**CHAPTER 1 INTRODUCTION**

Organic compounds can be prepared with structural variation in the vicinity of a reaction centre and thus it is possible to allow an almost continuous variation in its electrophilic or nucleophilic character. This capacity may then be used as a delicate probe into the effects caused by electronic perturbation upon reaction and from which the electronic demands of the reaction may be inferred. Many rate constants and equilibrium constants for organic reactions in solution have been measured and the spectra (IR, UV, NMR etc.) of thousands of organic compounds have been recorded. As this body of quantitative results has been enormous, it becomes important to summarize and analyze data. The summarizing has involved the development and application of empirical correlations by means of which one body of data can be related to another. At the same time, the data may be analyzed to reveal the fundamental factors underlying the phenomena in question. This general approach is commonly known as correlation analysis.

One of the most successful and intensively investigated empirical relationships towards quantitative exploration of reactivity in organic chemistry is the famous Hammett equation.1-15 The Hammett equation describes linear relationship involving log k or log K of substituted benzoic acids. Such correlations may be described as rate-rate, equilibrium-equilibrium or rate-equilibrium relationships. These relationships are usually referred to as Linear Free Energy Relationships (LFER). The term LFER has often been used to cover the whole correlation analysis in organic chemistry. A brief account of correlation analysis is given below:

**1.1 The Hammett equation**

The Hammett equation3,12,14,15 is usually expressed in the form of equations (1.1) and (1.2), where k or K is the rate or equilibrium constant respectively for a side-chain reaction of *meta*- or *para*-substituted benzene derivative.

log k = log ko + *ρ*σ (1.1) log K = log Ko + *ρ*σ (1.2)

The symbol ko or Ko denotes the statistical quantity approximating to k or K for the unsubstituted or parent compound. The empirical constant σ, known as substituent constant, measures the polar effect relative to hydrogen as a substituent in the *meta*- or *para*- position and is, in principle, independent of the reaction. The other constant *ρ*, known as reaction constant, depends on the nature of the reaction and measures the susceptibility of the reaction to polar effects. The value of *ρ* is determined by the reaction and its condition such as a reagent, solvent, catalyst and temperature and is independent of the nature of the substituents. The ionization of benzoic acids in water at 25o C is taken as the standard reaction for which *ρ* is defined as 1.0. The value of σ for a given substituent is thus log (K/Ko), where Ko is the ionization constant of the substituted benzoic acid itself. The magnitude of *ρ* measures the extent of transmission of the electronic effect of substituents. The validity of the above equations (1.1) and (1.2) is restricted to substituents in the *meta*- and *para-* positions of the benzene ring. These equations (1.1) and (1.2) were tested by Hammett15 on fifty-two reaction series and found to express a large body of experimental data with a mean deviation of about ±15 percent.

The electron density at the reaction site is determined by the ability of the substituent to withdraw or donate electrons and is measured by σ constants. Electron-attracting substituents have positive values of σ and electron-releasing substituents have negative values of σ. The σ scale covers roughly the numerical range 0 ± 1.0.

A reaction which is facilitated by reducing the electron density at the reaction centre has a positive value of *ρ* and one facilitated by increasing the electron density at the reaction centre has a negative value. The *ρ* scale covers roughly 0 ± 4. The sign of *ρ* in radical reactions cannot easily be predicted. However, the electron distribution in the transition state of radical reactions can be inferred from the experimental value. The dependence of *ρ* on temperature has the form16,17 of equation (1.3).

*ρ* = constant (1- β/T) (1.3)

The slope of *ρ* vs T-1 plot is usually positive,8 so that *ρ* decreases with temperature. The slope is usually small even almost zero18,19 but steep dependences20 and even reversal ones8 have also been described.

The dependence of *ρ* on solvent21-23 is very marked but is not well understood theoretically. It seems that the effect of solvent cannot be described by a single parameter equation.

Of the factors controlling the absolute values of *ρ*, the distance of the substituents from the reaction centre is very important and more so are the length and nature of the side chain. When the side-chain is extended by inserting in it a group Y, the constant *ρ* decreases in the ratio Лy (the transmission factor) defined in equation (1.4)

Лy = *ρ*yz / *ρ*z (1.4)

Where *ρ*yz is the reaction constant for the compound of the type Ar-Y-Z and *ρ*z is the reaction constant for the compound of the type Ar-Z.

The value of Л indicates the ability of the chain to transmit polar effects;24-27 however, in order to obtain results of general validity, π must be independent of the reaction centre chosen (Z), as indicated in Eq. (1.5).

*ρ*yz / *ρ*z = *ρ*yz ’ / *ρ*z ’ (1.5)

The equation (1.5), the so called *ρ* – *ρ* relationship, has been shown to hold in the dissociation of carboxylic acids, their reactions with diazodiphenylmethane and hydrolysis of their esters.25-29 For the insertion of a CH2 group in Ar-Z, π corresponds to the value of about 0.419,30 and with two CH2 groups it decreases to ca. 0.2.8,27,29 Replacing one CH2 group by a hetero atom (oxygen27,31,32 or Sulphur31,33,34), a sulphoxy,31,33 a sulphonyl group31,33 or an amino group35,36 has little effect on the value of π.

Conjugated chains transmit polar effects much better than saturated chains. A CH=CH group is approximately equivalent to one CH2 group.25,27,37,38

Transmission through the C≡C group is similar39 to that of the C=C bond but it is weaker than through the CH=CH group.27,40,41 Even longer conjugated chains transmit electronic influence effectively.42-45

As early as 1953, Jaffe8 examined the application of the Hammett equation to about 400 reaction series and on the basis of the correlation coefficient concluded that about 70% of the correlations were satisfactory (r > 0.95) or excellent (r > 0.99). This suggests that about 30 % of the rate or equilibrium data are outside the scope of the Hammett equation in its original form and mode of application.

Deviations are commonly shown by *para*-substituents of considerable +R or -R effect. When σ values based on the ionization of benzoic acids are used, deviations may occur with highly electron-withdrawing *para*-substituents (+R substituents) for reactions involving -R electron-rich reaction centres and with highly electron-releasing substituents (-R substituents) for reactions involving +R electron-poor reaction centers. These deviations, have been explained in terms of ‘cross conjugation’ i.e., conjugation involving substituent and reaction center. In each case, ‘exalted’ σ values are required for conformity to the Hammett equation. The special substituent constants for +R substituents are denoted by σ – and those for -R substituents are denoted by σ +.46 The values of σ – are based on the ionization of either anilinium ions or phenols in water. The values of σ + are based on the rates of solvolysis of t-cumyl chlorides in 90 % acetone-water at 25o C.

The use of σ + and σ –  greatly extends the range of applicability of the Hammett equation.47-49 However, the contribution of the resonance effect of a substituent relative to its inductive effect must, in principle, vary continuously as the electron-demanding quality of the reaction center varies, i.e., depending upon whether it is electron-rich or electron-poor. Hence for each substituent having a resonance effect, a sliding scale of substituent constants would be expected and not just a pair of discrete values of σ + and σ for -R substituents or σ –  and σ for +R substituents. This tends towards the situation in which the substituent constant becomes reaction dependent. Therefore, various multimeter extensions of the Hammett equation appeared, notably the Yukawa-Tsuno equation,50,51 the Taft-Lewis equation,52-56 and the Swain-Lupton equation.57

**1.2 Multiparameter extensions of the Hammett equation**

Yukawa and Tsuno50 proposed a method for dealing with -R substituents in their influence on reactions which are more electron-demanding than the ionization of benzoic acids. They suggested that values of (σ+- σ) would provide a scale of enhanced resonance effects and they modified the Hammett equation as

log k = log ko + *ρ*[σ +r (σ+ - σ ) ] (1.6)

The equation (1.6) implies the multiple linear correlations of log k with σ and (σ+- σ). The quantity r is a proportionality constant giving the contribution of the enhanced resonance effect for -R substituents. If r = 0 the equation is reduced to the simple Hammett equation and if r = 1, it corresponds to a straight forward correlation with σ +.

A corresponding equation with σ – constants to deal with the influence of +R substituents on reactions which are less electron-demanding than the ionization of benzoic acids was formulated by Yoshika *et al*.51

log k = log ko + *ρ*[σ +r ( σ -- σ ) ] (1.7)

According to Taft52-54, the Hammett σ values are quantitatively separable into inductive and resonance contributions through the following equations:

σm = σI + ασR (1.8)

σp = σI + σR (1.9)

The inductive effect given by σI is assumed to operate equally from the *meta*- and *para*-positions. The resonance effect given by σR, contributes to σm indirectly, α being the “relay coefficient”. Taft and Lewis53,54 set up a σI scale based on alicyclic and aliphatic reactivities. Based on the ionization of benzoic acid, a value for α of 0.33 was suggested.

Exner58 carried out a modified analysis based on the following equations:

σm = σI + 0.33 σR (1.10)

σp = λσI + σR (1.11)

The coefficient λ expresses any differences in the operation of the inductive effect as between the *meta*- and the *para*- position. Exner58 was in favour of λ = 1.14 i.e., the inductive effect operates more powerfully from the *para-*position. The dissection of parameters into σI and σR  type contributions gives the possibility of a ‘dual substituent parameter’ treatment for reaction series through an equation.53,54

log (k/ko) = *ρ*I σI + *ρ*R σR (1.12)

In Taft’s treatment, each substituent is characterized by position-independent σI and σR values, but the susceptibility to inductive and to resonance effect is to be expressed separately through position-dependent *ρ*I  and *ρ*R values. The separation into inductive and resonance effects has been performed for σ+, σ- and σo (based on ‘insulated’ system) constants to give σR+, σR- and σRo respectively.

Swain and co-workers57,59 have expressed the polar effect of any given substituent in terms of two basic characteristics: a field constant, F, and a resonance constant, R. All the various σ constants are the linear combinations for F and R of the form, Eq. (1.13)

σ = f F + r R (1.13)

The field, f, and resonance, r, are weighting factors which give the blend of field and resonance effects for the systems used to define the particular σ scale. This treatment has found extensive application in the correlation analysis of NMR data. Application to chemical reactivity seems to be restricted to a few instances.

**1.3 *ortho*-Effect**

Linear free energy relationship to the Hammett type have been used to correlate vast numbers of rate (k) and equilibrium constant (K) for reactions of *meta-* and *para*- substituted derivatives. Since the Hammett equation has been so successful in the treatment of the effects of groups in the *meta-* and *para-* position, it is not surprising that attempts have been made to apply it to *ortho-*positions also.60,61 The effect on a reaction rate or equilibrium constant of a group in the *ortho-*position is called *ortho-* effect. The *ortho-*substituents are bound to the adjacent position of the side-chain various kinds of proximity effects, such as steric and proximity electric effects, which are otherwise insignificant, generally operate on the side chain functions. Hydrogen bonding and other intramolecular interactions of *ortho-*substituents may sometimes play significant roles in reactivities of *ortho*-substituted derivatives. Unfortunately, these proximity effects contribute in varying degrees in different systems. Thus, the reactivities of *ortho-*substituted compounds are not explained by a single, generally applicable set of parameters. However, a correlation can be achieved in one of the following ways3.

log k = *ρ*\*σ o\* + h (1.14)

σ o\* is the *ortho-*substituent constant and *ρ*\* is the susceptibility constant.

log k = δ Es + h (1.15)

Es is the steric substituent constant and δ is the susceptibility constant. The ratio of the rate constant for an *ortho-* to that of corresponding *para-*substituted benzene derivatives, ko/kp may frequently be taken as an approximate measure of the steric effect of the *ortho-*substituents.62

log (k/ko) = = *ρ*\* σ o\* + δ Es (1.16)

The above equations (1.14), (1.15) and (1.16) are due to the work of Taft.

Charton’s treatment, on the *ortho-*substituent effect, is considered to be a better treatment because of its wider applicability in understanding the nature of the *ortho-*effect. He derives two multiparameter equations. They are as follows,

log k = α σI + β σR + h (1.17)

where σI and σR are the inductive and resonance substituent constants α and β are the localized and delocalized components and h is the intercept.

log k = α σI + β σR + φ ν + h (1.18)

where ν is the parameter for the steric effect and φ is the coefficient of the steric term. Thus, the separation of polar, resonance and steric effect has received much attention in recent years.

**1.4 Correlation with spectroscopic data**

Though correlation of the substituent constant σ was originally proposed to equilibria and reaction rates, the substituent constants have also been applied to optical spectroscopy,63 NMR spectroscopy6,7 and to mass spectroscopy of organic compounds.64 Thus correlations of infrared frequencies65-68 with substituent constants and also of 1H and 13C NMR substituent-induced chemical shifts (SCS)69-77 have received considerable attention. Substituent effects in the mass spectra of organic compounds are also often explained with the Hammett σ constants.64,78-81

**1.5 Investigation of substituent effects by 1H and 13C NMR spectra**

Soon after the first systematic studies of the 13C NMR of aromatic  
compounds were done it became evident that 13C SCS are likely to be useful for the three reasons.

i) The inherently high dispersion of 13C SCS means that data would be obtained with fairly high precision, ii) There appears to be a close relationship between the 13C chemical shift of a nucleus and the calculated charge density at that atom, thereby reinforcing the supposed parallelism with substituent electronic perturbations, iii) The 13C probe does not itself introduce any perturbation. Consequently, 13C chemical shifts have been used extensively as monitors of molecular structure and electronic distribution.

l3C NMR chemical shift measurements are increasingly used for the investigation of the electronic effects of the substituents and their mode of transmission through aromatic and other unsaturated systems. In benzene derivatives, a substituent exerts a characteristic substituent effect on the chemical shifts of the ring carbon atoms. The carbon shielding and the chemical reactivity parameter reflect the changes in local charge density arising from the electronic influence of the substituent and hence these two quantities can be correlated.

The substituents may affect the local charge density of an aromatic carbon by various effects (Iσ, F, πσ, πF, R, πorbital and σπ*).* These changes in charge density at the aromatic carbons affect the paramagnetic shielding term.82 Electron releasing substituents delocalize their lone pair of electrons into the π*-* system and increase the charge density at the *o-* and *p-* carbons of benzene derivatives. Electron attracting substituents can delocalize the π*-*electrons of the ring and thereby reduce the charge density at the *o-* and *p-* carbons. Thus, electron releasing substituents shield the *o-* and *p-* carbons while electron attracting substituents have a deshielding influence.

The effect of substituents in the ring on the chemical shifts of side-chain carbons is of obvious interest, especially in those cases where the side-chain carbon is conjugated with the ring. This allows resonance interaction with substituents to take place and the effect of distance on the extent of such interactions can be explored. The chemical shifts of sp2 and sp carbons directly bonded to the ring have been observed to show ‘reverse’ substituent effects83,84, i.e. electron attracting substituents apparently increase the electron density on the carbon concerned whereas electron releasing substituent decrease it. This phenomenon has been attributed to the polarization of the π- system of the side chain.

Correlation of the chemical shift with substituent constant (e.g. Hammett σ) has been widely used to investigate the nature of the effect of the substituent of the physical properties of compounds. Electron density around the nucleus of interest (C, H) is mostly affected by the electron donating and electron withdrawing ability of the substituent. Therefore, a correlation between the observed chemical shift and any parameter representing such ability seems to be well-founded, and would indicate that the effect of any other rate would be satisfactorily predicted by simply measuring the chemical shift of a given derivative, and there are numerous reports on the subject.85 Correlation of these parameters has now been applied, originally proposed to equilibria and reaction rates, to spectroscopic properties such as 1H and 13C NMR substituent induced chemical shifts (SCS) in recent years.85- 92

The proton chemical shifts are influenced by magnetic anisotropies of neighbouring groups and by intermolecular (e.g. solvent) effects. In contrast with 1H NMR chemical shifts, 13C chemical shifts are relatively insensitive to the magnetic anisotropy effects93 and to solvent and concentration effects.94

Extensive correlations of 13C chemical shifts in mono-substituted benzenes with Hammett σconstants were first reported by Spieseck and Schneider95, following the pioneering studies of Lauterbur.96 It was observed that the chemical shifts measured for the *para*-ring carbons δ (Cp)of a series of mono-substituted benzenes were approximately related to the *σ*p*+* values of the substituents.94,97 Attempts to find analogous relationships for δ(Cm)of mono substituted benzenes have met with varied success.95,97,98 Schulman *et al*.97 have shown that δ (Cm) values of the substituents with non-bonding electron pairs correlate well with σm+, but those of the remaining substituents give less satisfactory correlations.

A report on the correlation of NMR chemical shifts with Hammett values and analogous parameters99 has been given as,

δ= *⍴* σ + δo  (1.19)

In Eq. (1.19), δis the chemical shift; σis an appropriate reactivity (Hammett) parameter such as σ*+*p, σ*-*p*,* σm*,* σI, σR (BA), σoR, σ+R, σ-R. *⍴* is a proportionality constant and δo is the intercept. For several chemical structures, single parameter relationship does not give satisfactory correlations. Therefore, several dual substituent parameter (DSP) extensions of the Hammett approach have been developed. Among them, the most important are Swain and Lupton22 (Eq.1.20) and Ehrenson *et al.*100 (Eq.1.21).

δ =ƒ F+ r R + δ*°* (1.20)

δ *= ⍴*I σI *+ ⍴*R σR +δ*°* (1.21)

The important difference between the two is that Swain and Lupton apply a single set of F and R values whereas Ehrenson *et al*.101 allow a choice of four distinct σR scales (σR (BA), σ°R, σ-R and σ+R). Yukawa and Tsuno102 proposed an equation (1.6) for dealing with the enhanced resonance effects and they modified the Hammett equation as follows (Eq. 1.22),

δ *= ⍴*σ + r (σ+ - σ) + δo (1.22)

the quantity 'r' is a proportionality constant giving the contribution of the enhanced resonance effects for +M substituents.

The DSP analysis of sterically congested systems has been improved by TSP by using Charton’s steric parameter using Eq. (1.23).

δ= *⍴*I σI *+ ⍴*R σR+ φν + δo (1.23)

The DSP equation (1.21) is the most generally useful treatment and is well suited for the analysis of spectroscopic data. In equation (1.21), the derived *⍴*I and *⍴*Rvalues which are position-dependent, give a direct measure of the relative transmission of inductive and resonance effects. The DSP method represents a general approach for the correlation of substituent effects over a large range of different datasets. The generality is due to the independence of the *⍴*Iand *⍴*Rtransmission coefficients. Since inductive and resonance effects are transmitted by different mechanisms103 their relative importance may change from one system to another. This feature cannot be accommodated104 in a single parameter approach. The answer to the question whether a DSP method or a single parameter equation will best describe the SCS of the various systems is a subject of controversy. Paper presented in the last 2 decades may be mentioned to exemplify this. Cornelis *et al*.105 and Bottino *et al.*106 by an examination of a number of styrene derivatives reached the conclusion that the DSP treatment, in general, is not significantly superior to the simpler single parameter treatment. But Cornelis data enabled Craik and Co-workers104  to show the power of the DSP method. Anu *et al****.***107also have proved the power of the DSP method. It may be concluded that,

1. while in some situations there might be no significant importance in fits obtained by the DSP method compared with single parameter treatment, this is not so in the general case, and
2. the *⍴*Iand *⍴*Rvalues obtained from the DSP analysis are extremely useful in assigning mechanistic significance to proposed pathways for the transmission of substituent effects.

The relative importance of the resonance and inductive effects is expressed by blending factor (λ) obtained as the ratio of the coefficients r and ƒ or *⍴*Iand *⍴*R.

**1.6 The nature and mechanism of transmission of electronic effects**

In order to assess the influence of substituents on the chemical shift of organic molecules a clear understanding of the nature and transmission of the different types of substituent effects is necessary.

**1.6.1 The inductive effect**

The basis of this electronic perturbation originates in part from differences in electro negativity which causes polarization of both σ- and π- bonds and also from electrostatic effects experienced at the reaction center due to charges and dipoles resident on the substituent. A polarization of both σ- and π- bond by the substituent group is known as inductive effect Fig. (1.1), becoming progressively attenuated. The other, known as a field effect Fig. (1.2) is propagated through space and depends more on its intensity on proximity than on the number of bonds separating source and receptor. The electronic dipole field of the polar substituent-substrate bond can influence the reaction center across space and this is called field effect.108-112



Fig. 1.1



Fig. 1.2

The substituent effects in various aromatic systems act through polarization of π-electrons whether the polar nature of a substituent or substituent-carbon bond can polarize a π-system without charge transfer. This has been generally referred to as a π- inductive effect113, which can arise in two ways.

1. Induction of charge differences on the underlying σ- framework may lead to compensating changes in the π- electronic distribution and is designated as πσ effect. 108,114,115 The partial charges on CH2-X, which in turn cause a redistribution of charge by an alternate polarization of π- electrons as in

Fig. (1.3).

1. The π-system may also be polarized by a through-space electrostatic interaction with a remote dipole and this effect is termed as πF effect.



Fig 1.3

The π- system may also be perturbed by repulsive interactions with a neighbouring filled orbital on the substituent. This orbital repulsion effect is designated as πorbital Fig. (1.4).



Fig 1.4

The π-electron system may also be polarized as in Fig. (1.5) by charge or   
dipoles located on the substituent. This effect called **π**-polarization is basically  
different from π-inductive effect in the magnitude of charge density reorganization at the *ortho*- and *meta-* positions.



Fig. 1.5

**1.6.2 The resonance effect:**

The interaction of substituent orbitals of suitable systems with the π-orbitals of the ring can lead to charge transfer either to or from the substituent and this is called resonance effect (R). In order to exercise a resonance effect, a substituent must possess a p- or π- orbital which is available to conjugate with the π-MOs of the aromatic system.

1. X- is a donor group and typically possesses an unshared electron pair or

**π-e**lectrons on atom directly attached to the ring.  
 -NR2, -OR, -SR, -Cl, -CH= CH2  
 (ii) substituents Z have a π*-* acceptor centre adjacent to the ring.



This effect, important in systems such as C6H5-X, is transmitted to a remote probe site (Fig. 1.6) through the π-systems in appropriate molecules such as biphenyls etc.,



Fig. 1.6

In systems like C6H5-CH2-Y, hyperconjugation116 (Fig. 1.7) involving σ-π  
bond interaction accounts for the resonance properties. A final possible effect is  
any perturbation of σ-electron populations arising from a change occurring in the  
π-system and this has been designated as σ- πeffect (σπ).



Fig. 1.7

Of the various modes of transmission of electronic effects, the Iσ, F, πσ, and πF effects depend on substituent polarity, while R and σπ, effects depend on charge transfer ability.

**1.7 Antimicrobial activity**

The science dealing with the study of the prevention and treatment of diseases caused by micro-organisms is known as medical microbiology. Its sub-disciplines are virology (study of viruses), bacteriology (study of bacteria), mycology (study of fungi), phycology (study of algae) and protozoology (study of protozoa). For the treatment of diseases inhibitory chemicals employed to kill micro-organisms or prevent their growth, are called antimicrobial agents. These are classified according to their application and spectrum of activity, as germicides that kill micro-organisms, whereas micro-biostatic agents inhibit the growth of pathogens and enable the leucocytes and other defence mechanism of the host to cope up with static invaders. The germicides may exhibit selective toxicity depending on their spectrum of activity. They may act as viricides (killing viruses), bacteriocides (killing bacteria), algicides (killing algae) or fungicides (killing fungi). The beginning of modern chemotherapy has largely been due to the efforts of Dr. Paul Ehrlich (1910), who used salvarsan, as arsenic derivative effective against syphilis. Paul Ehrlich used the term chemotherapy for curing the infectious disease without injury to the host’s tissue, known as chemotherapeutic agents such as antibacterial, antiprotosoal, antiviral, antineoplastic, antitubercular and antifungal agents. Later on, Domagk (1953) prepared an important chemotherapeutic agent sulfanilamide.

**1.7.1 Classification of antibacterial agents**

The antibacterial agents are classified into three categories:

(I) Antibiotics and chemically synthesized chemotherapeutic agents.

(II) Non-antibiotic chemotherapeutic agents (Disinfectants, antiseptics and

preservatives)

(III) Immunological products.

**Antibiotics**

They are produced by micro-organisms or they might be fully or partly prepared by chemical synthesis.117 They inhibit the growth of micro-organisms in minimum concentrations. They can be classified on the basis of biosynthesis or chemical structure118 (Table 1.1).

**Table 1.1 Classification of antibiotics according to their chemical structure**

|  |  |  |
| --- | --- | --- |
| **S.No.** | **Name of the group** | **Example** |
| 1 | **Carbohydrate-containing antibiotics**  Pure sugars  Aminoglycosides  Orthosymycins  N-Glycosides  C-Glycosides  Glycolipids | Nojirimycin  Streptomycin  Everninomycin  Streptothricin  Vancomycin  Moenomycin |
| 2 | **Macrocyclic lactones**  Macrolide antibiotics  Polyene antibiotics  Ausamycins  Macrotetrolides | Erythromycin  Candicidin  Rifamycin  Tetranactin |
| 3 | **Quinones and related antibiotics**  Tetracyclines  Anthracyclines  Naphthoquinones  Benzoquinones | Tetracycline  Adriamycin  Actinorhodin  Mitomycin |
| 4 | **Amino acid and peptide antibiotics**  Amino acid derivatives  β-Lactum antibiotics  Peptide antibiotics  Chromopeptides  Depsipeptides  Chelate forming peptides | Cycloserine  Penicillin  Bacteriacin  Actinomycins  Valinomycin  Bleomycins |
| 5 | **Heterocyclic antibiotics containing oxygen**  Polyether antibiotics | Monensin |
| 6 | **Heterocyclic antibiotics containing nitrogen**  Nucleoside antibiotics | Polyoxins |
| 7 | **Aromatic antibiotics**  Cycloalkane derivatives  Steriod antibiotics | Cycloheximide  Fusidic acid |
| 8 | **Aromatic antibiotics**  Benzene derivatives  Condensed aromatic antibiotics  Aromatic ether | Chloramphenicol  Griseofulvin  Novobiocin |
| 9 | **Aliphatic antibiotics**  Compounds containing phosphorous | Fosfomycins |

**1.7.2 Mode of action**

Different antibiotics have different modes of action, owing to the nature of their structure and degree of affinity to certain target sites within bacterial cells. Antimicrobial drugs may either kill microorganisms outright or simply prevent their growth. There are various ways in which these agents exhibit their antimicrobial activity.119

1. **Inhibitors of cell wall synthesis**. While the cells of humans and animals do not have cell walls, this structure is critical for the life and survival of bacterial species.  A drug that targets cell walls can therefore selectively kill or inhibit bacterial organisms.  Examples: penicllins, cephalosporins, bacitracin and vancomycin.
2. **Inhibitors of cell membrane function**. Cell membranes are important barriers that segregate and regulate the intra- and extracellular flow of substances. A disruption or damage to this structure could result in leakage of important solutes essential for the cell’s survival.  Because this structure is found in both eukaryotic and prokaryotic cells, the action of this class of antibiotic are often poorly selective and can often be toxic for systemic use in the mammalian host.  Most clinical usage is therefore limited to topical applications. Examples: polymixin B and colistin.
3. **Inhibitors of protein synthesis**. Enzymes and cellular structures are primarily made of proteins. Protein synthesis is an essential process necessary for the multiplication and survival of all bacterial cells.  Several types of antibacterial agents target bacterial protein synthesis by binding to either the 30S or 50S subunits of the intracellular ribosomes. This activity then results in the disruption of the normal cellular metabolism of the bacteria, and consequently leads to the death of the organism or the inhibition of its growth and multiplication.  Examples: Aminoglycosides, macrolides, lincosamides, streptogramins, chloramphenicol and tetracyclines.
4. **Inhibitors of nucleic acid synthesis**. DNA and RNA are keys to the replication of all living forms, including bacteria. Some antibiotics work by binding to components involved in the process of DNA or RNA synthesis, which causes interference of the normal cellular processes which will ultimately compromise bacterial multiplication and survival.  Examples: quinolones, metronidazole, and rifampin.
5. **Inhibitors of other metabolic processes**. Other antibiotics act on selected cellular processes essential for the survival of the bacterial pathogens.    For example, both sulfonamides and trimethoprim disrupt the folic acid pathway, which is a necessary step for bacteria to produce precursors important for DNA synthesis.  Sulfonamides target and bind to dihydropteroate synthase, trimethophrim inhibit dihydrofolate reductase; both of these enzymes are essential for the production of folic acid, a vitamin synthesized by bacteria, but not humans.

**1.7.3 Potential antimicrobial micro-organisms**

**Bacteria**

The bacteria are microscopic organisms with relatively simple and primitive forms of prokaryotic type. Danish Physician Christian Grams, discovered the differential staining technique known as Gram staining, which differentiates the bacteria into two groups “Gram positive” and “Gram negative”, Gram positive bacteria retain the crystal violet and resist decolorization with acetone or alcohol and hence appear deep violet in colour; while Gram negative bacteria, which lose the crystal violet, are counter-stained by saffranin and hence appear red in colour.

**(1) *Staphylococcus aureus:* Family (*Micrococcaceae*)**

In 1878, Koch observed micrococcus like organisms in pus; Pasteur (1880) cultivated these cocci in liquid media. They are Gram-positive cocci, ovoid or spheroidal, non-motile, arranged in a group of clusters grow on nutrient agar and produce colonies, which are golden yellow, white or lemon yellow in colour. Pathogenic strains produce acids by fermentation glucose lactose and mannitol liquefy gelation and produce pus in the lesion.

The word *Staphylococcus* is derived from the Greek language (Gr. *Staphylo* = bunch of grapes; Gr. *Coccus* = a grain or berry), while the species name is derived from Latin language (*L. aureus* = golden). *Staphylococcus* is differentiated from *Micrococcus* another genus of the same family by its ability to utilize glucose, mannitol and pyruvate anaerobically. Cells of *Staphylococcus*, which are slightly smaller than those of *Micrococcus*, are found on the skin or mucus membrane of the animal body.

The basic habitat of *S. aureus* is the anterior nares, though it is also a normal flora of the human skin, and of the respiratory and gastrointestinal tracts. The individual cells are 0.8 to 0.9 μ in diameter. They are oval or spherical, non-motile, non-capsulated, non-sporulating strains with ordinary aniline dyes and are Gram-positive, typically arranged in groups or irregular clusters like branches of groups of pus seen singly or in pairs. They easily grow on nutrient agar; the optimum temperature for the growth is 35ºC. They are notorious as they cause suppurative (pyogenic or pus forming) conditions, mastitis of women and cows, boils and food poisoning. *S. aureus* grows rapidly and produces circular (1-2 mm) endive edge, convex, soft, glistening colonies having a golden yellow pigment. *S. aureus* can tolerate moderately high concentration of NaCl, hence they can be selectively isolated on the nutrient medium containing

7.5 % sodium chloride. It is also able to ferment mannitol to an organic acid. *S. aureus* also produces the coagulase which is able to clot citrated plasma. It also produces the enzymes catalase, hyaluronidase as well as other virulent factors like hemolysins, leucocidins, enterotoxins and exofoliatin.

**(2) *Escherichia coli*: Enterobacteriaceae**

They are Gram-negative rods, motile with peritrichous flagella or non-motile. They do not form spores. All are sometimes (i.e. from rarely to, invariably) found in the intestinal treatment of man or lower animals.

This genus comprises Escherichia coli and several variants. Escherich in 1885 discovered *Escherichia coli* which is a commensal of the human intestine and is found in the sewage, water or soil contaminated by faecal matters. These are Gram-negative rods, 2 to 4 μm length, commonly seen in coccobacillary form, which do not form any spore and have 4 to 8 peritrichous flagella, sluggishly motile, facultative anaerobes and grow in laboratory media. *E. coli* is generally non-pathogenic however, incriminated as pathogens because in certain instance some strains have been found to produce septicemia, inflammation of liver and gallbladder, appendix and other infections and this species is a recognized pathogen in the veterinary field.

**(3) *Pseudomonas aeruginosa***

*Pseudomonas* is a Greek word (Gr. *Pseudo* = false, Gr. *Monas* = a unit) while the word *aeruginosa* is of Latin origin (*L. aeruginosa* = full of copper rust i.e. green).

*P.aeruginosa* is Gram-negative short rod with variable length (1.5-3.0 x 0.5 μm). They are motile by means of one or two polar flagella. Organisms are non-sporulating and non-capsulated, however, a few strains possess slime layer made up of the polysaccharide. The primary habitat of *P.aeruginosa* is human and animal gastrointestinal tract, water, sewage, soil and vegetation. It is physiologically versatile and flourishes as a saprophyte in warm moist situations in the humus environment, including sinks, drains, respirators, humidifiers, etc. *P.aeruginosa* produces several virulence factors, including exotoxin-A., proteases, leukocidin, and phospholipase-*C. Pseudomonas is* an opportunistic pathogen capable of causing infections when the natural resistance of the body is low. They are mostly related to hospital infections and post burn infections. They also cause infections of the middle ear, eyes and urinary tracts. It is also associated with diarrhoea, pneumonia and osteomyelitis. Due to drug resistant nature of *P. aeruginosa,* it causes infection in patients receiving long term antibiotic therapy for wounds, burns and cystic fibrosis and other illness. Approximately 25% of burn victims develop an infection which frequently leads to fatal septicemia.

**Fungi**

There are perhaps over 10,000 species of fungi, but only less than 100 cause diseases in human.120 Fungi may cause benign, but unsightly infections of the skin, nail or hair, relatively trivial infection of mucous membranes (thrush) or systemic infection causing progressive often fatal disease.

**POTENTIALLY EFFECTIVE ANTIFUNGAL COMPOUNDS**

|  |  |  |
| --- | --- | --- |
|  | **Diseases** | **Compounds** |
| **1** | Dermatophytosis | Azoles(Itraconazole,Miconazole, Clotrimazole),Griseofulvin,Tolnaftate, Naftifine, Turbinatine |
| **2** | Aspergillosis | Amphotericin-B±5-Fluorocytosine, Itraconazole |
| **3** | Blastomycosis | Amphotericin-B,Itraconazole, Ketoconazole |
| **4** | Candidiasis | Amphotericin-B±5-Fluorocytosine, Nystatin,Azoles (Fluconazole, Ibaconazole, Ketoconazole, Clotrimazole, Miconazole,  Econazole etc) |
| **5** | Chromomycoaia | 5-Fluorocytosine,Itraconazole, Ketoconazole |
| **6** | Histoplasmosis | Amphotericin-B,Itraconazole, Ketoconazole |
| **7** | Pneumocytosis | Trimethoprim / Sulfamethoxazole, LY-303,366, Deferoxamine |
| **8** | Pseudallescheriasis | Amphotericin B, Miconazole |
| **9** | Sporotrichosis | Amphotericin B, Itraconazole, Potassium iodide |

**(1) *Candida albicans***

*Candida* species reproduce by budding like yeast cells and also show the formation of pseudomycellum. This pseudomycellum are chains of elongated cells formed from buds and are elongated without breaking of the mother cell. They are very fragile and separated easily. Mycelia also formed by the elongation of the germ tube that produced by a mother cell.

*Candida albicans* may remain as a commensal of the mucous membrane with or without causing any pathologic changes to the deeper tissues of the same fungus which may cause pathological lesion of the skin. Such a fungus under favourable conditions can cause superficial, intermediate of deep mycoses depending on the condition of the host.

**(2) *Aspergillus niger***

The spices of *Aspergillus* are widespread in nature, being found on fruits, vegetables and other substrates, which may provide nutriment. Some species are involved in food spoilage. They are important economically because they are used in a number of industrial fermentations, including the production of citric acid and gluconic acid. *Aspergillus* grow in high concentrations of sugar and salt, indicating that they can extract water required for their growth from relatively dry substances. Derivatives of N-methyl piperazine are therapeutically useful having antibacterial and antiprotozoal activity. These are active against Gram positive and Gram negative organisms. In addition, they are active against *Candida albicans* and other mycetes. They are also cytostatic.121 Keto oximes esters, i.e. 1,3-dichloro-2-propan-1-o-(benzoyl)-oxime, are useful in inhibiting the growth of bacteria and fungi. They also find use as herbicides and acaricides. Substituted 5-nitro-2-furylaminoximes and their herbicides are active antibacterial and antifungal agents and can be used in disinfectant compositions to control a variety of micro-organisms. O-(N-methylcarbamolyl)-carbethoxy-chloroform-aldoxime shows biocidal activity against *Aerobacter aerogenes* in paper pulp and fungicidal activity against *Septoria* in wheat grains.

Substituted glyoxal dithiosemicarbazones possess anaplasmicidal activity, being effective in the control of Anaplasmamarginale. Alloxan-5-thiosemicarbazone possesses bacteriostatic, bactericidal, and fungicidal and defoliant activities. It is especially useful for the control of spices of *Erwinia*, *Staphylococcus* and *Salmonella*. Aryl-5-fluoro-2-methoxyphenyl ketoximes and their thiosemicarbazones were found to be active against *Aspergillus niger* and *Aspergillus flavus*. Fluorinated diaryl ketoximes and their thiosemicarbazones possess antifungal activity.122

**1.8 Correlation with electrochemical properties**

The free energy relationship obtained by polarographic studies differs from that obtained from most other physical methods.123,124 The half-wave potentials of reversible systems are equivalent to logarithms of equilibrium constants, whereas those of irreversible systems are proportional to logarithms of rate constants. Hence the application of half-wave potentials in extra thermodynamic relationships is not merely empirical but is a logical extension of the treatment of kinetic and equilibrium data. Cyclic voltammetry, a popular tool in the last thirty-five years for studying electrochemical reactions has been employed by organic chemists in the study of biosynthetic reaction pathways125 and studies of electrochemically generated free radicals.126 An increasing number of inorganic chemists have been using cyclic voltammetry to evaluate the effects of ligands on the oxidation/reduction potentials of the central metal ion in complexes and multinuclear clusters.127 This type of information plays an integral part in many of the approaches directed toward solar energy conversion128 and in model studies of enzymatic catalysis.129 Knowledge of the electrochemistry of a metal complex can be useful in the selection of the proper oxidizing agent to put the metal complex in an intermediate oxidation state.130 Electrochemical methodology has also been exploited as a novel means of introducing functional groups and removing blocking agents.131

In the reaction series of the type x-Ar-R, if R is the electroactive group and X is the substituent in *meta*- or *para*- position, it is possible to write the equation (1.20).132

(E1/2 )XR = *ρ*R σX + (E1/2 ) HR (1.24)

In the equation (1.24), (E1/2 )XR  is the half-peak potential of the substituted compound and (E1/2 ) HR is that of the parent compound. *ρ*R is the proportionality constant, called the reaction constant, expressed in volts, that characterizes the susceptibility of the electroactive group R on a benzenoid ring to the effect of substituents placed in *meta*- or *para*- positions on the ring. Its value is dependent on the nature of the electroactive group, R, on the composition of the supporting electrolyte, on temperature and on other experimental conditions. It is independent of the kind and position of the substituent. σX is the Hammett substituent constant.3

There are many articles that deal with the theory and practice of modern voltammetry in-depth.133-135 Many authors have reported the substituent effects on peak potential measured by cyclic voltammetry.136-141

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