Medicinal Chemistry

Quantitative structure-activity relationships (QSAR)

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Quantitative structure-activity relationships (QSAR)

The QSAR approach attempts to identify and quantify the physicochemical properties of a drug and to see whether any of these properties has an effect on the drug's biological activity.

If such a relationship holds true,

- **an equation can be drawn up which quantifies the relationship and allows the medicinal chemist to:**

  say with some confidence that the property (or properties) has an important role in the pharmacokinetics or mechanism of action of the drug.

- **It also allows the medicinal chemist some level of prediction.**

Quantitative structure-activity relationships (QSAR)

By quantifying physicochemical properties, it should be possible to calculate in advance what the biological activity of a novel analogue might be.

There are two advantages to this.

First, it allows the medicinal chemist to **target efforts on analogues** which **should have improved activity** and thus **cut down the number of analogues that have to be made**.

Second, if an analogue is discovered which does not fit the equation, it implies that some other feature is important and provides a lead for further development .

Quantitative structure-activity relationships (QSAR)

1 Graphs and equations

In the simplest situation, a range of compounds is synthesized in order to vary one physicochemical property (e.g. log P) and to test how this affects the biological activity (log 1/C).

A graph is then drawn to plot the biological activity on the y-axis (log 1/C) versus the physicochemical feature (log P) on the x-axis (Fig. 13.1).

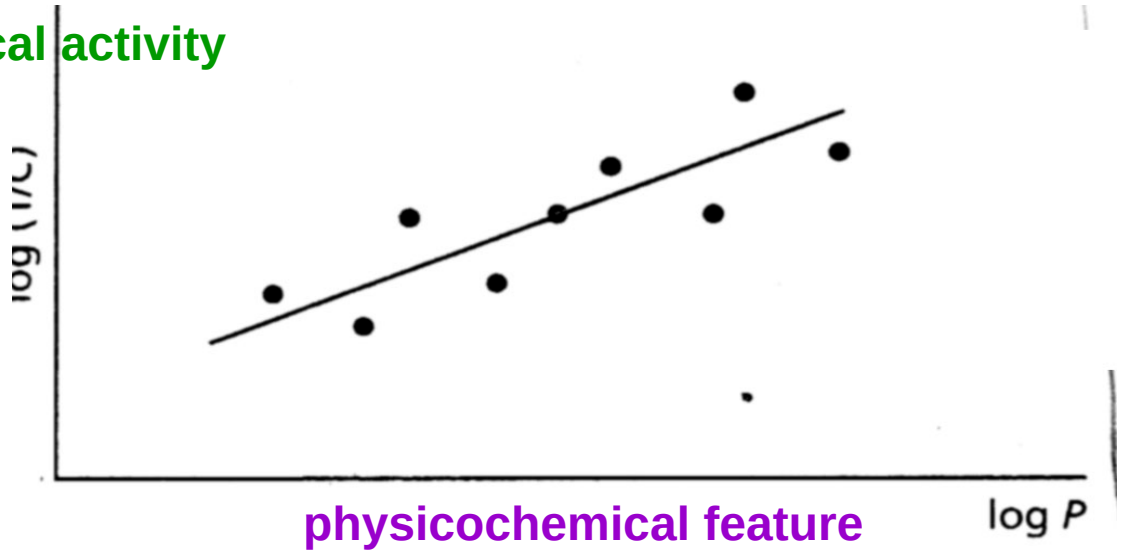


Figure 13.1 Biological activity versus log *P*.

Quantitative structure-activity relationships(QSAR)

1 Graphs and equations

It is necessary to draw the best possible line through the data points on the graph. This is done by a procedure known as `linear regression analysis by the least squares method'

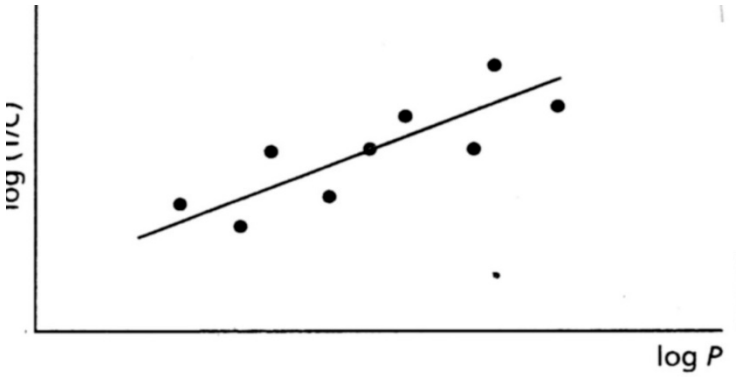


Figure 13.1 Biological activity versus log *P*.

To measure how close the data points are, vertical lines are drawn from each point (Fig. 13.2). These verticals are measured and then squared in order to eliminate the negative values. The squares are then added up to give a total (the sum of the squares)

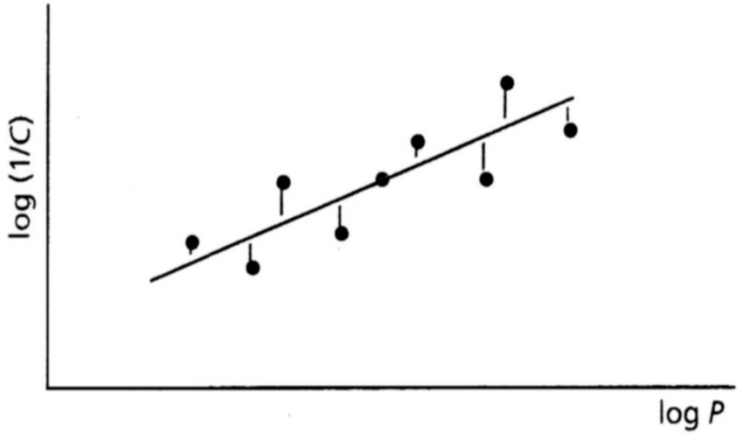


Figure 13.2 Proximity of data points to line of best fit.

Quantitative structure-activity relationships (QSAR)

1 Graphs and equations

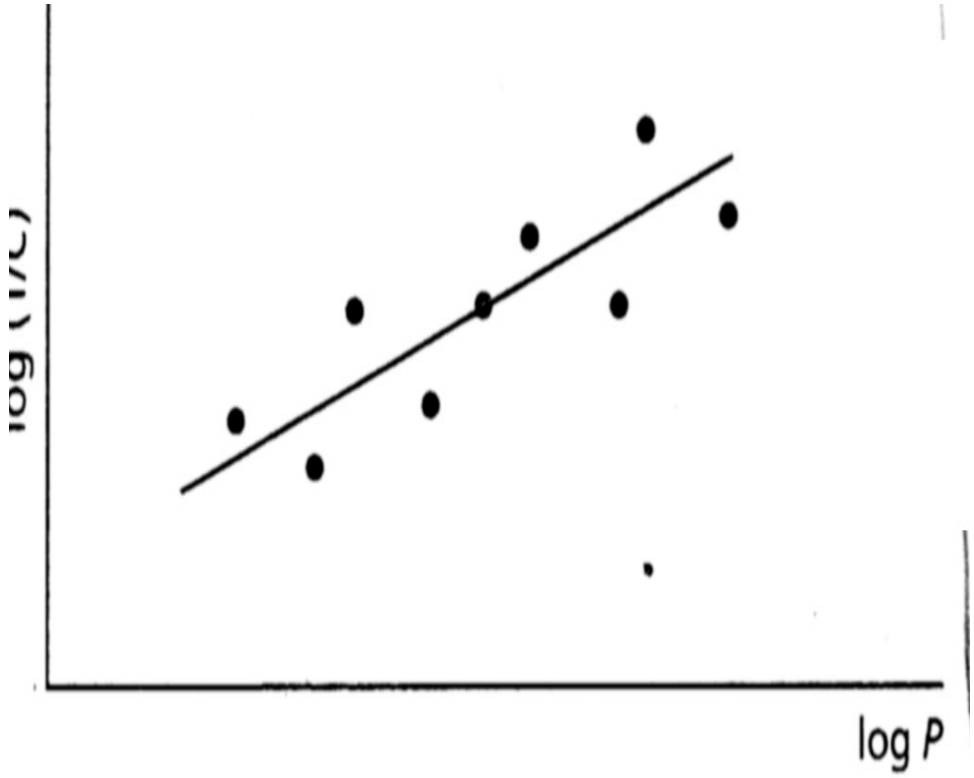


Figure 13.1 Biological activity versus log *P*.

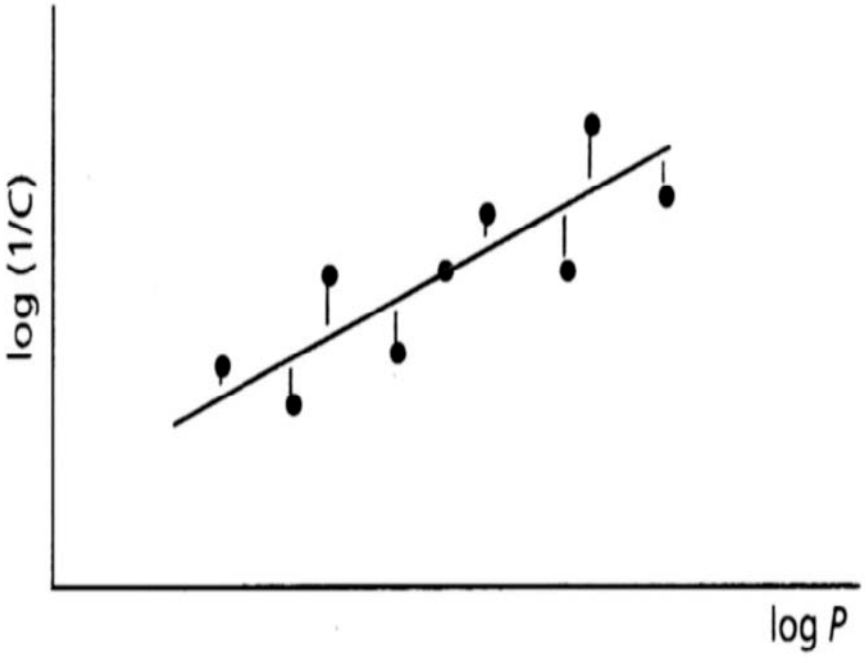


Figure 13.2 Proximity of data points to line of best fit.

Quantitative structure-activity relationships (QSAR)

1 Graphs and equations

The best line through the points will be the line where this total is a minimum. The equation of the straight line will be

$$y = k_1 x + k_2$$

where k_1 and k_2 are constants.

By varying k_1 and k_2, different equations are obtained until the best line is obtained. This whole process can be speedily done using relevant software.

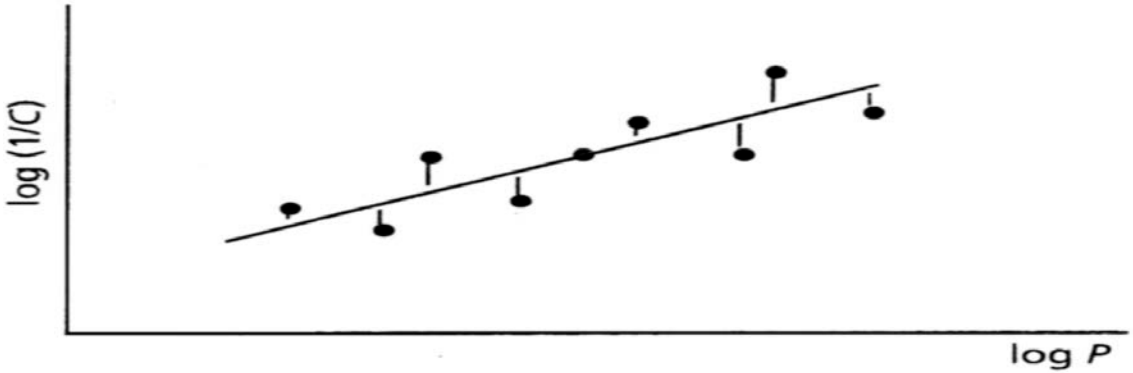


Figure 13.2 Proximity of data points to line of best fit.

Quantitative structure-activity relationships(QSAR)

1 Graphs and equations

medicinal chemist draws up an equation that quantifies the relationship & allows one to predict (to some extent) the biological activity.

the QSAR equation is to quantify the goodness of fit.

The regression or correlation coefficient (r) is a measure of how well the equation explains the variation in activity observed in terms of the physicochemical parameters in the equation.

For a perfect fit, r = 1, in which case the *observed activities would be the same as those calculated by the equation.*

Quantitative structure-activity relationships (QSAR)

1 Graphs and equations

For a perfect fit, r = 1, in which case the observed activities would be the same as those calculated by the equation.

Such perfection is impossible with biological data and so r values greater than 0.9 are considered acceptable.

The regression coefficient is often quoted as r^2 in which case values over 0.8 are considered a good fit. If r^2 is multiplied by 100 it indicates the percentage variation in biological activity that is accounted for تَبَرّرَ؛ تفَسّر by the physicochemical parameters used in the equation.

Thus, an r^2 value of 0.85 signifies that 85% of the variation in biological activity is accounted for by the parameters used.

Quantitative structure-activity relationships (QSAR)

1 Graphs and equations

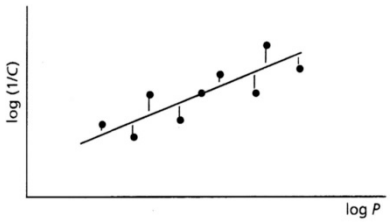


Figure 13.2 Proximity of data points to line of best fit.

another statistical measure for the goodness of fit should be quoted alongside r.

This is the standard error of estimate or the standard deviation (s).

Ideally, s should be zero, but this would assume there were no experimental errors in the experimental data or the physicochemical parameters.

In reality, s should be small, but not smaller than the standard deviation of the experimental data.

2 Physicochemical properties

Many physical, structural, and chemical properties have been studied by the QSAR approach, but the most common are

- **hydrophobic (log P) (π) ,**
- **electronic (σx) , and**
- **steric properties.**

- **This is because it is possible to quantify these effects.**

  Hydrophobic properties: can be easily quantified for complete molecules or for individual substituents.

- **While electronic and steric properties for complete molecules are more difficult to be quantified, and this is only really feasible for individual substituents.**

2 Physicochemical properties

2.1 Hydrophobicity

- **The hydrophobic character of a drug :**
  - **is crucial to how easily it crosses cell membranes and**
  - **may also be important in receptor interactions.**

- **Changing substituents on a drug**
  - **may well have significant effects on its hydrophobic character and hence its biological activity.**

- **Therefore, it is important to have a means of predicting this quantitatively.**

Quantitative structure-activity relationships(QSAR)

2 Physicochemical properties

2.1 Hydrophobicity

I. The partition coefficient (p)

The hydrophobic character of a drug can be measured experimentally by testing the drug's relative distribution in an *n*-octanol/water mixture;

Hydrophobic molecules will prefer to dissolve in the *n*-octanol layer of this two-phase system, whereas hydrophilic molecules will prefer the aqueous layer.

The relative distribution is known as the partition coefficient (P) and is obtained from the following equation:

$$P = \frac{\text{Concentration of drug in octanol}}{\text{Concentration of drug in aqueous solution}}$$

Hydrophobic compounds have a **high P** value, whereas **hydrophilic compounds** have a **low P** value.

Quantitative structure-activity relationships(QSAR)

2 Physicochemical properties

2.1 Hydrophobicity

I. The partition coefficient (p)

1) **Varying substituents on the lead compound will produce a series of analogues having different hydrophobicities and therefore different P values.**

2) **By plotting these P values against the biological activity of these drugs, *it is possible to see if there is any relationship between the two properties*.**

3) **The biological activity is normally expressed as 1/C, where C is the concentration of drug required to achieve a defined level of biological activity**

4) **The reciprocal of the concentration (1/C) is used , since more active drugs will achieve a defined biological activity at lower concentration.**

Quantitative structure-activity relationships(QSAR)

2 Physicochemical properties

2.1 Hydrophobicity

I. The partition coefficient (p)

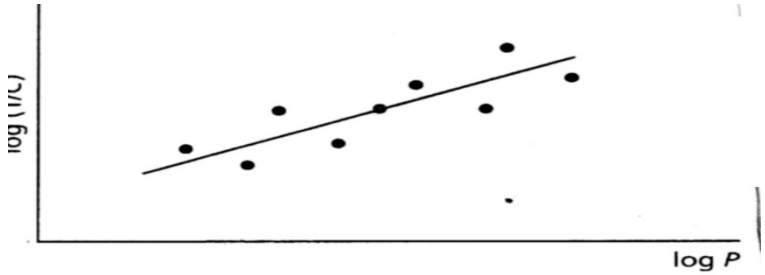


Figure 13.1 Biological activity versus log *P*.

5) The graph is drawn by plotting log (1/C) versus log P.

In studies where the range of the log P values is restricted to a small range (e.g. log P= 1- 4), a straight-line graph is obtained (Fig. *13.1)* showing that there is a relationship between hydrophobicity and biological activity.

Such a line would have the following equation:

$$\log (1\ IC) = k_1 \log P + k_2$$

Quantitative structure-activity relationships(

2 Physicochemical properties

2.1 Hydrophobicity

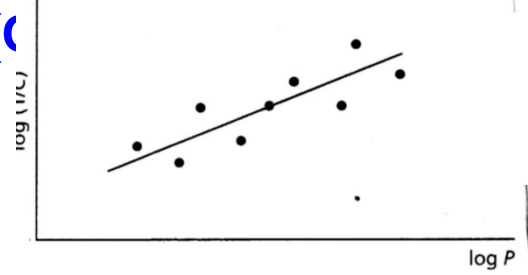


Figure 13.1 Biological activity versus log *P*.

I. The partition coefficient (p)

For example, the binding of drugs to serum albumin is determined by their hydrophobicity and a study of 42 compounds resulted in the following equation:

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

$$\log (1/C) = 0.75 \log P + 2.30 \quad (n = 42,\ r = 0.960,\ s = 0.159)$$

The equation shows that serum albumin binding increases as log P increases. Knowing how strongly a drug binds to serum albumin can be important in estimating effective dose levels for that drug:

When bound to serum albumin, the drug cannot bind to its receptor and so the dose levels for the drug should be based on the amount of unbound drug present in the circulation.

Quantitative structure-activity relationships(QSAR)

2 Physicochemical properties

2.1 Hydrophobicity

I. The partition coefficient (p)

6) If these studies were to be extended to include compounds with very high log P values(over 4) then we would see a different picture. The graph would be parabolic, as shown in Fig. 13.3.

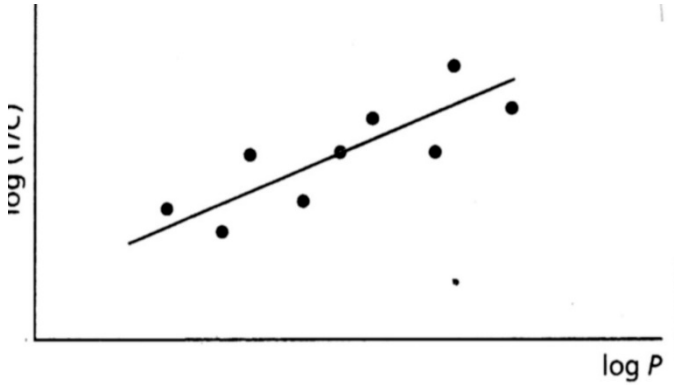


Figure 13.1 Biological activity versus log *P*.

Here, the biological activity increases as log P increases until a maximum value is obtained. The value of log P at the maximum (log P°) represents the optimum partition coefficient for biological activity. Beyond that point, an increase in log P results in a decrease in biological activity.

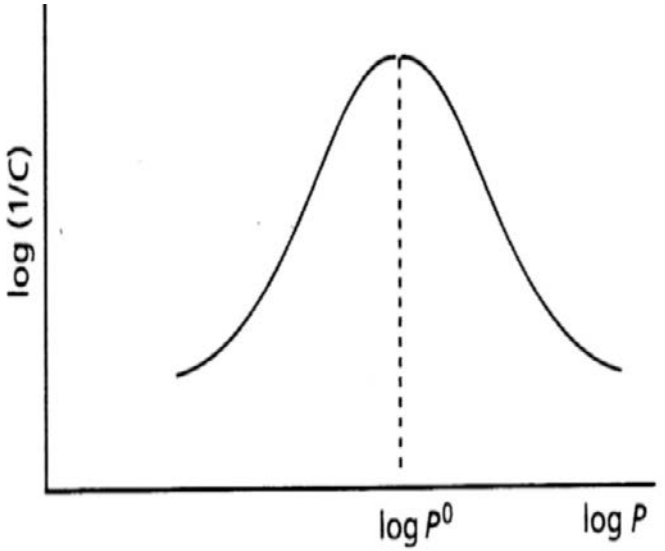
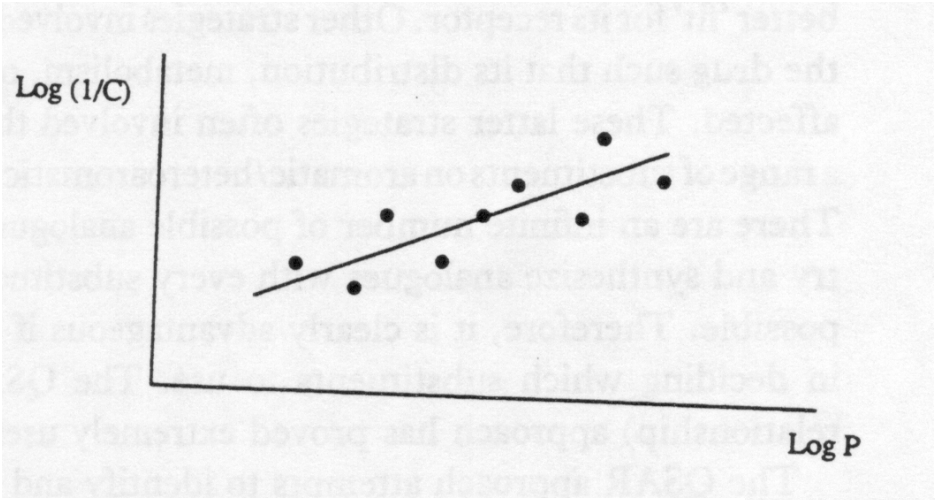
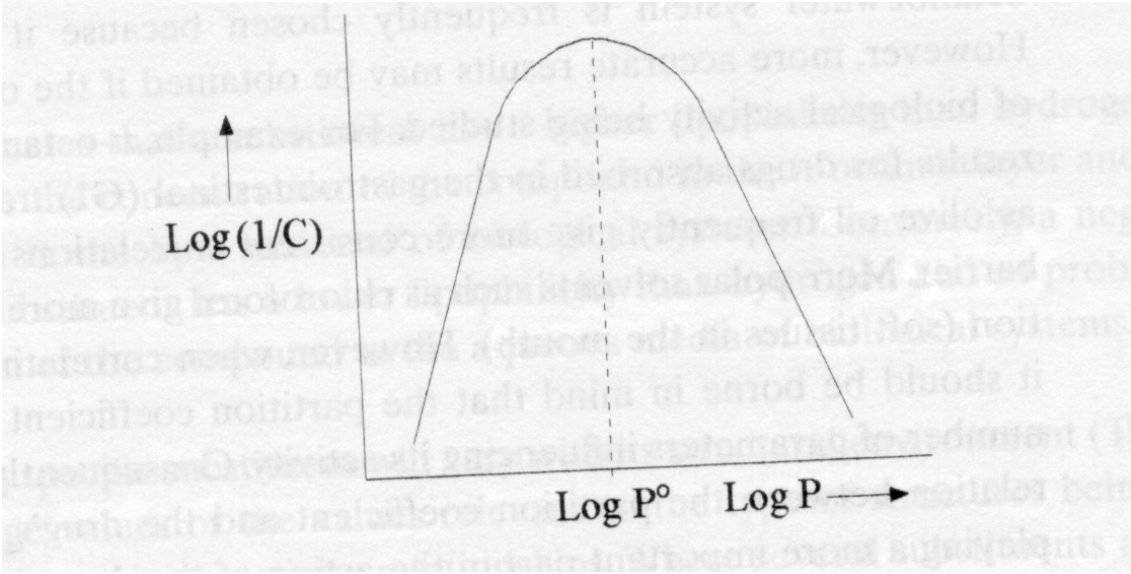


Figure 13.3 Parabolic curve of log (1/*C*) vs. log *P*.

Reasons: · poorly soluble in aqueous phase
· trapped in fat depots
. more susceptible to metabolism

Log P: Hydrophobicity





Quantitative structure-activity relationships(QSAR)

2 Physicochemical properties

2.1 Hydrophobicity

I. The partition coefficient (p)

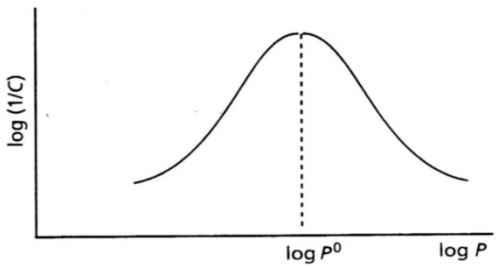


Figure 13.3 Parabolic curve of log (1/C) vs. log P.

7) The general anaesthetic activity of a range of ethers was found to fit the following parabolic equation:

$$\log (1 / C) = - 0.22 (\log P)^2 + 1.04 \log P + 2.16$$

According to this equation, anaesthetic activity increases with increasing hydrophobicity (P), as determined by the log P factor.

The negative $(\log P)^2$ factor shows that the relationship is parabolic and that there is an optimum value for log P ($\log P^\circ$) beyond which increasing hydrophobicity causes a decrease in anaesthetic activity.

With this equation, it is now possible to predict the anaesthetic activity of other compounds, given their partition coefficients.

2 Physicochemical properties

2.1 Hydrophobicity

I. The partition coefficient (p)

8) Since different anaesthetics have similar log P° values; the log P value of any compound can give some idea of its potential potency as an naesthetic.

For example, the log P values of the gaseous anaesthetics ether, chloroform, and halothane are 0.98, 1.97, and *2.3* respectively. Their anaesthetic activity increases in the same order.

Quantitative structure-activity relationships(QSAR)

2 Physicochemical properties

2.1 Hydrophobicity

I. The partition coefficient (p)

Since general anaesthetics have a simple mechanism of action based on the efficiency with which they enter the central nervous system:

it implies that log P values should give an indication of how easily any compound can enter the central nervous system.

In other words, compounds having a log P value close to *2* should be capable of entering the central nervous system efficiently. This is generally found to be true.

For example, the most potent barbiturates for sedative and hypnotic activity are found to have log P values close to *2.*

2 Physicochemical properties

2.1 Hydrophobicity

I. The partition coefficient (p)

9) As a rule of thumb, drugs which are to be targeted for the central nervous system should have a log P value of approximately 2.

Conversely, drugs which are designed to act elsewhere in the body should have log P values significantly different from 2 in order to avoid possible central nervous system side effects.

Quantitative structure-activity relationships(QSAR)

2 Physicochemical properties

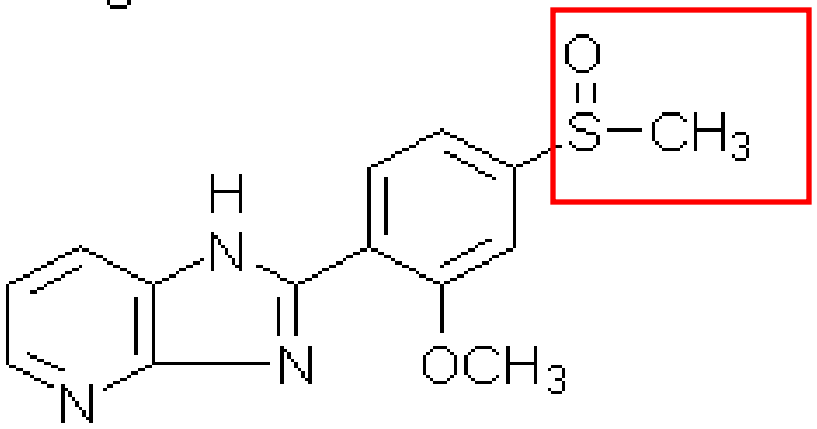
2.1 Hydrophobicity

I. The partition coefficient (p)

Example:

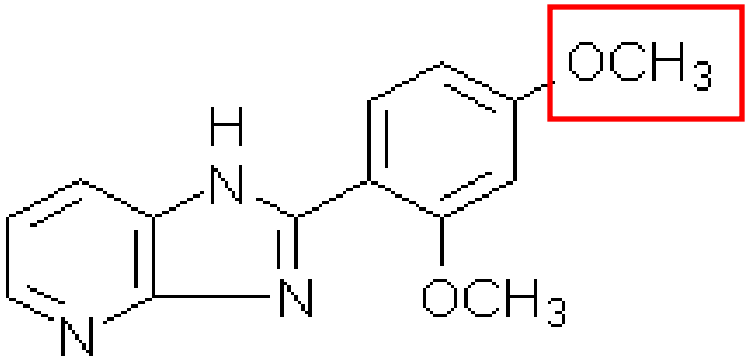
decreased CNS side effects

log P = 1.17



Sulmazole

log P = 2.49



-S(O)Me: same size as –OMe but more hydrophilic

Cardiotonic agent:

(bright vision in some patient ;entering CNS)

2 Physicochemical properties

2.1 Hydrophobicity

II. The substituent hydrophobicity constant (π)

1. **hydrophobicity of a compound can be quantified using the partition coefficient *P*.**
2. **In order to get *P*, we have to measure it experimentally and that means that we have to synthesize the compounds.**
3. **It would be much better if we could calculate *P* theoretically and decide in advance whether the compound is worth synthesizing.**
4. **QSAR would then allow us to target the most promising-looking structures. For example, if we were planning to synthesize a range of barbiturate structures, we could calculate log *P* values for them all and concentrate on the structures which had log *P* values closest to the optimum log *P*° value for barbiturates.**

2 Physicochemical properties

2.1 Hydrophobicity

II. The substituent hydrophobicity constant (π)

5. **Partition coefficients can be calculated by knowing the contribution that various substituents make to hydrophobicity.**

6. **This contribution is known as the substituent hydrophobicity constant π) and is a *measure of how hydrophobic a substituent is, relative to hydrogen.***

7. **The value can be obtained as follows:**

   Partition coefficients are measured experimentally for a standard compound such as benzene with and without a substituent (X).

8. **The hydrophobicity constant (π_X) for the substituent (X) is then obtained using the following equation:**

$$\pi_X = \log P_X - \log P_H$$

Quantitative structure-activity relationships(QSAR)

2 Physicochemical properties

2.1 Hydrophobicity

II. The substituent hydrophobicity constant (π)

$$\pi_X = \log P_X - \log P_H$$

where P_H is the partition coefficient for the standard compound and P_x is the partition coefficient for the standard compound with the substituent.

A positive value of π indicates that the substituent is more hydrophobic than hydrogen;

A negative value indicates that the substituent is less hydrophobic than hydrogen.

The π values for a range of substituents are shown in Table *13.1.*

The *p* value for the lead compound would have to be measured experimentally, but once that is known, the *p* value for analogues can be calculated quite simply.

π

$\pi_x = \log P_x - \log P_H$

- H is for standard compound

- positive π = substituent more hydrophobic than H
- negative π = less hydrophobic than H

Quantitative structure-activity relationships(QSAR)

2 Physicochemical properties

2.1 Hydrophobicity

II. The substituent hydrophobidty constant (π)

Table 13.1 Values of π for various substituents

Group	CH_3	*t*-Bu	OH	OCH_3	CF_3	Cl	Br	F
π (aliphatic substituents)	0.50	1.68	−1.16	0.47	1.07	0.39	0.60	−0.17
π (aromatic substituents)	0.52	1.68	−0.67	−0.02	1.16	0.71	0.86	0.14

π values for various substituents on aromatic rings

CH_3	t-Bu	OH	$CONH_2$	CF_3	Cl	Br	F
0.52	1.68	-0.67	-1.49	1.16	0.71	0.86	0.14

Theoretical Log P for chlorobenzene

= log P for benzene + π for Cl

= 2.13 + 0.71 = 2.84

Quantitative structure-activity relationships(QSAR)

2 Physicochemical properties

2.1 Hydrophobicity

II. The substituent hydrophobidty constant (π)

As an example, consider the log *P* values for benzene (log *P*= 2.13), chlorobenzene (log *P*= 2.84), and benzamide (log P= 0.64) (Fig. 13.4).

Benzene is the parent compound, and the substituent constants for Cl and $CONH_2$ are 0.71 and -1.49 respectively.

Having obtained these values, it is now possible to calculate the theoretical log *P* value for metachlorobenzamide:

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

$$= 2.13 + 0.71 + (-1.49)$$

$$= 1.35$$

The observed log P value for this compound is 1.51.

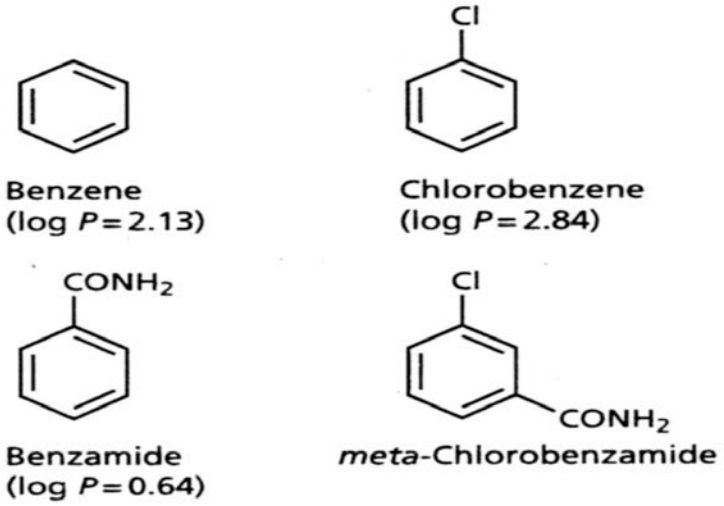


Figure 13.4 Values for log *P*.

2 Physicochemical properties

2.1 Hydrophobicity

II. The substituent hydrophobicity constant (π)

In order to distinguish calculated log *P* values from experimental ones, the former are referred to as Clog *P* values.

There are software programs which will calculate Clog P values for a given structure.

Quantitative structure-activity relationships (QSAR)

2 Physicochemical properties

2.1 Hydrophobicity

III. *P* vs. π

1 -The partition coefficient *P* is a measure of the drug's overall hydrophobicity, and is therefore an *important measure* of *how efficiently a drug* is

- ***transported to its target* and**
- ***bound to its binding site.***

2 - The π factor *measures* the *hydrophobicity* of a

- ***specific region* on the *drug's skeleton* and**
- ***if it is present in the QSAR equation,***

it(π)could emphasize any important hydrophobic interactions involving that region of the molecule with the binding site.

a measure of how hydrophobic a substituent is, relative to hydrogen.

III. *P* vs. π

3 - Most QSAR equations have a contribution from *P* or from π, but there are examples of drugs for which they have only a slight contribution. For example:

a study on antimalarial drugs showed very little relationship between antimalarial activity and hydrophobic character.

This finding supports the theory that these drugs act in red blood cells, since previous research has shown that the ease with which drugs enter red blood cells is not related to their hydrophobicity.

2 Physicochemical properties

2. 2 Electronic effects

1 - The electronic effects of various substituents will clearly have an effect on a drug's ionization or polarity.

This in turn may have an effect on:

- **how easily a drug can pass through cell membranes** or
- **how strongly it can interact with a binding site.**

It is therefore useful to measure the electronic effect of a substituent.

2 Physicochemical properties

2. 2 Electronic effects

2 - As far as substituents on an aromatic ring are concerned, the measure used is known as the :

Hammett substituent constant (σ).

This is a 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.

3 - Benzoic acid is a weak acid and only partially ionizes in water (Fig. 13.5).

An equilibrium is set up between the ionized and non-ionized forms, where the relative proportions of these species are known as the equilibrium or dissociation constant K_H (the subscript H signifies that there are no substituents on the aromatic ring).

$$K_H = \frac{[PhCO_2^-]}{[PhCO_2H]}$$

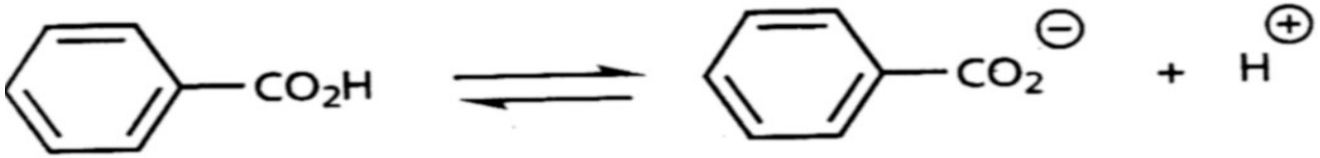


Figure 13.5 Ionization of benzoic acid.

2 Physicochemical properties

2. 2 Electronic effects

4 - When a substituent is present on the aromatic ring, this equilibrium is affected.

A - Electronwithdrawing groups, such as a nitro group,result in the aromatic ring having a stronger electronwithdrawing and stabilizing influence on the carboxylate anion.

The equilibrium will therefore shift more to the ionized form such that the substituted benzoic acid is a stronger acid and has a larger K_X value (X represents the substituent on the aromatic ring) (Fig. 13.6).

Quantitative structure-activity relationships (QSAR)

2 Physicochemical properties

2. 2 Electronic effects

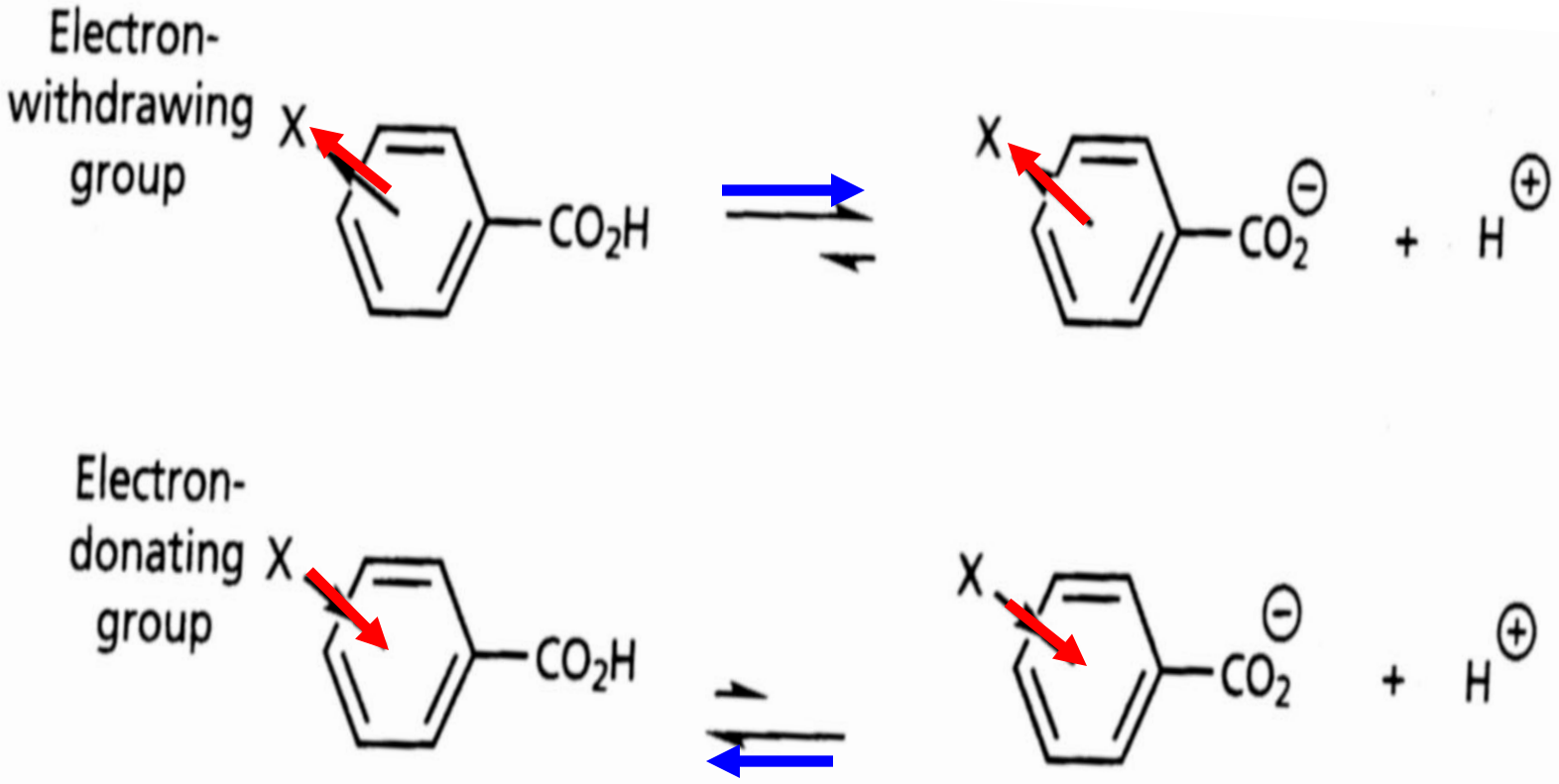


Figure 13.6 Position of equilibrium dependent on substituent group X.

2 Physicochemical properties

2. 2 Electronic effects

B - If the substituent X is an electron-donating group such as an alkyl group, then the aromatic ring is less able to stabilize the carboxylate ion. The equilibrium shifts to the left and a weaker acid is obtained with a smaller K_X value (Fig. 13.6)..

2 Physicochemical properties

2. 2 Electronic effects

5 - The Hammett substituent constant (σ_x) for a particular substituent (X) is defined by the following equation:

$$\sigma_X = \log(K_X/K_H) = \log K_X - \log K_H$$

Benzoic acids containing electron-withdrawing substituents will have larger Kx values than benzoic acid itself (K_H) and therefore the value of σ_x for an electron-withdrawing substituent will be positive.

Substituents such as Cl, CN, or CF3 have positive σ values.

2 Physicochemical properties

2. 2 Electronic effects

The Hammett substituent constant (σ_x) for a particular substituent (X) is defined by the following equation:

$$\sigma_X = \log(K_X/K_H) = \log K_X - \log K_H$$

Benzoic acids containing electron-donating substituents will have smaller K_x values than benzoic acid itself and hence the value of σ_x for an electron-donating substituent will be negative.

Substituents such as Me, Et, and *t-Bu* have negative values of σ.

The Hammett substituent constant for H is zero.

2 Physicochemical properties

2. 2 Electronic effects

6 - The Hammett constant takes into account both resonance and inductive effects. Therefore, the value of σ for a particular substituent will depend on whether the substituent is *meta* or *para*.

This is indicated by the subscript *m* or *p* after the σ symbol.

For example, the nitro substituent has :

σ_p=0.78 and σ_m =0.71.

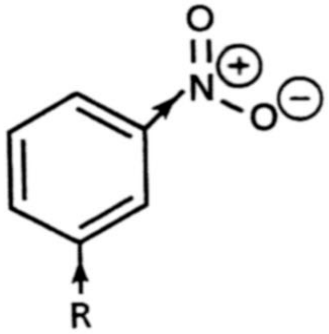
In the *meta* position, the electron-withdrawing power is due to the inductive influence of the substituent, whereas at the *para* position inductive and resonance both play a part and so the σ_p value is greater (Fig. *13.7).*

Quantitative structure-activity relationships (QSAR)

2 Physicochemical properties

2. 2 Electronic effects

meta Nitro group—electronic influence on R is inductive



para Nitro group—electronic influence on R is due to inductive and resonance effects

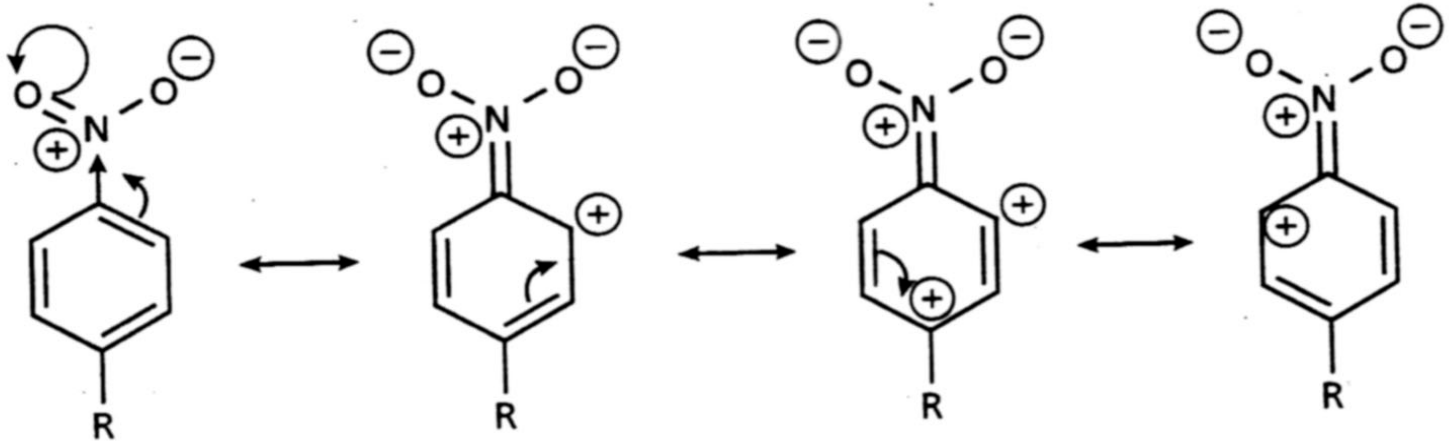


Figure 13.7 Substituent effects of a nitro group.

Quantitative structure-activity relationships (QSAR)

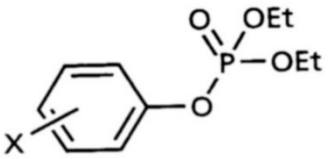
2 Physicochemical properties

2. 2 Electronic effects

The insecticidal activity of diethyl phenyl phosphates is one of the few examples where activity is related to electronic factors alone:

$$\log(1/C) = 2.282\sigma - 0.348$$

$$(r^2 = 0.952, r = 0.976, s = 0.286)$$



Diethyl phenyl phosphates

The equation reveals that substituents with a positive value for σ (i.e. electron-withdrawing groups) will increase activity (these drugs do not have to pass into or through a cell membrane to have activity).

In fact, these drugs are known to act on an enzyme called acetylcholinesterase which is situated on the outside of cell membranes.

The value of r is close to 1, which demonstrates that the line is a good fit, and the value of r^2 demonstrates that 95% of the data are accounted for by the σ parameter.

2.3 Steric factors

1. **The bulk, size and shape, of a drug will influence how easily it can approach and interact with a binding site.**

   - A bulky substituent may act like a shield and hinder the ideal interaction between a drug and its binding site.

   - Alternatively, a bulky substituent may help to orientate a drug properly for maximum binding and increase activity.

2 Physicochemical properties

2.3 Steric factors

2. **Steric properties are more difficult to quantify than hydrophobic or electronic properties.**

   Several methods have been tried, of which three are described here.

3. **It is highly unlikely that a drug's biological activity will be affected by steric factors alone, but these factors are frequently found in Hansch equations.**

2 Physicochemical properties

2.3 Steric factors

Steric Effects

much harder to quantitate

Examples are:

- **Taft's steric factor (Es) (~1956), an experimental value based on rate constants**
- **Molar refractivity (MR)--measure of the volume occupied by an atom or group--equation includes the MW, density, and the index of refraction--**
- **Verloop steric parameter--computer program uses bond angles, van der Waals radii, bond lengths.**

3 Hansch equation

1- biological activity of most drugs, however, is related to a combination of physicochemical properties.

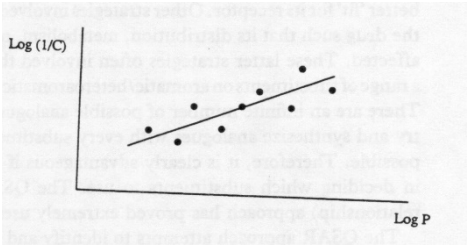
2 - In such cases, simple equations involving only one parameter are relevant only if the other parameters are kept constant.

3- These equations are known as Hansch equations and they usually relate biological activity to the most commonly used physicochemical properties (log *p* or π , σ ,and a steric factore)

Quantitative structure-activity relationships (QSAR)

3 Hansch equation

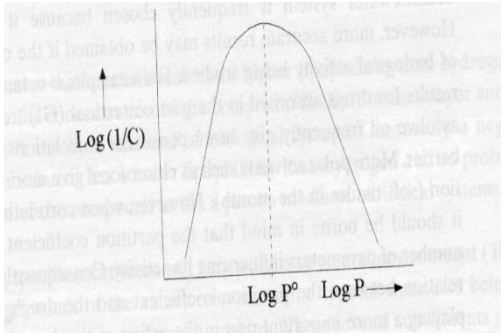
4- If the range of hydrophobicity values is limited to a small range then the equation will be linear, as follows:



$$\log(1/C) = k_1 \log P + k_2 \sigma + k_3 E_S + k_4$$

5- If the log P values are spread over a large range, then the equation will be parabolic

$$\log(1/C) = -k_1 (\log P)^2 + k_2 1\log P + k_3 \sigma + k_4 E_S + k_5$$



The constants k_1 - k_5 are determined by computer software in order to get the best fitting equation

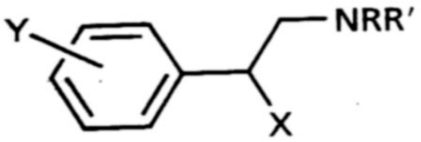
3 Hansch equation

6- Not all the parameters will necessarily be significant.

For example, the adrenergic blocking activity of *β*-halo-arylamines (Fig. 13.11) was related to π and σ and did not include a steric factor.

This equation tells us that biological activity increases if the substituents have a positive π value and a negative σ value.

In other words, the substituents should be hydrophobic and electron donating.



β-Halo-arylamines

$$\log\left(\frac{1}{C}\right) = 1.22\pi - 1.59\sigma + 7.89$$

$$(n = 22,\ r^2 = 0.841,\ s = 0.238)$$

Figure 13.11 QSAR equation for β-halo-arylamines.

4 Craig plot

1) **Although tables of π and σ factors are readily available for a large range of substituents, it is often easier to visualize the relative properties of different substituents by considering a plot where the y-axis is the value of the σ factor and the x-axis is the value of the π factor.**

Such a plot is known as a Craig plot.

The example shown in Fig. *13.12* is the Craig plot for the σ and π factors of *para*-aromatic substituents.

There are several advantages to the use of such a Craig plot.

π: ***a measure of how hydrophobic a substituent is, relative to hydrogen***

σ: ***a measure of the electron-withdrawing or electron-donating ability of a substituent***

Quantitative structure-activity relationships (QSAR)

4 Craig plot

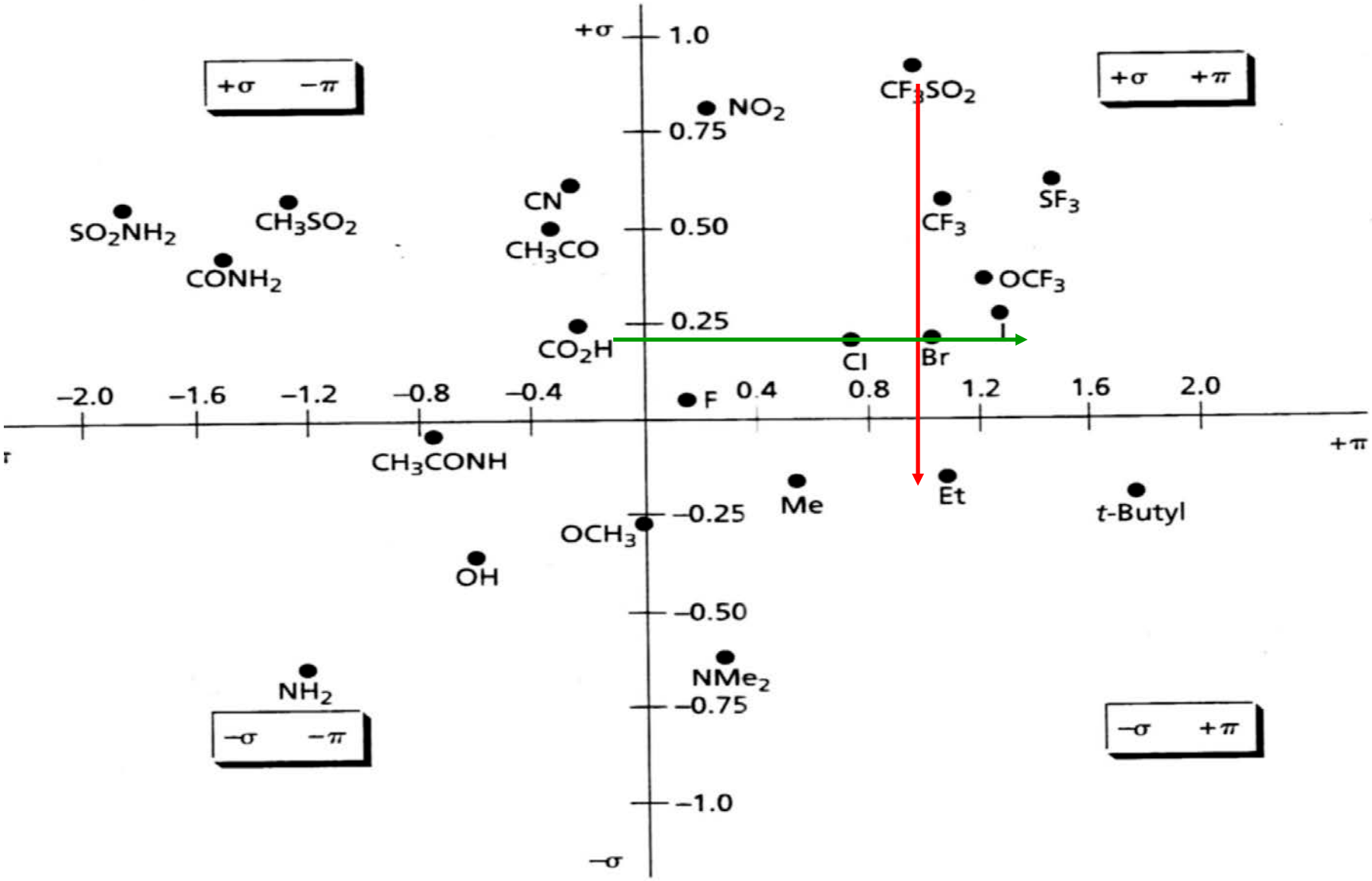


Figure 13.12 Craig plot.

4 Craig plot

2) The plot shows clearly that there is no overall relationship between π and σ.

The various substituents are scattered around all four quadrants of the plot.

It is possible to tell at a glance :

- **which substituents have positive π and σ**
- **which substituents have negative π and σ**
- **which substituents have one positive and one negative parameter**

4 Craig plot

3) **It is easy to see which substituents have similar π values.**

For example, the ethyl, bromo, trifluoromethyl, and trifluoromethylsulfonyl groups are all approximately on the same vertical line on the plot.

In theory, these groups could be interchangeable on drugs where the principal factor affecting biological activity is the π factor.

Similarly, groups which form a horizontal line can be identified as being isoelectronic or having similar a σ values (e.g. CO_2H, Cl, Br; I).

5 - Bioisosteres

1. **Tables of substituent constants are available for various physicochemical properties.**

A knowledge of these constants allows the medicinal chemist to:

identify substituents which may be potential bioisosteres.

Thus, the substituents CN, NO_2, and COMe have similar hydrophobic, electronic, and steric factors, and might be interchangeable.

Such interchangeability was observed in the development of cimetidine.

5- Bioisosteres

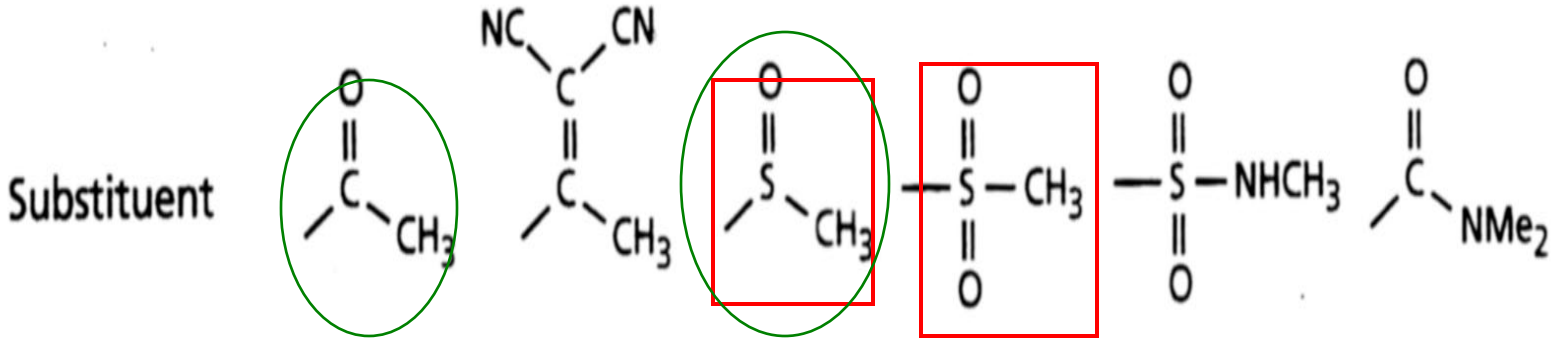
2. ***The important thing to note is that groups can be bioisosteric in some situations, but not others.***

   Consider for example the table shown in Fig. 13.17. This table shows physicochemical parameters for six different substituents.

If the most important physicochemical parameter for biological activity is σ_P, then the $COCH_3$ group (0.50) would be a reasonable bioisostere for the $SOCH_3$ group (0.49).

If, on the other hand, the dominant parameter is π, then a more suitable bioisostere for $SOCH_3$ (– 1.58) would be SO_2CH_3 (– 1.63).

5 - Bioisosteres



Substituent						
π	−0.55	0.40	−1.58	−1.63	−1.82	−1.51
σ_p	0.50	0.84	0.49	0.72	0.57	0.36
σ_m	0.38	0.66	0.52	0.60	0.46	0.35
MR	11.2	21.5	13.7	13.5	16.9	19.2

Figure 13.17 Physicochemical parameters for six substituents.

π: a *measure* *of how hydrophobic a substituent is, relative to hydrogen*

σ: *a measure* *of the electron-withdrawing or electron-donating ability of a substituent*

6 - 3D QSAR

In recent years, a method known as 3D QSAR has been developed in which the 3D properties of a molecule are considered as a whole rather than by considering individual substituent or moities.

This has proved remarkably in useful the design of new drugs. Moreover, the necessary software and hardware are readily affordable and relatively easy to use.

The philosophy of 3D QSAR revolves around the assumption that the *most important features about a molecule* are its *overall size* and *shape*, and *its electronic properties (electrostatic fields).*

6 - 3D QSAR

If these features can be defined, then it is possible to study how they affect biological properties.

There are several approaches to 3D QSAR, but the method which has gained ascendancy was developed by the company Tripos and is known as CoMFA (Comparative Molecular Field Analysis).

CoMFA methodology is based on the assumption that drug-receptor interactions are noncovalent and that changes in biological activity correlate with the changes in the steric and/or electrostatic fields of the drug molecules.

KEY POINTS

- **QSAR relates the physicochemical properties of a series of drugs to their biological activity by means of a mathematical equation.**

- **The commonly studied physicochemical properties are hydrophobicity, electronic factors, and steric factors.**

- **The partition coefficient is a measure of a drug's overall hydrophobicity. Values of log *P* are used in QSAR equations, with larger values indicating greater hydrophobicity.**

KEY POINTS

- **The substituent hydrophobicity constant (π) is a measure of the nydrophobic character of individual substituents.**

  The value is different for aliphatic and aromatic substituents and is only directly relevant to the class of structures from which the values were derived.

  Positive values represent substituents more hydrophobic than hydrogen;

  negative values represent substituents more hydrophilic than hydrogen.

KEY POINTS

- **The Hammett substituent constant (σx) is a measure of how electron-withdrawing or electron-donating on aromatic substituent is.**

It is measured experimentally and is dependent on the relative position of the substituent on the ring.

The value takes into account both inductive and resonance effects.

Quantitative structure-activity relationships(QSAR)

2 Physicochemical properties

2.1 Hydrophobicity

I. The partition coefficient (p)

P = [drug] in octanol / [drug] in water

Vary log P & see how this affects the biological activity.

Biological activity normally expressed as 1/C,

where C = [drug] required to achieve a defined level of biological activity.

The more active drugs require lower concs.

2 Physicochemical properties

2.1 Hydrophobicity

I. The partition coefficient (p)

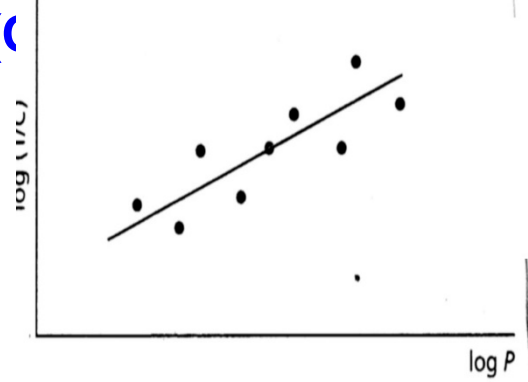


Figure 13.1 Biological activity versus log *P*.

Plot log 1/C vs. log P

Typically over a small range of log P, *e.g.* 1-4, a straight line is obtained

***e.g.* log 1/C = 0.75 log P + 2.30**

If graph is extended to very high log P values, then get a parabolic curve. Reasons:

- **poorly soluble in aqueous phase**
- **trapped in fat depots**

more susceptible to metabolism

Log P

Parabolic curve:

$\log 1/C = - k_1 (\log P)^2 + k_2 \log P + k3$

- When P small, dominated by log P term
- When P large, log P squared dominates & so activity decreases

Log P Values: Uses

With these equations for anesthetics (ethers only), it is possible to predict activity if log P known (doesn't work if structure very different)

ether	chloroform	halothane
0.98	1.97	2.3

(anesthetic activity increases in same order)

Drugs with Log P values close to 2 should be able to enter the CNS efficiently

e.g. barbiturates have log P values close to 2 also; want to make sure log P value is much lower if you don't want possible CNS side effects

2 Physicochemical properties

2. 2 Electronic effects

Uses

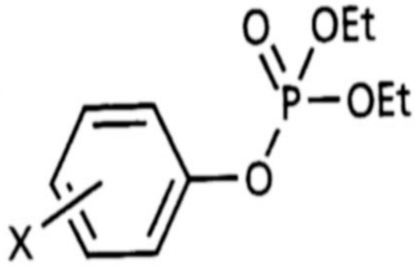
Only one known example where just Hammett constants effectively predict activity (insecticides, diethyl phenyl phosphates.

These drugs do not have to pass into or through a cell membrane to have activity).

Log (1/C) = 2.282 **σ** – 0.348

$$\log(1/C) = 2.282\sigma - 0.348$$

$$(r^2 = 0.952, r = 0.976, s = 0.286)$$



Diethyl phenyl phosphates

Quantitative structure-activity relationships(QSAR)

2 Physicochemical properties

2.1 Hydrophobicity

II. The substituent hydrophobicity constant (π)

$$\pi_X = \log P_X - \log P_H$$

where P_H is the partition coefficient for the stanadrd compound and P_X is the partition coefficient for the standard compound with the substituent.

A positive value of π indicates that the substituent is more hydrophobic than hydrogen; a negative value indicates that the substituent is less hydrophobic. The π values for a range of substituents are shown in Table *13.1.*

These ππ values are characteristic for the substituent and can be used to calculate how the partition coefcient of a drug would be affected if these substituents were present.

The *p* value for the lead compound would have to be measured experimentally, but once that is known, The *p* value for analogues can be calculated quite simply

2 Physicochemical properties

2.1 Hydrophobicity

III. *P* vs. π

P **measures drug's overall hydrophobicity & measures drug's transportability**

π measures the hydrophobicity of a specific region on the drug ; hydrophobic bonding to a receptor

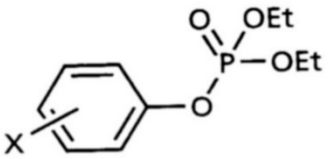
2 Physicochemical properties

2. 2 Electronic effects

The insecticidal activity of diethyl phenyl phosphates is one of the few examples where activity is related to electronic factors alone:

$$\log(1/C) = 2.282\sigma - 0.348$$

$$(r^2 = 0.952, r = 0.976, s = 0.286)$$



Diethyl phenyl phosphates

The equation reveals that substituents with a positive value for σ (i.e. electron-withdrawing groups) will increase activity. The fact that the a hydrophobic parameter is not present is a good indication that the drugs do not have to pass into or through a cell membrane to have activity. In fact, these drugs are known to act on an enzyme called acetylcholinesterase which is situated on the outside of cell membranes.

The value of r is close to 1, which demonstrates that the line is a good fit, and the value of r^2 demonstrates that 95% of the data are accounted for by the σ parameter.

6 Free-Wilson approach

In the Free-Wilson approach to QSAR, the biological activity of a parent structure is measured then compared with the activities of a range of substituted analogues.

An equation is then derived which relates biological activity to the presence or otherwise of particular substituents (X_1-X_n):

$$\text{activity} = k_1X_1 + k_2X_2 + k_3X_3 + \cdots + k_nX_n + Z$$

6 Free-Wilson approach

In this equation, X_n is defined as an indicator variable and is given the value 1 or 0, depending on whether the substituent (*n*) is present or not.

The contribution that each substituent makes to the activity is determined by the value of k_n.

Z **is a constant representing the overall average activity of the structures studied.**