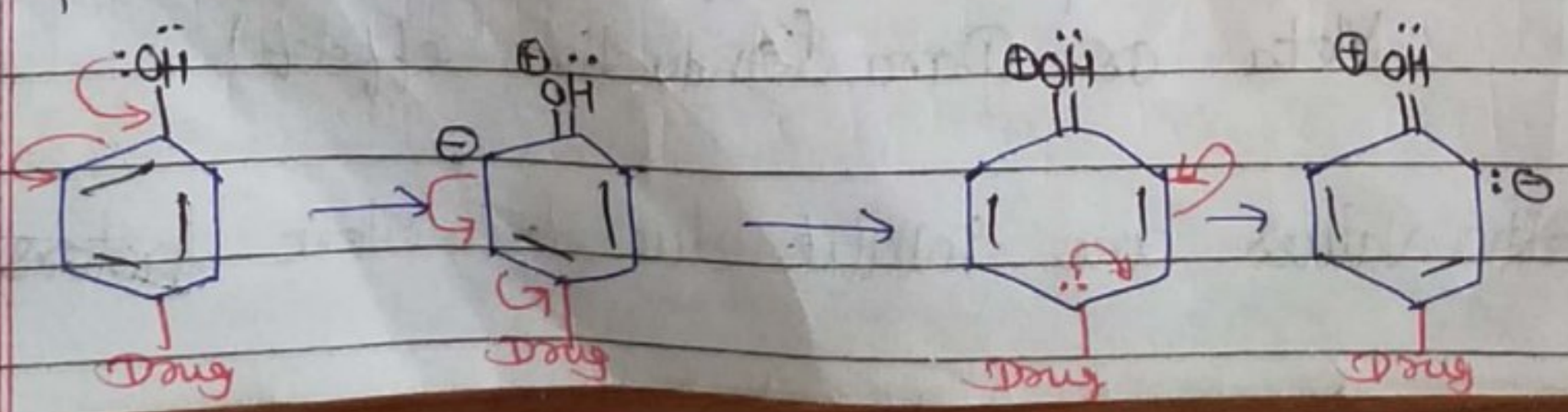
$\sigma_m (OH) = 0.12$ $\sigma_p (OH) = -0.37$

* meta-substitution



donating e-withdrawing (inductive effect only)

Para-substitution:



e⊖ donating by resonance more important than inductive effect

[Chain length ↑ = bulkiness ↑
Branching ↑

3. Steric Substitution Constant :
It is a measure of the bulkiness of the group it represents and it effect on the closeness of Contact between the drug and receptor site. It so much harder to quantitate.

(i) Taft's Steric factor [Es] - Es was first parameter used to demonstrate the relationship between the shape and size (bulk) of a drug, the dimensions of its target site and its activity.

- Measured by Comparing the rates of hydrolysis of substituted aliphatic esters against a standard ester under acidic conditions.

$$Ex = \log Kx - \log Ko$$

*bulkier, the substit, More -ve are the Es values)

Es is defined as

$$Es = \log (Kx)_A - \log (K_{CH_3})_A = \log \left(\frac{Kx}{K_{CH_3}}\right)_A$$

Where Kx and K_{CH_3} are the rate constants for the substituted (substitution is X) and unsubstituted ($X=CH_3$) esters or acids, respectively, and the subscript A denotes hydrolysis in acid solution.
The bulkier the substituent, the more negative are the Es constant values.

(iii) Molar refractivity (MR) : defined as measure of the Volume occupied by an atom or group.

- eq. includes the MW, density (d) and the index of refraction (n) -

$$MR = \frac{(n^2-1)M}{(n^2+2)d}$$

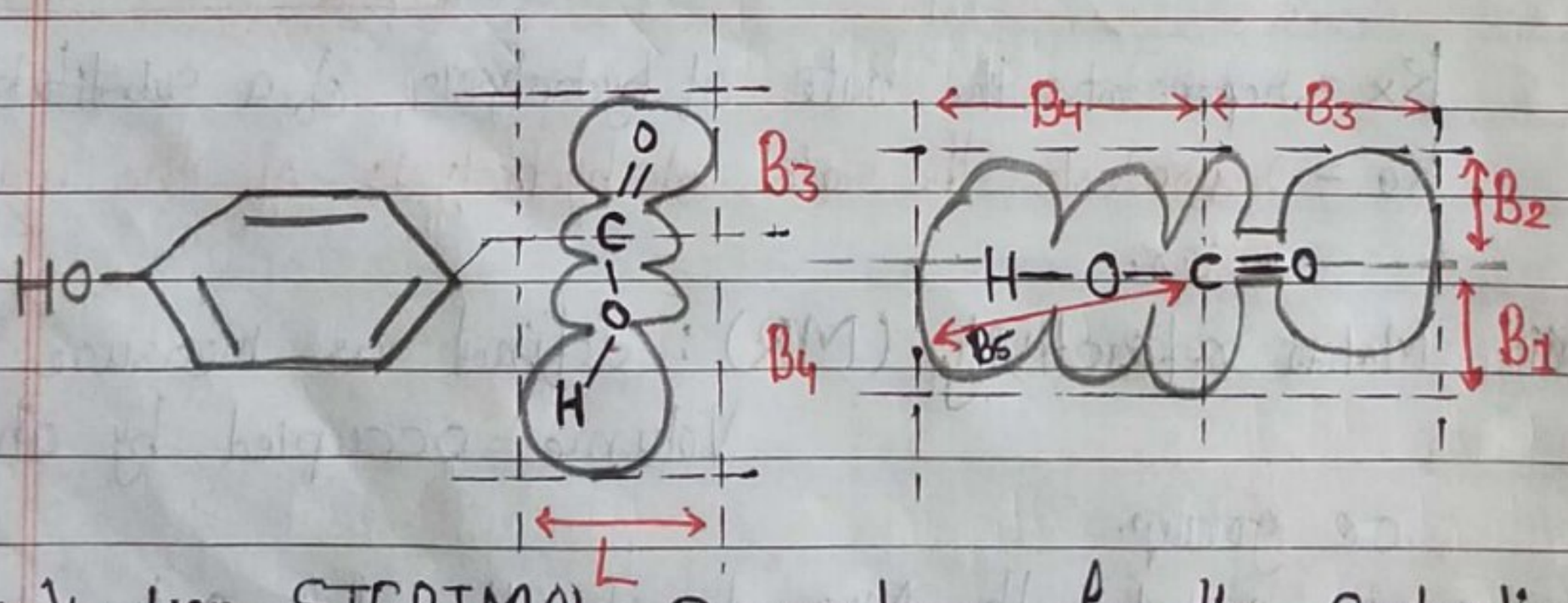
(Sterimol) Com. programe)

(iii) Verloop Steric Parameter : defined as Computer program uses bond angles, Van der waals radii, bond lengths.

* Taft Parameter (applicable for simple homogeneous organic reactions), Verloop STERIMOL Parameters for Characterizing the Steric features of the substituents in more Complex biological Systems-
It includes set of five descriptors (L, B_1, B_2 B_3, B_4) to describe the shape of a substituents

* L = length of substituent along the axis of the bond b/w the first atom of the substituent and parent mol.

* The width parameters B_2-B_4 are all perpendicular to L and form angles of 90° to each other.
* B_1 as the smallest and B_5 the largest width parameter, which does not have any directional relationship to L.



* Verloop STERIMOL Parameters for the Carboxylic acid group of Para-hydroxy benzoic acid.

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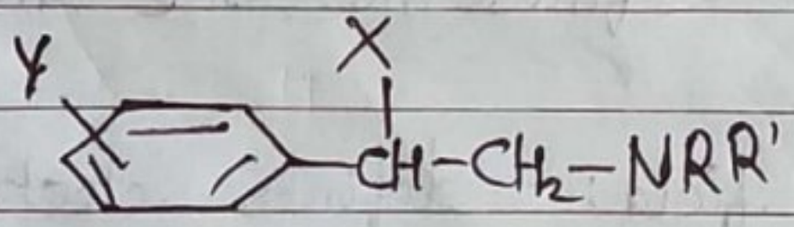
* Hansch Equation or Analysis:

1. A QSAR equation relating various physicochemical properties to the biological activity of a series of Compounds.
2. Usually includes log P, electronic (σ) and steric factors [Es]
3. Start with simple equations and elaborate as more structures are synthesized.
4. Typical equation for a wide range of log P is parabolic.

$$\text{Log}(1/C) = -k_1 (\log P)^2 + k_2 \log P + k_3 \sigma + k_4 Es + k_5$$

Example: Adrenergic blocking activity of β-halo-β-arylamines.



⇒ Conclusions:

- Activity increases if π is positive (i.e. hydrophobic substituents)
- Activity increases if S is negative (i.e. e-donating substituents)

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3-D QSAR:

1. In 3D-QSAR, 3D Properties of a molecules are Considered as a whole rather than Considering individual Substituents.
2. 3D-QSAR involve the analysis of the quantitative relationship between the biological activity of a set of Compound and their three-dimensional Properties using Statical Correlation methods.
3. 3D-QSAR revolves around the important features of molecules, its overall size and shape, and its electronic Properties.
4. Physical prop. are measured for the molecule as a whole.
5. Properties are calculated using Computer software.
6. No experimental Constants or measurements are involved.
7. Properties are known as "fields"
8. Steric field :- defines the size and shape of the molecule.
9. Electrostatic field :- defines electron rich/poor regions of molecule.
10. Hydrophobic properties :- are relatively unimportant.

Thank you