CHAPTER 1
INTRODUCTION

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PART A

INTRODUCTION TO SPECTROPHOTOMETRY

1A.1 SPECTROPHOTOMETRY

Spectrophotometry is one of the most useful tools available to the chemist and biochemist. It offers a high degree of precision, sensitivity, and accuracy. In addition, it is less expensive and applicable to the measurement of a variety of substances. Newly emerging fields like pollution control, toxicology, food adulteration, forensic sciences, etc. demand these sorts of methods for routine analysis. Among the instrumental techniques, spectrophotometry occupies a unique position because of its simplicity, sensitivity, accuracy and speed [1]. The spectrophotometric method is based on a simple relationship between the color of a substance and its electronic structure. A molecule or an ion exhibits absorption in the visible or ultra-violet region when the radiation causes an electronic transition in molecules containing one or more chromophoric groups. The color of a molecule may be intensified by substituents called auxochromic groups, which displace the absorption maxima towards longer wavelength (bathochromic shift). The quantitative applicability of the absorption method is based on the fact that the number of photons absorbed is directly proportional to the number or concentration of atoms, ions or molecules [2].

1A.2 CALIBRATION CURVE

The common method of using the spectrophotometer requires the construction of a calibration curve for the constituents being determined. For this purpose, suitable quantities of the constituents are taken and treated in exactly the same way as the sample solution for development of the color, followed by the measurement of the absorption at the optimum wavelength. The absorbance is then plotted against concentration of the constituents. A straight line is obtained if Beer's law is obeyed. This calibration curve may then be used in future determinations of the constituents under the same conditions. The calibration curve needs checking at intervals.

1A.3 RINGBOM'S PLOT

Ayres [3] pointed out that a straight line obtained in Beer's law curve does not show directly the concentration range within which accurate determination of

the colored species is possible. The optimum range for highest precision is determined by plotting percentage transmittance against log of the metal ion concentration as was suggested by Ringbom [4]. The optimum concentration range corresponding to a nearly constant and high rate of change in transmittance with concentration is indicated by a virtually linear portion of the Ringbom's plot.

1A.4 CHOICE OF THE WAVELENGTH

It is important to avoid making measurements in a region where the molar absorptivity changes rapidly with the wavelength. In such a region, even a small error in setting the wavelength scale will result in a large change in the apparent molar absorptivity [5]. Therefore, it is necessary to select the wavelength corresponding to the maximum absorption (ε). When the transmittance of the solutions increases continuously over the wave length range covered by the light filter, Beer's law will not be obeyed.

1A.5 SENSITIVITY OF SPECTROPHOTOMETRIC METHODS

The awareness of the sensitivity is very important in spectrophotometric determination of trace amount of metals. Sensitivity is often described in terms of molar absorptivity (ε, $lmol^{-1}cm^{-1}$) of the metal- ligand complex. The numerical expression is the molar absorptivity (ε) at the wavelength of maximum absorbance of the colored species [6-8].

$$\varepsilon = \frac{A}{cl}$$

where A is the absorbance, c is the concentration and l is the path length of the cell used. Maximum value of molar absorptivity is obtained by using monochromatic radiation of narrow band width. Savvin [9] suggested a relation between sensitivity and molar absorptivity. According to him the sensitivity parameter is low sensitivity; $\varepsilon < 2x10^4$ $lmol^{-1}cm^{-1}$ moderate sensitivity; $\varepsilon = 2\text{-}\ 6x10^4$ $l\ mol^{-1}cm^{-1}$ and high sensitivity, $\varepsilon > 6x10^4$ $lmol^{-1}cm^{-1}$. It is generally stated [10] that the molar absorptivity will not exceed approximately 10^5. Other way of specifying sensitivity are as specific

absorptivity [11] or the Sandell's sensitivity [12]; both methods give the sensitivity in terms of mass of analyte per unit volume of solution. Such an approach is perhaps more convenient than using molar absorptivities as a basis for comparison. The Sandell's sensitivity is the concentration of the analyte (in μg/ml) which will give an absorbance of 0.001 in a cell of path length 1 cm and is expressed as μg cm^{-2}. Detection limits can be reduced to somewhat by solvent selection because molar absorptivities depend on the solvent system.

1A.6 ACCURACY AND PRECISION

The accuracy and precision of spectrophotometric method depends on three major factors.1) Instrumental limitations, 2) chemical variables and 3) operator's skill. Under ideal conditions it is possible to achieve relative standard deviations in concentrations as low as about 0.5 % which enables the determination in the range of micro quantities. The precision of spectrophotometric method also depends on concentration of the determinant. Visual methods generally give results with a precision of 1–10 %.The precision of the photometric method is of course, higher and varies from 0.5 – 2 % under suitable measuring conditions. Precision is conveniently expressed in terms of the average deviation from the mean or in terms of standard deviation or in terms of coefficient of variation.

1A.6.1 Detection Limit

Detection limit is the smallest concentration of a solution of an element that can be detected with 95 per cent certainty [13-14]. This is the quantity of the element that gives a reading equal to twice the standard deviation of a series of any least ten determinations taken with solutions of concentrations which are close to the level of the blank. Several approaches for determining the detection limit are possible, depending on whether the procedure is a non-instrumental or instrumental. Based on the standard deviation of the reagent blank and the slope of the calibration curve of the analyte, the detection limit (D_L) may be expressed as:

$$D_L = \frac{3.3\,\sigma}{S}$$

where σ is the standard deviation of the reagent blank and S is the slope of the calibration curve.

1A.6.2 Quantitation Limit

The quantitation limit is generally determined by the analysis of samples with known concentrations of analyte with those of blank samples and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision [15-16]. Based on the standard deviation of the reagent blank and the slope of the calibration curve of the analyte, the quantitation limit (Q_L) may be expressed as:

$$Q_L = \frac{10\,\sigma}{S}$$

Where σ is the standard deviation of the reagent blank and S is the slope of the calibration curve.

1A.7 COLOR DEVELOPMENT

There are only a few elements, which give sufficiently intense absorption by them and are spectrophotometrically measurable. Majority of the substances are generally determined indirectly in a variety of ways, such as; 1) substances may be converted by a suitable reagent to an absorbing product, 2) adding complexing agent to get colored complexes. Organic complexing agents are found to be more selective and sensitive color developing agents than inorganic ones.

1A.7.1 Requirements of a Color Developer

A color developer should possess a high molar absorptivity, high selectivity and the spectrum of the complex should be significantly different from that of the reagent.

1A.7.2 The Criteria for Satisfactory Spectrophotometric Analysis

Since the color development in spectrophotometry involves diverse type of reactions, a number of points need to be ensured before applying the method

for a particular application. Some of the points have to be considered are discussed in the following sections.

1A.7.2.1 Specificity of the Color Reactions

Very few reactions are specific for a particular substance. This may be achieved by isolating the substance by the normal methods of inorganic analysis. But these separation methods are often tedious and time consuming. Further, there is every possibility for appreciable loss of the analyte during these separations. The specificity in colorimetric reactions can be achieved by introducing other complex forming compounds. These are required to suppress the action of interfering substance by the formation of complex ions or non-reactive complexes. When the colorimetric reaction takes place within well-defined limits of pH, adjustment of pH may also sometimes help to achieve the desired specificity in certain cases. The methods of selective absorption, chromatographic separations and ion exchange separations are also of use in certain cases.

Solvent extraction also finds its application in achieving specificity in the spectrophotometric determinations. The interfering substances are removed by extraction with an organic solvent, sometimes after suitable chemical treatment. Alternatively the substance to be determined can also be isolated from the interfering species by converting it into an organic complex, which is then selectively extracted with a suitable organic solvent.

1A.7.2.2 Proportionality between Color and Concentration

For colorimeters, it is important that color intensity should increase linearly with concentration of the compound to be determined. This is not necessary for photoelectric colorimeters or spectrophotometers. Since a calibration curve may be constructed relating the instrumental reading of the color with the concentration of the solution. It is desirable that the system follows Beer's law even when photoelectric colorimeters are used.

1A.7.2.3 Stability of the Color and Clarity of the Solutions

The color produced must be stable so as to allow accurate readings to be taken. Stability of the color is influenced by experimental conditions like temperature, pH etc. The solution must be free from precipitate if comparison is to be made with a clear standard. Turbidity scatters as well as absorbs the light.

1A.7.2.4 Reproducibility and Sensitivity

The colorimetric procedure must give reproducible results under specific experimental conditions. The reaction need not necessarily represent a stoichiometric chemical change. It is desirable, particularly when minute amounts of substances are to be determined, that the color reactions be highly sensitive. It is also desirable that the reaction product absorbs strongly in the visible rather than in the ultraviolet region, as the interfering effect of other substances is usually more pronounced in the ultraviolet region.

1A.8 CHOICE OF SOLVENT

The solvent, which is to be used in spectrophotometric determination, must meet certain requirements. Before using a particular solvent, it must be ensured that it does not interact with the solute. The solvent must not show significant absorption at the wavelength to be employed in the determination. For inorganic compounds, water normally meets these requirements, but for majority of organic compounds, it is necessary to use an organic solvent. All solvents show absorption at some point in the ultraviolet region and care must be taken to choose a solvent for a particular determination which does not absorb in the requisite wavelength region. Any impurity present in the solvents may affect the absorption at certain wavelength and it is therefore, essential to employ materials of highest purity.

1A.9 DERIVATIVE SPECTROPHOTOMETRY

The derivative method in UV/visible and IR spectrophotometry was introduced in 1953 [17]. The derivative spectrophotometry has only recently become a generally applied analytical method, since the rapid progress in the technology of microcomputers has made it possible to directly present the first, second and

higher order derivative spectra. The great interest towards derivative spectrophotometry (DS) is due to the increased resolution of spectral bands, allowing the detection and location of the wavelengths of poorly resolved components of complex spectra and reducing the effects of spectral background interferences. Because of these characteristics, the process of isolation and preconcentration of active components, usually required in qualitative and quantitative spectrophotometric procedures applied in the analysis of complex systems, is completely avoided [18].

One of the important characteristics of derivative spectrophotometry is the precise determination of the position of absorption maxima. For a single peak spectrum having a broad band, the position of absorption maxima can be only approximately determined. The derivative spectra can be used to accurately locate the peak. The first derivative of this band ($dA/d\lambda$) passes through zero at the peak maximum, minimum and shoulder points and can be used to accurately locate the peak position [19]. In contrast, the second and higher even derivatives ($d^2A/d\lambda^2$,$d^4A/d\lambda^4$,…) contain a peak of changeable sign (negative in the second order, positive in the fourth order, etc.)which has the same position as a peak maximum in the normal spectrum. The width of this peak progressively decreases with increasing order of the even derivative, which causes a sharpening of the peak enabling its exact identification [20].

1A.10 SPECTROPHOTOMETRIC STUDIES OF COMPLEX IONS

Spectrophotometery is a valuable tool for determining the composition of complex ions in solution and for determining their formation constants. The power of the technique lies in the fact that quantitative absorption measurements can be performed without disturbing the equilibria under consideration. Although many spectrophotometric studies of complexes involve systems in which a reactant or a product absorbs, nonabsorbing system can also be investigated successfully. The most common techniques for complex-ion studies are (1) The method of continuous variation, and (2) the mole-ratio method.

1A.10.1 The method of continuous variation

In the method of continuous variation, cation and ligand solutions with identical analytical concentrations are mixed in such a way that the total volume and the total moles of reactants in each mixture is constant but the mole ratio of reactant varies systematically. The absorbance of each solution is then measured at a suitable wavelength and corrected for any absorbance the mixture might exhibit if no reaction had occurred. The corrected absorbance is plotted against the volume fraction of one reactant, that is $V_M/ (V_M+V_L)$ where V_M is the volume of the cation solution and V_L is the volume of the ligand solution. A maximum (or minimum if the complex absorbs less than the reactants) occurs at a volume ratio V_M/V_L corresponding to the combining ratio of cation and ligand in the complex. The curvature in the experimental lines is the result of incompleteness of the complex reaction. A formation constant for the complex can be evaluated from measurements of the deviations from the theoretical straight lines, which represent the curve that would result if the reaction between the ligands and the metal proceeded to completion.

1A.10.2 The mole ratio method

In the mole ratio method, a series of solutions is prepared in which the analytical concentration of one of the reactants (usually the cation) is held constant while that of the other is varied. A plot of absorbance versus mole ratio of the reactant is then made. If the formation constant is reasonably favorable, we obtain two straight lines of different slopes that intersect at a mole ratio corresponding to the combining ratio of the complex [21].

1A.11 LIMITATIONS

The common but unrecognized problem in measuring the absorbance is stray light error. All wavelength isolation devices tend to produce some low intensity radiations at wavelengths other than the desired one. This is usually due to the optical imperfections, or simply from scattered light due to dust particles on optical surface. Thus the stray light errors will result in a negative bias for absorbance readings which can be represented in the equation.

$$T_{obs} = \frac{T_{true} + \rho}{1 + \rho}$$

Where ρ is the fraction of all the light coming from the wavelength isolation device, which is stray light, and T_{obs} and T_{true} are the observed and true transmittances, respectively. Normally the absolute amount of stray light tends to be relatively constant with respect to the wavelength. But the fraction of stray light is highly wavelength dependent because the amount of energy of the selected wavelength depends on the source intensity at that wavelength. Thus, stray light errors are most predominant at long and short wavelengths and when high absorbance is measured.

Another common error encountered on making the measurements is finite slit width effect. If any light is to pass through the slit, it must have a finite width. However, due to its width, more than one wavelength of light, called the bandwidth, emerges. Thus, the narrower the spectral band width, the better conformity to Beer's law. If the spectral bandwidth is too wide, negative deviation from the Beer's law occurs, resulting in a false absorbance reading. Another important error caused is by mismatched cells. If the cells holding the analyte and the blank solutions are not equivalent in optical characteristics, an intercept will occur in the calibration curve. This error can be avoided by using either carefully matched cells or a linear regression procedure to calculate both the slope and the intercept of the calibration curve. Another way to avoid the mismatched cells problem with single beam instrument is to use only one cell and keep it in same position for about blank and analyte measurements. After obtaining the blank reading, the cell is filled with analyte solution.

Another problem related with measuring absorbance is the use of polychromatic radiation. Polychromatic sources have a continuous distribution of wavelengths which are used in conjunction with a grating or with a filter, to isolate a nearly symmetric band of wavelength around the wavelength to be employed. To avoid the error due to this, it is advisable to select a wavelength band of maximum absorption, where the analyte absorptivity changes little with wavelength.

One of the problems while measuring the absorbance is related to concentration. At concentrations exceeding ≈ 0.01 M, the average distances between the ions or molecules of the absorbing species are diminished to the point where each particle affects the charge distribution, and thus the extent of absorption of its neighbours. Because the extent of interaction depends on concentration, the occurrence of this phenomenon causes deviation from the linear relationship between absorbance and concentration. A similar effect sometimes occurs in dilute solutions of absorbers that contains high concentration of other species, particularly electrolytes. When the ions are very close to one another, the molar absorptivities of the analyte can be altered because of electrostatic interaction, and leads to produce analytical errors. Errors also occur when distilled water blank is used instead of a true blank for 100 % transmittance or baseline reading. Even though there are no known absorbing species in distilled water as well as in the blank reagent solution, the difference in the refractive indices between the sample solution and the reference solution must be kept reasonably close or reflective loses at the cell windows may not be the same. However, reflections from the solution-window interfaces may be different if the refractive indices of the sample and the blank are not nearly the same.

In addition to the above instrumental errors some chemical errors may appear when, the absorbing species undergoes association, dissociation or reaction with the solvent to give products that absorb differently from the analyte.The extent of such departures can be predicted from the molar absorptivities of the absorbing species and the equilibrium constants for the equilibria involved. We are usually unaware of such processes affecting the analyte; there is no opportunity to correct the measurement. Typical equilibria that give rise to this effect include monomer-dimer equilibria, metal complexation equilibria, acid-base equilibria and solvent-analyte association equilibria.

1A.12 APPLICATIONS

The greatest use of spectrophotometry lies in its application to quantitative measurements. The reasons for this stem from the ease with which most spectrophotometric measurements can be made, their sensitivity, precision, and

the relatively low cost of the instrument purchase and operation. A variety of techniques have been developed for different types of samples. Direct determinations are made when the analyte molecule contains a chromophore, thus allowing the direct measurement of its absorbance. Indirect determinations are commonly used when the analyte molecule does not contain a suitable chromophore. In these instances the analyte is made to quantitatively react with a molecule containing a chromophore and correlating the diminution of absorbance with the concentration of the analyte or by reacting with a reagent, which produces chromophoric groups.

1A.13 PRESENT INVESTIGATION

Chapter ll present spectrophotometric determination of Osmium(VIII) using Ethylene thiourea (ETU) as chromogenic reagent.

PART B

INTRODUCTION TO NITROGEN DONOR HETEROCYCLES

1B.1 GENERAL
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1B.1 GENERAL

The field of coordination chemistry is one of the most intellectual, attractive and experimentally demanding frontiers in modern chemical sciences. The study of coordination chemistry in the modern day context began with Alfred Werner and Sorphus Mads Jorgenson.The pioneering contribution of Werner to the study of coordination chemistry fetched him the Nobel Prize in chemistry in 1913. Research has came long way from the time of Werner's coordination chemistry has experience over the last few decades. Their work was a stepping stone for the development of modern Inorganic Chemistry which is truly a multidisciplinary one in the present day context.

Coordination compounds brought about a synthetic revolution in Inorganic chemistry which leads to novel products with novel applications in wide range of areas such as analytical chemistry, fungicides, paints, pigments, polymers, pharmaceuticals, catalysis photoconductors etc. The analytical applications of coordination compounds cover a broad spectrum including colorimetric, spectrophotometric and polarographic analysis. The involvement of metal ions in biological systems has culminated in the emergence of a new branch in chemistry viz. bioinorganic chemistry. Haemoglobin, myoglobin, chlorophyll, cytochrome and vitamin B_{12} are some of the most important complex compounds in living systems. Inorganic compounds particularly metallic ions and complexes are essential cofactors in a variety of enzymes and proteins. Another exciting application of metal complexes is in the field of medicine and therapy. Many of the complexes and complex formers are known to be used as drugs in certain diseases and also for metal detoxification in the case of metal poisoning. Another important application of metal complexes is in the photolytic splitting of water producing hydrogen, a non polluting fuel which may be a solution for the fuel crisis in the future.

The elegance and the variety of the coordination compounds and the intriguing range of concepts that are required to interpret their behavior have attracted many researchers to study of their synthesis and to seek an understanding of their chemical reactions. The study of complexes has

enabled the inorganic chemists to make significant progress in refining the concept of chemical bonding and associated properties of those compounds.

1B.2 NATURE OF METAL IONS

In 1950 Ahrland et al. [22] made a generalized classification of metal ions and donor atoms. They made an extensive review of the relative affinities of the donor and acceptor atoms or ions. According to their classification, the lighter members of groups in periodic table are considered as 'class a' metal ions while the heavier members of the groups in the periodic table are considered as 'class b' metal ions. Further 'class a' group metal ions are small and non polarisable acceptors whereas 'class b' metal ions are large and polarisable acceptors. The order of stability of coordination compounds is as follows: among 'class a' metal ions $F^- > Cl^- > Br^- > I^-$;O >> S; N >> P and among 'class b' metal ions $F^- < Cl^- < Br^- < I^-$; O << S; N << P.

Pearson [23-25] gives another but similar generalization of acceptor and donor elements in the form of HSAB classification. He qualitatively defined a 'hard base' act as donor atom or ion which has low polarizability,high electronegativity,empty d- orbitals of high energy and which is difficult to oxidize. In a similar way a 'soft base' is defined as a donor atom or ion which has high polarizability,low electronegativity with low lying empty d-orbitals and which is readily oxidizable. On the same analogy, an acceptor atom or 'soft acid' which has low or zero positive charge, large size and has nearly filled d-levels, while that of a 'hard acid' having a small size, high positive oxidation state with fewer electrons in the d-levels. Accordingly 'class b' metal ions form a triangular area in the central part of the periodic table. The apex of the triangle is at Cu(I) and the base extending from W to Po.Thus, Pearson classified 'class a' metals as 'hard acids' and 'class b' metals as 'soft acids'. Ligand atoms such as N, O and F are 'hard bases' and those similar to P, S and I are 'soft bases'. Pearson formulated a rule for the 'hard-soft' interaction which states that hard acids prefer to bind with hard bases while soft acids prefer to bind with soft bases. Whenever a hard acid reacts with a hard base, an ionic bond is formed while combination of a soft acid with soft base leads to the formation of a covalent bond. It is not implied that

complexes of 'hard acids' and 'soft bases' or vice versa can not exist and unstable. There are many exceptions to Pearson's concept of hard and soft acids and bases. For example, thiourea contains both sulfur (soft base) and nitrogen (hard base) as donor atoms.Yet, its coordination with most of the metal ions including hard acids mainly through soft sulfur [26]. Myers [27] stated that there is no rigid correlation between 'class a' and 'class b' behavior and polarisability, especially for acceptors, viz. metal ions. Consequently he dropped the terms, 'hard' and 'soft'.

William and Hale [28] disagreed with the qualitative notations of hard and soft acids and bases. They thought that 'a' and 'b' classification is a little more than a reflection of σ-bonding and the gross controlling factor for the classification being clearly the relative importance of ionic and covalent bonding which is measured by the values of r_e/I.P, where r_e is the donor-acceptor bond distance and I.P is the ionization potential of the acceptor. The ionic character of the bond decreases with the increase in numerical value of r_e/I.P. Irving and Williams reviewed the data for complexes of the bivalent metal ions of the first transition series. The stability constants for complexes of M^{2+} ion with various ligands through oxygen and nitrogen atoms, usually follow the sequence Mn < Fe < Co < Ni < Cu > Zn.This order is known as Irving-Williams order of stability [29]. The stability of metal chelates increases with a decrease in the size of the metal ion. The rare exceptions to this order are due to spin pairing, which leads to an extra stabilization of the low spin configuration. The stability of the complex ion also depends on the number of d-electrons in the central atom.

1B.3 OXIDATION STATE OF METAL IONS

The behavior of metal ions as 'hard acids' or 'soft acids' can be determined by the knowledge of the oxidation state of metal ions. Therefore, the knowledge of oxidation state of metal ion is another important factor in deciding the preferred coordination site in ligand containing hetero-donor atoms. Normally, metal ions exhibiting multiple oxidation states tend to behave as soft acids in their low oxidation states and hard acids in their high oxidation states [22]. Thus Cu(I) exhibits ' soft acid' character with a number of sulfur

containing ligands [30] ,while Cu(II) often shows 'hard acid' character with oxygen containing ligands and sulfoxides [31-32]. The generalization however fails in some cases. Jorgensen [33] pointed out that magnesium ion shows soft acid character in high as well as low oxidation states. The hard or soft acid-base character of any acceptor or donor can vary with the nature of the substituent in the chelates.

1B.4 NATURE OF DONOR ATOMS

In general, the donor atoms bonding directly to the central metal ion in the complex are those from group V to VII in the periodic table and have high electronegativities.The most common donor atoms are N, P, As < Sb, O, S, Se, Te, F, Cl, Br and I. The strength of the 'metal-donor' bond depends on many factors such as electronegativity, polarizability, structure of the ligand molecule containing the donor atoms etc. No uniform pattern for the donor-acceptor relation of metal-sulfur link is established so far on the basis of electronegativity, free energy change of ligation (ΔG) and M-S ($d\pi$-$p\pi$ or $d\pi$-$d\pi$) bonding [30].

The relative polarisabilities of the donor atoms are found to be in the order of $F < O^{2-} < Cl^{-} < Br^{-} < I^{-} < S^{2-} < Se^{2-} < Te^{2-}$.This sequence is just reverse of the electronegativity series. Since increase in polarizability of an ion increases its tendency to show covalent character as compared to M-O, M-Cl, M-Br, and M-F bonds. In general sulfur donor atom in a ligand molecule does not exist as free ion but forms part of the molecule. Hence its electronegativity value is different from that of the free ion. As a result, the covalent character of the metal sulfur bond may not be higher than that of M-Se and M-Te. Instead, this character could be quite the reverse i.e. M-Te >M-Se ≈M-S. The polarisabilities of sulfur donors [34] decrease in the order $S^{2-} > RS^{-} > R_2S$.The number of lone pairs on sulfur also decrease in the same order. Consequently mercaptans are more polarisable but not as effective as d- electron acceptors like thio-ethers [35]. That is the reason why ligands having thiolic (-SH) group, coordinate more readily with transition metal ions than sulfides.

Polarisability of the nucleophile seems to be the most important factor in bond formation with an electrophile. Nevertheless, it should be emphasized that there is no perfect scale of nucleophilicity. However, a scale has been developed to give nucleophilic reactivity constants n^0_{pt} with reference to trans $Pt(py)_2Cl_2$ as the standard. The value of n^0_{pt} for sulfur ligands vary considerably from 3.29 for $(PhCH_2)_2S$ to 7.34 for $S_2O_3^{2-}$. In comparison with this, the thiolate ligand PhS^- has a value of the order 7.17. Ligands with highest values of n^0_{pt} are Cl^-(3.04), n^0_{pt} NH_3 (3.06), pyridine (3.13) and Br^- (4.18). Ligands with highest values of n^0_{pt} are tertiary arsines and phosphines, which have values in the range of 7.54 to 8.85. PPh_3 is known to form dative π-bond with transition metal ions [36].

Some data are also available on nucleophilic reactivity of sulfur ligands [15].The methyl mercury cation (CH_3Hg^+) has been used as a reference for bases since it acts as a Lewis acid as follows:

$$CH_3Hg^+ + L \quad \leftrightarrow \quad (CH_3HgL)^+$$

The value for $pK_{(CH3Hg+)}$ as given by the dissociation constant for

$$(CH_3HgL)^+ \leftrightarrow (CH_3Hg)^+ + L$$

can be determined for a number of Lewis bases. Sulfur ligands have very high value of $\rho K_{(CH3Hg)+,}$ eg: S^{2-} 21.3, RS in cysteine 15.9 ; $S_2O_3^{2-}$ 10.95 and SO_3^{2-} 8.16. For comparison, the values of some other ligands are CN^- 14.6; I^- 8.66; NH_3 7.65; Br^- 6.7; Cl^- 5.3 and F^- 1.55. Sulfur resembles oxygen in its electronic configuration in respect of s and p orbitals. But the low effective nuclear charge of sulfur atom results in enhanced covalent character of the π-bond [37] which can increase the bond strength. It is free from complications of hydrogen bonding too, although it shows increased power of catenation.

The nephelauxetic series [38-40] corresponding to various metal ions and ligand molecules give an idea of the magnitude of covalent character of the bond formed between the central metal ion and the ligand. Sulfur ligands are expected to have high nephelauxetic effect, but data are insufficient to

ascertain this fact. However, sulfur ligands do take a later position in the nephelauxetic series. The series of donor atoms {arranged according to the decreasing value of (1-β)} is roughly F < O < N < Cl < Br < S ≈ I < Se. From consideration of both electrostatic and covalent models, the strength of the bond with the metal ion can be expected to be in the order RO^- > RS^- > and R_2O > R_2S. However sulfur has vacant d-orbitals which can be used for dπ-dπ bonding. Consequently, if π bonding takes place, it can cause a reversal of the order, so that the bond strength with the same metal ion will be larger for RS^- and R_2S than for RO^- and R_2O respectively. In certain cases, π bonding is more predominant in sulfur compounds than in phosphorous compounds [41]. The dependence of trans effect on the degree of π bonding, however, seems to give rise to activation of trans position due to strong polarisability in sulfur containing ligands [33,42]. Sulfur atom, thus has a strong tendency to bond more strongly with 'b class' metal ions.

It has been found experimentally from spectral studies of a large number of complexes containing various metal ions and ligands, that the ligands may be arranged in a series according to d-orbital splitting parameter Δ or 10 Dq.This series for the more common ligand is I^- < Br^- < Cl^- < F^- < OH^- < $C_2O_2^{-}$ ≈ H_2O < NCS^- < py < NH_3 < en < dipy < o–phen < NO_4^{2-} < CN^-. The position of sulfur in the spectrochemical series of the ligands is not very specific or unambiguous [43]. Although some sulfur donors including S-bonded SCN < $(RO)_2PS_2^-$ and S^{2-} are placed towards the lower end of the series, probably between H_2O and N-bonded NCS^-; the S-bonded $S_2O_3^{2-}$ has a late position near NO_2^-.The position of RS in the spectrochemical series has not been clearly established.

The efforts [44, 45] made to rationalize the conflicting and in many cases insufficient data on the coordinating ability of sulfur donors are no doubt commendable but they have not achieved much of success. Klopman's [46] semiquantitative approach involving conditions for the perturbation of the 'frontier orbitals' when they come closer lead to a large covalent contribution in soft acid soft base interaction.

1B.5 STRUCTURE OF SULFUR DONOR LIGANDS

The coordinating ability of sulfur atoms in heterocyclic rings is very poor [35] due to the pseudo-aromatic nature of the ring. The pseudo-aromatic nature of the ring has two fold effects. They are: the lone pairs of the sulfur atom less available for donation and the p-orbitals are less capable of accepting electrons from metals in backbonding. The coordination power of the various types of sulfur containing ligands towards 'b class' and 'border line' metals is $RS^- > R_2S > RCS >>$ ring sulfur.

All ligands except the 'hardest' base namely fluoride ion cause the spin pairing of Co(III).Thiols, monothiodiketones and other charged sulfur ligands such as diethyldithiophosphate, but not thioethers or thiones, cause spin pairing of Ni(II). However, only the 'softest' bases such as cyanide ion, diarsine and certain charged sulfur ligands cause spin pairing of Fe(III). A series of ligands in the decreasing order of spin pairing ability can be represented as follows [47]; $CN^- > RCS^{2-} \approx ROCS^{2-} \approx R_2NCS^{2-} >> RNHS^{2-} \approx (EtO)_2PS^{2-} \approx RCSCHCOR' > R_2S$.

1B.6 NATURE OF SULFUR-NITROGEN DONORS

What applies to complexes of sulfur ligands applies to complexes of sulfur-nitrogen chelating agents as well. However, presence of nitrogen in the ligands tends to lower the solubility of the complex ion in non-aqueous solvents so that the complexes of sulfur-nitrogen donors are, in general, either sparingly soluble or insoluble in non-polar solvents [35]. The available data indicates that the ability of sulfur-nitrogen ligands to lower the interionic repulsion energy is less than that of sulfur-sulfur ligands. This is presumably due to nitrogen which has a lower position in nephelauxetic series compared to sulfur. Consequently sulfur-nitrogen donors would be expected to give rise to high values of β than sulfur-sulfur donors.

The coordination chemistry of sulfur-nitrogen chelating agents was extensively reviewed in 1974 by Akbar Ali and Livingstone [48]. Here the factors influencing the physical and chemical properties peculiar to sulfur-nitrogen ligands have been highlighted.This includes a large number of

sulfur-nitrogen bidentates.Carcinostatic and antiviral activity of such ligands and their complexes were linked to these properties. Kuehn and Isied [49] in an exhaustive review of the reactivity of metal ion -sulfur bonds, have given details of studies which deal with biological, spectral, thermodynamic and kinetic aspects of metal-sulfur interactions; including a large number of sulfur-nitrogen and sulfur-oxygen chelates.

1B.7 GENERAL CHARACTERISTICS OF METAL-SULFUR BONDS

The high affinity of metal for sulfur is clearly demonstrated by the enormous variety of metal sulfide minerals in nature. Qualitatively this might be understood using Pearson's concept of hard and soft acids and bases. It is better described, however by the covalency of the metal-sulfur bond particularly with soft metals. In contrast to O and N, as donor atoms S has low lying unoccupied 3d-orbitals available. Molecular orbital calculations reported in the literature, however, indicate that this influence might be over estimated. It has to be assumed that the high polarisability of the electrons on the sulfur atom is responsible for the variety of structures and the reactivity of metal complexes with sulfur containing ligands.

All degrees of covalency of metal - sulfur bonds are known, from almost completely ionic bonds to those with bond order of about 3. If no other ligands are present, a higher covalency is usually obtained when the metal d-valence orbital ionization potential (VOIP) matches the sulfur 3p VOIP. Lower oxidation states are occurring in complexes of the electron rich metals (Hg(II), Cu(I) etc). Additionally π accepting ligands will decrease the electron density on the metal and can thus allow for the increased electron density in the metal-sulfur bond. The electron density on the coordinated sulfur atom mainly determines the reactivity. This can be reduced by the formation of stronger metal-sulfur bonds, and also by the substitutents H and R, as in SH_2, SH^-, SR^- and SR_2. However complexes with the hydrogen containing ligands may easily undergo deprotonation reactions and are therefore, less stable. This is the main reason for having relatively few complexes with H_2S and SH^- as ligands but many examples of compounds with SR^- and SR_2 ligands.

The coordinating ability (ie, the stability constants of the complexes) of sulfur containing ligands increases with dipolemoment in the order H_2S < RSH < R_2S. The stability of the complexes decreases in the order S^{2-} > RS^- > R_2S. Here the polarisability and number of lone pairs are the dominant factors. In the spectrochemical series, R_2S is placed between H_2O and NH_3 but RS^- and HS^- come between F^- and Cl^- [50]. SH^- complexes may undergo deprotonation reactions; however, due to their generally low acidity, quite strong bases are required and these, in principle, are always capable of attacking the metal centres.Therefore, a deprotonation is often paralleled by destructive processes. Different preparative routes to the deprotonated complexes have been reported [51-52]. Another type of reaction utilizing the acidity of the proton is alkylation with diazoalkanes. Derivatives of hydrosulfide complexes can also be obtained by inserting for eg, acetylene or phenyl acetylene into the S-H bond. If the system is sufficiently electron rich, a tetrasulfur complex is formed with S_8; accompanied by evolution of H_2S [53].

An important feature of metal - sulfur bonds in general is the occurrence of π bonding over a wide range of bondlenghts, if sulfur 3p lone pairs are available. The overlap integral S_π(M-nd, S-3p) varies only to a relatively small extent with the metal - sulfur distance. Besides, if the M-nd and S-3p VOIPs are nearly equal, depending on geometry, electron population and additional ligand, very different electron density distribution within the metal - sulfur bonds are possible.

1B.8 METAL-SULFUR AND METAL-NITROGEN STRECHING FREQUENCIES

There is little information about the frequencies of metal- sulfur vibrations are available [54-55] and therefore not much light is thrown on the magnitude of bond strength. Available data reveal that the magnitude of stretching frequencies of the metal sulfur bond is depending on the nature of the ligand as well as the central metal ion [56-60]. Metal sulfur stretching frequencies lie in the range of 480-210 cm^{-1}. In chelate complexes however, coupling of frequencies corresponding to ν(M-S) and ring deformation can also take place [56]. In many instances two bands are observed. One being a medium to

high intensity band,while other being a weaker band at a frequency 10-40cm^{-1} lower than the stronger band. The frequencies for ν(Pd-S) and ν(Pt-S) for a large number of complexes lie within the range of 400-280 cm^{-1} [61]. However, the frequency for ν(M-S) is not very sensitive to the magnitude of the atomic mass of M. Monothiol-β- diketone complexes of a wide range of bi and trivalent metals [62] have ν(M-S) in the range of 399-376 cm^{-1}. Furthermore, there is no marked difference between thiolate complexes and thioether complexes in regard to the values of stretching frequencies ν(M-S).

Metal-Nitrogen stretching frequencies can be observed over a wide range, viz.from 600 cm^{-1} below 200 cm^{-1}. For unidentate amines, ν(M-N) is observed usually in the range of 500-700 cm^{-1}, while for pyridine [56] complexes it is seen unusually in the lower range viz.287 down to 200 cm^{-1} or even below. For a range of tetragonal diamine complexes of Co(II) and Ni(II), ν(M-N) is noticed [63] in the range of 400-338 cm^{-1}.Consequently in chelate complexes it is often possible to identify the band for ν(M-S) with certainty. However, in some Ni (II) complexes with tridentate ligands of N, S, N type, the bands for ν(M-N) and ν(M-S) were reported at 415-412 cm^{-1} and 328-326cm^{-1} respectively [64].

1B.9 THIOAMIDE BANDS

Thioamide bands play an important role in deciding the mode of linkage of the donor atoms with the acceptor metal ion. The available data in the literature [65] shows that the metal sulfur stretching vibrations depend on the nature of the ligand as well as the cation present in the complex. However, most of the assignments for the vibrations are empirical and little care is exercised in establishing that the band assigned to ν(M-S) in reality corresponds to ν(M-S) stretching bands. With nitrogen and sulfur donor ligands ν(M-S) and ν(M-N) may as well lie in the same frequency range in the infrared spectra of the complexes.This might pose problems in the assignment of the ν(M-S) band. However, in some important works [66-67], ν(M-S) band assignment has been confirmed by recording the spectra of the corresponding selenium complexes. If a particular band is indeed the band, it should be absent at the particular position in the infrared spectrum of the

corresponding selenium complex and a new band corresponding to ν(M-Se) should appear at lower wavenumber side. Since, in many cases, it is very difficult to prepare the selenium analogue of sulfur complexes, it would be useful to find out some alternative method to prove if a particular complex has either M-S or M-N bonding or simultaneously M-S and M-N bonding. Organic compounds containing thioamide moiety (H-N-C=S) have been studied by several workers and suggested that all such compounds give rise to four characteristics infrared bands [68-72] known as 'thioamide bands'. They are mixed bands [74] due to contribution from δ(N-H), ν(C=S), ν(C=N) and ν(C-H).

The approximate positions of the four thioamide bands in the infrared spectra of the sulfur-nitrogen ligands and their assignments [73] are given in Table 1B.1.It has been reported by several workers that the thioamide band IV can be used as a diagnostic aid in identifying the type of metal -ligand bonding [74-84]. However, several other group of workers [85-89] have indicated that the thioamide band IV alone cannot be used as a criterion for indicating whether coordination has taken places through S or N or through both simultaneously. A clear idea of the nature of the bonding between the ligand and the metal ion can be derived from a study of the nature of change in the position and intensities of all the four thioamide bands.

Table 1B.1

Region	Band	Assignment
1550-1600	I	δ(N-H)(major) + ν(C=N) (minor) + ν(C-H) (minor)
1250-1300	II	ν(C=N)(major) + δ(N-H) (minor) + ν(C=S) (minor)
500-1000	III	ν(C=N)(major) + ν(C=S) (minor)
750-850	IV	Predominantly ν(C=S)

The shift in the position of the thioamide bands as generally observed on complexation can be summarized as follows:

1. Metal-sulfur bonding results in the shifting of the position of thioamide band IV by about 50 cm^{-1} towards lower wavenumber side. On the

contrary, bonding between metal and nitrogen generally results in either no shift or a low shift to the extent of 30-40 cm^{-1} towards higher wavenumber side. A shift of about 70-100 cm^{-1} in the position of thioamide band IV towards lower wavenumber side tends to support the bonding scheme involving metal-sulfur bond [90].

2. The position of thioamide band II experiences a shift of the order of 30cm^{-1} towards higher wavenumber side.
3. The thioamide band III is either considerably lowered in intensity or its position is slightly shifted towards higher wavenumber side.
4. The position of the thioamide band I is shifted towards higher wave number side or lower wavenumber side to the extent of 10-30 cm^{-1} depending on the nature of the ligand.

Based on the spectral data of the large number of complexes of sulfur and nitrogen containing chelating agents, Singh et al. [74] made the following conclusions:

a. Chelate formation by coordination through nitrogen as well as sulfur is indicated by

i. a shift towards lower wavenumber side to the extent of 30-50 cm^{-1} in the position of thioamide band IV

ii. a shift towards higher wavenumber side to the extent of 30-40 cm^{-1} in the position of band II and

iii. retention in intensities of band I and III.

B.Coordination only through nitrogen results in

I.either no shift or a slight shift of the order of 15-20 cm^{-1} towards higher wave number side in the position of thioamide band IV

ii. a shift of the order of 10-35 cm^{-1} towards higher wavenumber side in the position of thioamide band II and

iii. a shift of about 10-30 cm^{-1} towards lower wavenumber side in the position of band I.

Conclusion based on these shifts should be drawn with great caution because the shifts can be caused by other factors also.

1B.10 SCHIFF BASES

Schiff base complex compounds have taken a wide place in coordination chemistry and have important role in the development of inorganic chemistry, biochemistry and environmental chemistry. Schiff bases have a chelating structure and are in demand because they are straight forward to prepare and are moderate electron donors with easily tunable electrons. The general preparation of schiff bases and metal complexes using these were first published in 1860's [91-92]. Schiff bases or imines have the general formula RN=CR', where R and R' are alkyl, aryl or cycloalkyl or heterocyclic groups. Imines play an important role in many biochemical reactions because some of the enzymes like an imine group of an amino acid, to react with an aldehyde or ketone to form an imine linkage [93].

These types of complexes with transition and heavy metals are used in organic synthesis, analytical studies, catalysis and medicine [94-95]. The bonding ability of the ligands depending on the nature of atoms that act as coordination site, their electronegativity and sterric factors. By virtue of the presence of lone pairs of electrons on the nitrogen atom, electron donating character of the double bond and low elecronegativity of nitrogen, nitrogen of the azomethine group (>C=N) act as good donor site in schiff base derived complexes. The formation of chelates gives an extra stability to the complexes especially when the ring is five or six membered. Hence, the presence of functional groups with replaceable hydrogen atom near to >C=N will be additional factor of stability.

1B.11 INTRODUCTION TO PREADMET

The success of a drug's journey through the body is measured in the dimensions of absorption, distribution, metabolism, and elimination (ADME). The ideal oral drug will be rapidly and completely absorbed from the alimentary canal and will find its way directly and specifically to its site of action. It will not bind to or interact with related receptors, and it will not bind non-specifically to passing serum proteins. The ideal compound may be a substrate for the liver enzymes and transporters that break down or clear alien compounds from the body, but in an entirely predictable fashion.

Consequently, there is no risk in its action as it will not give any toxic metabolites and every chance that the compound will have an appropriate half-life and passing gradually through the kidneys without harming them.

But in the real world, chemical compounds rarely exhibit this ideal combination of characteristics. Few are fully absorbed from the gut. The percentage that does cross is distributed at various sites in the body including, the intended site of action. A large proportion passes through the liver where it may be metabolized by enzymes. Drugs may induce the activity of these molecular "bouncers" whose main biological role is to show the door to non-nutritious compounds, which the rather more welcoming guardians of the gut, lung, and other epithelia have foolishly allowed entry. The door in this case, is usually the kidney. Elimination, process dependent on the complex series of molecular, cellular, and physiological process that constitute drug absorption, distribution, and metabolism.

The ADME properties of a drug, together with its pharmacological properties are conventionally viewed as part of drug development—the process of making a molecule as effective as possible as a medicine. Toxicology—the T in ADMET—is the art of making sure that the molecule causes no harm, regardless of what good it does. While a drug that kills is hardly likely to be a good drug, innovation in toxicology tends to be constrained by the need to fulfill regulatory requirements [96]. Using the PreADMET the result of ADME prediction can be used as the most outstanding and practical guidance for the early drug discovery.PreADMET is a web-based application for predicting ADME data and building drug-like library using in silico method.

A significant bottleneck remains in the drug discovery procedure, in particular in the later stages of lead discovery, is analysis of the ADME and overt toxicity properties of drug candidates. Over 50% of the candidates failed due to ADME/Tox deficiencies during development. Even though the early stage in vitro ADME reduces the probability of the failure at the development stage, it is still time-consuming and resource-intensive. Therefore, PreADMET which has been developed in response to a need for rapid prediction of drug-likeness and ADME/Tox data.

1B.11.1 DRUG-LIKENESS

In recent years, compounds to synthesize and estimate potential for drug through combinatorial chemistry and high throughout screening have rapidly increased in drug discovery. One of tools for predicting drug-likeness, discriminating between drug-like compounds and non-drug compounds uses widely. The following rules are drug-likeness rules provided in PreADMET.

1B.11.1a Lipinski's rule

Lipinski's Rule, so called "Rule of Five", is published by Christopher A. Lipinski et al. in Pfizer Central Research (Groton, NJ, USA). They selected a subset of 2245 compounds from WDI (World Drug Index) database and defined drug-like character through this subset. The results are the followings [97]:

- No. hydrogen bond donors ≤ 5 (The sum of OHs and NHs)
- No. hydrogen bond acceptor ≤ 10 (The sum of Os and Ns)
- Molecular weight ≤ 500
- C logP ≤5 (MlogP ≤ 4.5). About 90 % of the above subset is included in defined rage with better solubility and permeability

1B.11.1b Leadlike rule

Identification and optimization of lead compounds as chemical staring points are very important in combinatorial chemistry. Lead-like rule is published by Simon J. Teague et al. and defined to consider designing libraries with druglike physicochemical properties. They have divided the common sources of lead compounds for drug discovery into three types. [98]. The first type is lead-like leads, the second type is high-affinity leads and the third type is druglike leads. Lead-like leads have low-affinity (> 0.1 M), low molecular weight (< 350) and ClogP (< 3). High-affinity leads are compounds which have high-affinity (<< 0.1 μM), high molecular weight (>> 350) and low ClogP (< 3). Druglike leads have low-affinity, druglike molecular weight (350-500) and lipophilicity (3-5). Lead-like compounds have been optimized for affinity and pharmacokinetic properties by increasing molecular weight and lipophilicity, and are more useful in combinatorial chemistry.

1B.11.1c CMC-like rule

CMC-like rule is similar to rule of five. This is published by Arup K. Ghose et al. They defined druglike character for the CMC database, which is removed several classes of compounds such as diagnostic imaging agents, solvents, and pharmaceutical aids. In this study, the qualifying range (covering more than 80% of the compounds) of the calculated log P is between -0.4 and 5.6, with an average value of 2.52. For molecular weight, the qualifying range is between 160 and 480, with an average value of 357. For molar refractivity, the qualifying range is between 40 and 130, with an average value of 97. For the total number of atoms, the qualifying range is between 20 and 70, with an average value of 48 (Table lB.2) [99].

Table lB.2

Drug class	Qualifying Range in CMC Database			
	A logP (80%)	AMR (80%)	Mol. wt (80%)	No.of Atoms (80%)
CMC clean	-0.4 ~ 5.6	40 ~ 130	160 ~ 480	20 ~ 70
inflammatory	1.4 ~4.5	59 ~ 119	212 ~ 447	24 ~ 59
depressant	1.4 ~ 4.9	62 ~ 114	210 ~ 380	32 ~ 56
psychotic	2.3 ~ 5.2	85 ~ 131	274 ~ 464	40 ~ 63
hypertensive	-0.5 ~ 4.5	54 ~ 128	206 ~ 506	28 ~ 66
hypnotic	0.5 ~ 3.9	43 ~ 97	162 ~ 360	20 ~ 45
neoplastic	-1.5 ~ 4.7	43 ~ 128	180 ~ 475	21 ~ 63
infective	-0.3 ~ 5.1	44 ~ 144	145 ~ 455	12 ~ 64

1B.11.1d MDDR-like rules

MDDR-like rule is published by Tudor I. Oprea. The rule of five test produced similar results when applied to the ACDF and MDDRF subset, which 80% of ACDF and MDDRF pass the rule of five tests. ACD database is non-drug database and MDDR database is drug database. ACDF and MDDRF are databases removed the reactive functional groups such as acyl-halides, sulfonyl-halides, Michael acceptors, etc. In this study, therefore, he has concluded that the rule of five test cannot be used to discriminate between drugs and non-drugs. Descriptors used to MDDR-like rule are the number of rings, the number of rigid bonds and the number of rotatable bonds. The probability of finding a 'druglike' compound is higher in its ranges (e.g., No.Rings $\geq$ 3, No. Rigid bonds $\geq$ 18, No. Rotatable bonds $\geq$ 6), while the probability of finding a 'nondrug-like' compound is higher in the ranges (e.g., No.Rings $\leq$ 2, No. Rigid bonds $\leq$ 17, No. Rotatable bonds $\leq$ 5).

1B.11.1e WDI-like rule

This measurement is based on compounds that have molecular properties within the 90 % upper bound found in the WDI (World Drug Index) (Table l B. 3) [100].

Table lB.3

Descriptors	90% cutoff	Descriptors	90% cutoff
MW	550	Kappa-2A	12
Rotbond	13	Kappa-3A	8
Hbond acceptor	9	CHI-V-0	20
Hbond donor	5	CHI-V-1	12
AlogP	5	CHI-V-2	10
MolRef	120	CHI-V-3P	8
Balaban Jx	2.8	CHI-V-3C	2.2
PHI	8	Wiener	4000
Kappa-1A	25	Zabreb	175

1B.11.1f Reactive functional group

Filtering by reactive functional group is the one of the important steps for the drug discovery. A compound with a reactive functional group is reactive in human body, and it has possibility to cause toxicity. Additionally, a compound with a reactive functional group leads to reaction during a process of an in vitro experiment, such as a case of HTS. This may results some serious error of activity for drug. These compounds can be filtered off or removed, at the beginning of drug discovery. PreADMET can find compounds with electrophilic functional group which tends to make a covalent bond with protein, causing false positive. And PreADMET also finds compounds with 3 prohibited functional groups that are extremely unusual in drug discovery. The number of both kinds of functional groups is 23 in total [101-102].

1B.11.2 ADME PREDICTION

Reports show that a lot of drug candidates are failed during clinical tests because of the problems related to ADME, and nowadays researchers consider ADME properties as important conditions to choose compounds as drug candidates [103].

1B.11.2a Caco2 cell permeability

Numerous in vitro methods have been used in the drug selection process for assessing the intestinal absorption of drug candidates. Among them, Caco-2 cell model and MDCK cell model has been recommended as a reliable in vitro model for the prediction of oral drug absorption [104]. Caco-2 cells are derived from human colon adenocarcinoma and possess multiple drug transport pathways through the intestinal epithelium.For prediction of Caco-2 cell permeability in PreADMET, chemical structures at pH 7.4 are applied, because Caco-2 cell permeability and MDCK cell permeability are measured at about pH 7.4. Although there are some differences in the experimental values by compounds or their metabolisms, we can put into general categories (Table lB.4) [105].

Table lB.4

Classification	P_{Caco-2} (nm/sec)
Low permeability	less than 4
Middle permeability	4 ~ 70
High permeability	more than 70

1B.11.2b MDCK cell permeability

MDCK cell means Madin-Darby Canine Kidney cell. Advantage of MDCK cells is that its growth period is shorter than Caco-2 cell. MDCK cells are cultured for 3 days and Caco-2 cells are cultured for 21 to 25 days. According to Jennifer D. Irvine et al., correlation of MDCK and Caco-2 permeability is high as $R^2 = 0.79$. These results prove that MDCK cell system may use as good tool for rapid permeability screening. In PreADMET, therefore, provides prediction models for Caco-2 cell system and MDCK cell system. Although there are some differences in the experimental values by compounds or their metabolisms, we can put into general categories (Table l B. 5) [106].

Table lB.5

Classification	P_{MDCK} (nm/sec)
Low permeability	less than 25
Middle permeability	25 ~ 500
High permeability	more than 500

1B.11.2c Human Intestinal Absorption

Predicting human intestinal absorption of drugs is very important for identifying potential drug candidate. In PreADMET one can predict the percentage human intestinal absorption (%HIA). Human intestinal absorption data are the sum of bioavailability and absorption evaluated from ratio of excretion or cumulative excretion in urine, bile and feces [107]. For prediction of HIA in PreADMET, chemical structures at pH 7.4 are applied, because HIA is measured by in vivo test.

This is one of options of PreAMDET and user can choose for this option.Although there are some differences in the experimental values by compounds or their metabolisms, we can put into general categories (Table 1B.6) [108].

Table lB.6

Classification	HIA (Human Intestinal Absorption)
Poorly absorbed compounds	0 ~ 20 %
Moderately absorbed compounds	20 ~ 70 %
Well absorbed compounds	70 ~ 100 %

1B.11.2d Skin Permeability

In the pharmaceutical, cosmetic and agrochemical fields, it is important to predict the skin permeability rate for a crucial parameter for the transdermal delivery of drugs and for the risk assessment of all chemicals that come into contact with the skin either accidentally or by design. In PreADMET one can predict in vitro data on human for skin permeability.PreADMET predicts in vitro skin permeability and the result value is given as $\log K_p$. K_p (cm/hour) is defined as:

$Kp= K_m*D/h$

where K_m is distribution coefficient between stratum corneum and vehicle, and D is average diffusion coefficient (cm^2/h), and h is thickness of skin (cm)[109].

1B.11.2e Blood Brain Barrier Penetration

Blood-Brain Barrier (BBB) penetration is represented as BB= [Brain]/[Blood], where [Brain] and [Blood] are the steady-state concentration of radio labeled compounds in brain and peripheral blood. Predicting BBB penetration means predicting whether compounds pass across the blood-brain barrier or not. This is crucial in pharmaceutical sphere because CNS-active compounds must pass across it and CNS-inactive compounds mustn't pass across it in order to avoid of CNS side effects. In

PreADMET can predict in vivo data rates for BBB penetration (Table 1B.7) [110].

Table 1B.7

Classification	BB (C_{brain}/C_{blood})	logB
High absorption to CNS	more than 2.0	more than 0.3
Middle absorption to CNS	2.0 ~ 0.1	0.3 ~-1.0
Low absorption to CNS	less than 0.1	less than -1.0

1B.11.2f Plasma Protein Binding

Generally, only the unbound drug is available for diffusion or transport across cell membranes, and also for interaction with a pharmacological target. As a result, a degree of plasma protein binding of a drug influences not only on the drug's action but also its disposition and efficacy. In PreADMET can predict percent drug bound in plasma protein as in vitro data on human. Although there are some differences in the experimental values by compounds or their metabolisms, we can put into general categories (Table 1B.8)

Table 1B.8

Classification	Plasma Protein Binding (%PPB)
Chemicals strongly bound	more than 90%
Chemicals weakly bound	less than 90%

1B.11.3 TOXICITY PREDICTION

One of the reasons for the failure of drug discovery is its toxicity [CMR international 2003]. It means that designing drugs with the consideration of their toxicity is very important. PreADMET predicts mutagenicity and carcinogenicity of compounds, helping you to avoid toxic compound.

1B.11. 3a Ames test

Ames test is a simple method to test mutagenicity of a compound, which is suggested by Dr. Ames. It uses several strains of the bacterium Salmonella typhimurium that carry mutations in genes involved in histidine synthesis, so that they require histidine for growth. The variable being tested is the mutagen's ability to cause a reversion to growth on a histidine-free medium [111-112]. PreADMET predicts toxicity to TA98, TA100 and TA1535 which are often used in Ames test. And the result can be calculated both with consideration of metabolite (Metabolic activation by rat liver 10% homogenate, +S9) and without consideration of metabolite (No metabolic activation, -S9). The actual value of the prediction result is "positive" or "negative"(Table 1B.9)

Table 1B.9

Type	NTP Definition	Description
Negative	No change of population (vs. blank plate)	negative prediction
Positive	Change of population, more than double of blank plate's change	positive prediction

1B.11.3b Rodent Carcinogenicity

Carcinogenicity is a toxicity that causes cancer in body. Generally carcinogenicity test requires long time (usually 2 years), currently only in vivo test methods are established. Usually the test uses mice or rats, exposing them to a compound. And the variable to be observed is existence of cancer. PreADMET predicts the result from its model, which is built from the data of NTP (National Toxicology Programme) and US FDA, which are the results of the in vivo carcinogenicity tests of mice and rats for 2 years (Table 1B.10).

Table 1B.10

Type	NTP Definition	Description
negative	Clear evidence of carcinogenic activity	negative prediction
positive	No evidence of carcinogenic activity	positive prediction

1B.12 COMPUTATIONAL CALCULATIONS

Computational chemistry is a set of techniques for investigating chemical problems on a computer. It mainly deals with molecular geometry, energies of molecules and transition states, chemical reactivity, IR, UV and NMR spectra, the interaction of a substrate with an enzyme and the physical properties of a substance.

1B.12.1 TOOLS OF COMPUTATIONAL CHEMISTRY

The five main tools available in computational chemistry are

1. Molecular mechanics(MM): Molecular mechanics based on a model of a molecule as a collection of balls (atoms) held together by springs (bonds).Of a given molecule; changing the geometry until the lowest energy is found enables us to do a geometry optimization ,ie, to calculate a geometry of the molecule. Molecular mechanics is a fast technique.

2. Ab initio calculations: These are based on the Schrödinger equation. The ab initio method solves the Schrödinger equation for a molecule and gives us the molecule's energy and wavefunction.Regardless of its level, an ab initio calculation is based only on basic physical theory and is in this sense' from first principles' .Ab initio calculations are relatively slow.

3. Semiempirical calculations (SE): These are like ab initio, based on Schrödinger equation. The Schrödinger equation cannot be solved exactly for any molecule with more than one electron. Thus approximations are made in solving it, and the very complicated integrals that must be calculated in the ab initio method are not actually evaluated in SE calculations instead , the program draws on a kind of library of integrals

that was compiled by finding the best fit of some calculated entity like geometry or energy to the experimental values. This plugging of experimental values into a mathematical procedure to get the best calculated values is called parameterization. It is the mixing of theory and experiment that makes the method "semi empirical". SE calculations will give good results for molecules for which the program has not been parameterized. Semi empirical calculations are slower than MM but much faster than ab initio calculations.

4. Density functional calculations (often called density functional theory DFT): These are like ab initio and SE calculations, based on Schrödinger equation. However, unlike ab initio and SE calculations, DFT doesn't calculate a wavefunction, but rather derives the electron density distribution. DFT calculations are faster than ab initio, but slower than SE.

5. Molecular dynamics calculations: Molecular dynamics calculations apply the laws of motion to molecules.

1B.12.2 MOLECULAR MECHANICS

The basic principles of MM rests on a view of molecules as balls held together by springs. MM began in the 1940s with attempts to analyze the rates of racemization of biphenyls and SN^2 reactions. The potential energy of a molecule can be written as the sum of terms involving bond stretching, angle bending, dihedral angles and non bonded interactions. Giving these terms in explicit mathematical forms constitutes devising a forcefield, and giving actual numbers to the constants in the forcefield constitutes parameterizing the field. MM is used mainly to calculate geometries and energies for small to medium-sized molecules. Such calculations are fast and can be very accurate, provided that the forcefield has been carefully parameterized for the types of molecules under study. Calculations on biomolecules is a very important application of MM; the pharmaceutical industry designs new drugs with the aid of MM: for example, examining how various candidate drugs fit into the active sites of biomolecules (docking) and the related aspect of QSAR are of major importance. MM is of some limited use in calculating the geometries

and energies of transition states. Organic synthesis now makes considerable use of MM, which enables chemists to estimate which products are likely to be favored and to devise more realistic routes to a target molecule than was hitherto possible. In molecular dynamics MM is used to generate the forces acting on molecules and hence to calculate their motions, and in Monte Carlo simulations MM is used to calculate the energies of the many randomly generated states.

MM is fast, it can be accurate, it is un demanding of computer power, and it provides reasonable starting geometries for quantum mechanical calculations. MM ignores electrons, and so can provide parameters like dipole moment only by analogy. One must be cautious about the applicability of MM parameters to the problem at hand. Stationary points from MM, even when they are relative minima, may not be global minima. Ignoring solvent effects can give erroneous results for polar molecules.

1B.12.3 SEMI EMPIRICAL CALCULATIONS

Semi empirical quantum mechanical calculations are based on the Schrodinger equation. It deals with SCF SE methods, in which repeated diagonalization of the Fock matrix refines the wavefunction and the molecular energy is takes place. These calculations are much faster than ab initio ones, mainly because the number of integrals to be dealt with is greatly reduced by ignoring some, (hence "empirical"), and other integrals are calculated only approximately. In order of increasing sophistication, these SCF SE procedures have been developed: PPP, CNDO, INDO, and NDDO. The PPP method is limited to n electrons, while CNDO, INDO and NDDO use all the valence electrons. All four use the ZDO approximation, which sets the differential of the overlap integral equal to zero; this greatly reduces the number of integrals to be calculated. Traditionally, these methods were parameterized mostly using experimental quantities (usually ionization energies and electron affinities), but also (PPP and CNDO) making some use of minimal- basis-set (i.e. low-level ab initio calculations. Of these original methods, only versions of INDO parameterized to reproduce UV spectra (INDO/S and its variant ZINDO/S) are much used nowadays. Today by far the most popular SCF SE

methods are AM1 and PM3, which are NDDO-based, but carefully parameterized to reproduce experimental quantities (primarily heats of formation). AM1 and PM3 perform similarly and usually give quite good geometries, but less satisfactory heats of formation and relative energies. A modification of AMI called SAM1, as yet relatively little-used, is said to be an improvement over AMI [113].

1B.12.4 HYPERCHEM

HyperChem is the molecular modeling and simulation software that helps to perform complex chemical calculations on our desktop computer.

1B.13 PRESENT INVESTIGATION

Chapter III deals with complexing behaviour of schiff base derived from substituted 1,2,4-triazine with 0-hydroxy acetophenone,chloro benzadehyde and methoxy benzaldehyde.A number of metal complexes were synthesised and characterized on the basis of analytical data, magnetic susceptibility,TG studies,electronic, infrared and ESR spectral measurements,molecular modeling studies and pharmacokinetic studies.

PART C

INTRODUCTION TO CORROSION INHIBITION STUDIES

1C.1 GENERAL

Except noble metals like gold, platinum, iridium and possibly silver and palladium which have inherent thermodynamic stability in most environments, practically all metals have an intrinsic tendency for corrosion. The intensity of corrosion and its rate depend on many factors. The subject of metallic corrosion has gained considerable importance during last few decades because of the increasing awareness of the enormous losses caused by corrosion damage. Economic factor is the prime consideration for much of the current research in the field of corrosion. The second reason for the interest is the need for conservation of depleting natural metal resources. If the present rate of exploitation and utilization of metal resources continues, it may be exhausted very soon. Rapidly diminishing metal resources will have far more pronounced effects on civilization than the energy crisis. Corrosion costs of automobiles-fuel systems, radiators, exhaust systems and bodies-are in the billions. Costs of corrosion will escalate substantially during the next decade because of worldwide shortages of construction materials, higher energy costs, aggressive corrosion environments in coal conversion processes, large increase in numbers and scope of plants, and other factors. Productions of metals used for corrosion resistance and to replace corroded parts require large amounts of energy, thus compounding the nation's energy problems. Infact our economy would be drastically changed if there were no corrosion.

Corrosion considerations are critical in many applications. For instance, the chemical industry uses very aggressive environments for synthesis, and purity is usually extremely important. Therefore, the reactors and vessels must be essentially inert and resist the aggressive attack of the process environment. Corrosion resistant alloys have wide usage in this industry. Microelectronics is another area in which corrosion is important even though the environment is typically not very aggressive. Other corrosive environments and industries in which corrosion is critical include oil and gas recovery and processing, marine and seawater applications, underground pipelines, power plants, and Al alloys in aerospace applications. The rate of corrosion will depend on a

number of factors, including thermodynamic, kinetic, and mass-transport-related aspects.

1C.2 TYPES OF CORROSION

Corrosion can be defined as an irreversible reaction of a material with the environment, which usually (but not always) results in a degradation of the material or its properties. So there are several aspects of corrosion: the material, the environment, and the material properties [114]. Metals are generally produced by reduction of ores that are found in nature.

The corrosion of metals can take many forms, which are important to understand since the best methods of corrosion prevention depend upon the form of corrosion. The most basic form of corrosion is uniform corrosion during which a metallic object is more or less uniformly consumed and converted to ionic species. Much of our fundamental understanding of corrosion, such as thermodynamics and kinetics, is based on uniform corrosion. Passivity is the state of a metal that is protected by a thin surface oxide film. Pitting is a form of localized corrosion that occurs when the thin passive film that protects the metal lost that region. The rate of attack at pits can be extremely high so pitting can lead to perforation of a structure or initiation of a crack. Localized corrosion often initiates at an occluded region where the environment has limited access. This form of corrosion, called crevice corrosion, is extremely important in fastened structures. Localized corrosion is sometimes observed at grain boundaries when the composition of the grain boundary or region near the grain boundary is different from the metal grain. This type of corrosion, called intergranular corrosion is a severe problem with stainless steels and aluminum alloys. If the corrosive attack is localized at one component of a structure made from different metals that are electrically connected is called galvanic corrosion. The corrosion of metal alloys often results in preferential reaction of one or more of the alloying elements, called dealloying. A common by-product of the corrosion process is hydrogen. Hydrogen can interact with metals in various ways to result in degradation of properties, primarily mechanical properties. A generic name for such degradation is hydrogen damage. The mechanical properties of

metals can be severely degraded by the combined effects of the environment and an applied stress. Stress corrosion cracking is the premature failure of metal structures as a result of these effects. Corrosion fatigue occurs when the applied stress is fluctuating rather than constant.

1C.3 ELECTROCHEMICAL ASPECTS OF CORROSION

Corrosion is an electrochemical process [115]. These reactions typically involve the transfer of charge across the interface. There are two types of charge transfer reactions. Ion transfer reactions involve the transfer of ions from the electrode to the electrolyte, or vice versa. Electron transfer reactions involve the transfer of charge between ions in the electrolyte (or adsorbed on the surface), and typically occur heterogeneously at an electrode surface. Redox reactions are pure electron transfer reactions that occur at inert electrode surfaces.

1C.3.1 CORROSION REACTIONS

Corrosion often involves oxidation of metal atoms to form ionic species with higher oxidation state and the liberation of electrons.

For example

$$M \rightarrow M^{z+} + ze^{-} \qquad (1)$$

These are called half-cell reactions because the electrons liberated by the oxidation reaction must be consumed by a reduction reaction occurring on the same electrode. A reduction reaction that is common in acids is hydrogen evolution:

$$2H^{+} + 2e^{-} \rightarrow H_2 \qquad (2)$$

The complete corrosion reaction for Fe in an acid would be the sum of the oxidation and reduction reactions:

$$Fe + 2H^{+} \rightarrow Fe^{2+} + H_2 \qquad (3)$$

Anodes and cathodes can be spatially separated at fixed locations associated with heterogeneities on the electrode surface. Alternatively, the locations of

the anodic and cathodic reactions can fluctuate randomly across the sample surface. The former case results in a localized form of corrosion, such as pitting, crevice corrosion, intergranular corrosion, or galvanic corrosion, and the latter case results in uniform corrosion.

1C.4 CORROSION PROTECTION BY INHIBITION

A corrosion inhibitor is a substance that, when added at small concentrations to a corrosive environment, effectively reduces the corrosion rate of a metal exposed to that environment. Corrosion protection by inhibitors is of considerable practical importance, and is the subject of significant research activities [116-118]. Usually, corrosion inhibition results from the formation of an adsorption layer or protective film, which influences the electrochemical reactions involved in the corrosion process (also termed interface and interphase inhibition, respectively) [119]. In other cases, the inhibitor promotes the passivation of the metal or modifies the solution chemistry, for example, by scavenging aggressive species. Inhibitors are mainly used for the control of homogeneous corrosion; their application to localized corrosion is less developed.

The overall corrosion rate of a freely corroding metal is determined by the anodic and cathodic partial reactions, both of which can be affected by the inhibitor. It is therefore common to distinguish anodic, cathodic, and mixed inhibitors, dependent on the type of electrochemical reactions that are inhibited. In these cases, the inhibitor can either lower the rate of the rate-determining step of the corresponding reaction(s) or introduce a new rate-determining step. The efficiency by which the corrosion process is reduced usually depends on the inhibitor concentration as well as characteristic system parameters, such as the solution pH, the concentration of aggressive species in the solution, the nature and the state of the metal surface, and the hydrodynamic conditions. Practical criteria for the selection of corrosion inhibitors from the great variety of inorganic and organic substances with inhibiting properties are not only their inhibition efficiency but also safety of use, economic constraints, and compatibility with other chemicals in the system, and environmental concerns. The use of highly efficient inorganic

inhibitors such as chromates and zinc salts, are used less due to their toxicity and are nowadays largely replaced by organic inhibitors. Examples of commonly used inhibitors as well as their classification and predominant inhibition mechanisms are listed in Table lC.1.

Table lC.1 Examples of substances used as corrosion inhibitors

Species	Type	Mechanism
Orthophosphates	Anodic	Non oxidizing passivator
Polyphosphates	Cathodic	Film-forming
Phosphonates	Mixed	Film-forming
Tannins and lignins	Cathodic	Film-forming
Benzoates	anodic	Non oxidizing passivator
Silicates	Mixed	Film-forming
Chromates	Anodic	Oxidizing passivator
Nitrites and nitrates	Anodic	Oxidizing passivator
Molybdates	Anodic	Non oxidizing passivator
Zinc salts	Cathodic	Film-forming
Aromatic azoles	Mixed	Adsorption, film-forming
Amines and amides	Mixed	Adsorption
Acetylenic alcohols	Mixed	Adsorption
Sulfur-containing compounds	Mixed	Adsorption

1C.5 TYPES OF INHIBITORS

1C. 5.1 Anodic Inhibitors

Inhibitors that directly affect the anodic reaction, that is, the metal dissolution process, are termed anodic inhibitors. Addition of an anodic inhibitor to the corrosion system can either lower the rate (i.e. the exchange current density) of the anodic process or influence the reaction mechanism, resulting in a change in the Tafel slope, as compared to that in inhibitor-free solution. In the case that both the anodic and the cathodic process are determined by the

activation-controlled reaction rates, this causes an anodic shift of the corrosion potential. Anodic inhibitors may be divided into two types, viz, oxidizing inhibitors which can inhibit anodic processes at concentrations of about 100 ppm and non oxidizing inhibitors which are effective only at appreciably higher concentrations. The latter are usually basic in nature with some buffering capacity in the basic region of the pH scale. Thus chromates act as inhibitors in the absence of oxygen, molybdates and tungstates do so in the presence of atmospheric oxygen.Whilst pertechnates (TcO_4) are very good (but very expensive) inhibitors even at concentrations as low as 5 to 10 ppm. Permanganates on the other hand have little inhibitive action.

1C.5.2 Cathodic Inhibitors

In a similar way, an inhibitor can interfere with the cathodic partial reaction. In this case, corrosion potential is shifted to more negative potentials, resulting in a reduced corrosion current density. Again, the inhibitor can affect both the rate and the mechanism of the cathodic process. Cathodic inhibitors may also be effective under diffusion controlled cathodic reaction conditions either by inducing a cross over to reaction-controlled conditions or by reducing the surface concentration of species involved in this reaction .For example, by the formation of surface films that block their transport to the surface. Examples are the salts of Mg, Mn, Zn and Ni which decrease the corrosion rate of iron and steel. Oxygen diffusion is slowed down by the precipitation of the hydroxides of these metals due to the increase in the basicity near the water-line caused by oxygen reduction. The precipitated hydroxides form a reasonably adherent deposit. Also, addition of lime to waters raises both the pH and serves as a cathodic inhibitor.

1C.5.3 Passivating Inhibitors

Some of the most effective inhibitors stifle corrosion by promoting passivation of the metal surface, that is, by shifting the corrosion potential into the range positive of the critical passivation potential Ep. To induce passivation of an active surface, the corrosion current density has to exceed the critical current density. This can be achieved either by increasing current

density via, enhancing the rate of the cathodic reaction or by decreasing the critical current density. The first case usually refers to inhibitors that are easily reduced on the metal surface, resulting in an increasing cathodic current density. Since these inhibitors are oxidizing in their action on the metal, they are often termed oxidizing inhibitors, in contrast to non oxidizing inhibitors, which require the presence of oxygen in solution to achieve inhibition in near-neutral solution. Most passivating inhibitors, however, rely predominantly on the second mechanism, in which the anodic process is inhibited [120].

1C.5.4 Mixed and Ohmic Inhibitors

Some substances inhibit corrosion by reducing simultaneously the rate of the anodic and cathodic reactions involved in the corrosion process and are therefore called mixed inhibitors. Mixed inhibition not only requires that both of the electrochemical reactions are influenced by the inhibitor, which indeed is often the case, but also that the corrosion rate is actually limited by anodic as well as cathodic reactions. As an example, again a diffusion-limited cathodic reaction may be considered, in which inhibition may rely solely on the reduction of the cathodic reaction rate even if the anodic reaction is also affected by the inhibitor. Inhibition may also be (partially) caused by the presence of ohmic potential drops (e.g. because of the formation of poorly conducting films) between anodic and cathodic surface areas. Here the rates of the partial reactions are additionally reduced due to the opposite negative and positive potential shifts in the anodic and cathodic areas, respectively, resulting in a further decrease in current density.

1C.5.5 Scavenging Inhibitors

Another type of inhibitors is the "scavenging inhibitors". These do not function by impeding ionic reactions, but by using up some ingredient of the cathodic reaction in the electrolyte and thus reducing its concentration. The cathodic reaction will then become slower or may even stop and consequently corrosion will stop. A typical example of this type is sodium sulphite which absorbs oxygen from the electrolyte causing oxygen depletion at the cathode.

1C.5.6 Vapour phase Inhibitors

Vapour phase inhibitor (V.P.I) have a high vapour pressure. It volatizes, travels through air to reach the metal it is intended to protect. Its principle is the same as the one for the moth balls [121].

In practical formulations, it is common to use several different inhibitor species, frequently a combination of anodic and cathodic inhibitors. The simultaneous use of two or more different inhibitor species often results in a more efficient inhibition than the sum of the individual effects of the inhibitors. For example, the inhibition of mild steel in chloride-containing solution by polyphosphate is only effective upon the addition of Ca^{2+} traces [122].

1C.6 INHIBITION BY ADSORBTION

The adsorption of ions or neutral molecules on bare metal surfaces immersed in solution is determined by the mutual interactions of all species present at the phase boundary. These include electrostatic and chemical interactions of the adsorbate with the surface, adsorbate–adsorbate, and adsorbate–solvent interactions. Inhibitors are usually specifically adsorbed species that adsorb directly on the metal surface in a process involving (partial) desolvation of the adsorbate species and replacement of solvent molecules from the electrode surface. Consequently, the interaction of the adsorbate with the surface has to exceed that of the solvent. Commonly, one distinguishes chemisorption, in which the adsorbate chemically interacts with the surface, and physisorption, caused by much weaker van der Waals or (hydrophobic) adsorbate–solvent interactions. The dependence of the adsorbate surface coverage θ on the concentration of the adsorbate species in the solution C is described by the adsorption isotherm. Different types of adsorption isotherms are

Temkin isotherm $\exp \int(\boldsymbol{\theta}) = K_{ads} C$ (4)

Langmuir isotherm $\frac{\theta}{1-\theta} = K_{ads} C$ (5)

Frumkin isotherm $\frac{\theta}{1-\theta} \exp -2 \int(\boldsymbol{\theta}) = K_{ads} \mathbf{C}$ (6)

Freundluich isotherm $\theta = K_{ads} C$ (7)

The adsorption process is influenced by the electrode potential, the nature and surface structure of the metal, the molecular structure of the adsorbate, and the presence of other species in the electrolyte.

Qualitatively, the role of the functional group has been often explained by the HSAB principle, which states that hard acids prefer to react with hard bases, whereas soft acids preferably react with soft bases [123-125]. Hard acids or bases have low polarizability and acceptor atoms with low electronegativity or donor atoms with high electronegativity, respectively (i.e. are hard to reduce or oxidize) while soft acids and bases exhibit the opposite properties. Since bare metals can be classified as soft acids, the general tendency of the adsorption energy to increase with the functional group in the order O< N < S can be associated with the corresponding increase in polarizability. The structure of the rest of the molecule can affect the adsorption energy via influencing the electron density on the hetero atom. Generally, the electron density of the functional group and the inhibition efficiency increase upon replacement of a hydrogen atom by electron-donating substituents. In addition, strongly polar substituents increase the dipolemoment of the molecule, resulting in a stronger adsorption. The molecular structure not only determines the adsorbate–substrate interactions but also the lateral interactions between the adsorbed molecules. Attractive adsorbate–adsorbate interactions, for example, due to van der Waals forces between molecules with long hydrocarbon chains, result in the formation of condensed, often ordered 'self-assembled monolayer,'(SAM) in which the strength of adsorption is increased. Reciprocally, repulsive interactions (e.g. dipole–dipole interactions) weaken the adsorption. Furthermore, the interactions with other species in the solution can also stabilize or destabilize the molecular adsorption at solid–liquid interfaces. This includes the interaction of water with hydrophilic and hydrophobic groups of the molecules, which may promote the aggregation of hydrophobic groups at the interface via formation of SAM or hemimicelles (''hydrophobic effect'') [126], an effect which is particularly important for physisorbed species. Dissolved species, such as anions or cations, may co-adsorb with the inhibitor species, resulting in a stronger adsorption ('cooperative adsorption'), or compete with the inhibitor

species (‘‘competitive adsorption’’) and displace them (at least partially) from the metal surface. An example of cooperative adsorption is the adsorption of quaternary ammonium cations, which co-adsorb with halides on several metal surfaces [127] .The adsorption of inhibiting species on reactive metals, is predominantly estimated from macroscopic corrosion data, in which the inhibitor coverage often is simply equated with the reduction in corrosion rate.

1C.7 MECHANISMS OF PROTECTION AND DEGRADATION

The thermodynamic tendency for a metal to corrode in aqueous medium depends on its thermodynamic stability in that medium, as described by its Pourbaix diagram [128]. If it is not stable in the metallic form, or in the presence of oxidizing species in solution, the metal will undergo oxidation that shall lead either to ions in solution or to solid corrosion products. If these products are not passivating, then the process will lead to active corrosion of the metal. For the case of iron in contact with dissolved oxygen, the reactions involved will be

$$Fe \rightarrow Fe^{2+} + 2e^{-} \qquad \text{anodic reaction} \tag{8}$$

$$\frac{1}{2}O_2 + 2e^{-} + H_2O \rightarrow 2OH^{-} \quad \text{cathodic reaction} \tag{9}$$

The anodic reaction is therefore the anodic dissolution of iron. The free electrons resulting from this reaction are consumed at the cathodic sites, in the reaction of oxygen reduction, with formation of hydroxyl ions. The overall reaction will then be

$$Fe + \frac{1}{2}O_2 + H_2O \rightarrow Fe(OH)_2 \tag{10}$$

Ferrous hydroxide is soluble in water, but in the presence of oxygen it may be converted into ferric oxide:

$$2Fe(OH)_2 + \frac{1}{2}O_2 \rightarrow Fe_2O_3.H_2O + H_2O \tag{11}$$

This species is less soluble than ferrous hydroxide, and precipitates on the surface. In the absence of oxygen, the cathodic reaction can also be

$$H_3O^+ + e^- \rightarrow \frac{1}{2} H_2 + H_2O \qquad (12)$$

Under conditions of oxygen or electrolyte concentration gradients, or due to heterogeneities of the metallic substrate, the cathodic and anodic sites may be separated. For each of the two electrodes, the equilibrium potential for their actual conditions can be determined by the Nernst equation. The electromotive force (EMF) for the corrosion process to occur is the difference between the two equilibrium potentials. When the cathode and the anode are short-circuited, a mixed potential result, known as corrosion potential, E_{corr}. The value of E_{corr} lies between the two separate electrode potentials, although shifted towards the equilibrium potential of the faster reaction. This situation can be easily visualized with the help of the Evans (E − log i) diagrams. It can thus be concluded that for corrosion to initiate at the metallic substrate at neutral pH, the presence of both water and oxygen is required. Organic coatings retard both the initiation of corrosion and its rate of development, in two ways: by a barrier mechanism and by an inhibiting mechanism.

1C.8 MEASURES OF CORROSION RATE

Corrosion rates can be given in a number of different units using different measures of material loss. The easiest way to determine the corrosion rate is by immersing a sample into a corrosive environment for a period of time and measuring the weight loss during that time (Gravimetric method). The weight loss must be normalized by the sample area in order to determine a corrosion rate, so one set of proper units for corrosion rate is weight loss per unit area per unit time; for instance, $mgcm^{-2}s^{-1}$. It is very common to divide this measure of weight loss corrosion rate by the density of the corroding material to get a corrosion rate in units of thickness lost per unit time; for instance, mils per year (mpy, which is thousandths of an inch per year) or mm yr^{-1}.

$$\text{Corrosion rate} = \frac{534W}{DAt}(\text{mpy}) \text{ or } \frac{87.6W}{DAt} \quad (\text{mmy}) \qquad (13)$$

1C.9 ELECTROCHEMICAL TECHNIQUES

The relationship between current and potential at an electrode/electrolyte interface can be probed by either controlling the potential or measuring the current, or by controlling the current and measuring the potential. In order to investigate the relationship over a range of values, the controlled parameter is either stepped or scanned. The most common approach for determining the current/potential relationship is potentiodynamic scanning. The potential is scanned at a fixed rate between two set values and the current is measured at periodic intervals. By automatically switching between measuring resistors with a range of values, potentiostats can accurately determine currents over many orders of magnitude.

1C.9.1 Tafel Extrapolation method

The mixed potential theory provides the basis for the determination of corrosion rate by Tafel extrapolation. A Potentiodynamic polarization experiment for Tafel extrapolation typically starts at a potential about 250 mV negative to the OCP, and scans upward through the potential of zero current (which might be different than the original OCP) to a value that is about 250mV positive to the original OCP. The ±250-mV range of potential is sufficient to allow the observation of a Tafel region if it exists. Less polarization is required if the Tafel slope is low. The line describing the behavior in the Tafel region can be extrapolated to the corrosion potential to determine the corrosion rate. Potentiodynamic polarization over a wide range of potential provides more information about the system than just the corrosion rate. Extrapolation of these regions to the reversible potentials of the oxidation and reduction reactions provides a measure of the exchange current density of the reactions (Fig.1C.1).

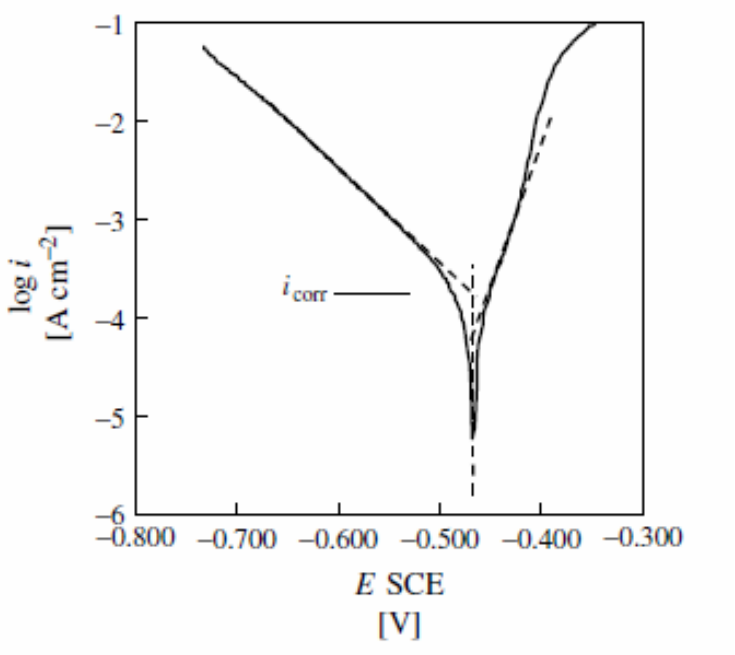

Fig.1C.1 Potentiodynamic polarization curve

1C.9.2 Linear Polarization method

The corrosion rate can be determined from the polarization resistance using the Stern–Geary equation, if the Tafel slopes are known:

$$i_{corr} = \frac{\beta_a \beta_c}{(\beta_a + \beta_c) 2.303 R_p} \qquad (14)$$

The Stern–Geary equation is the basis for the linear polarization method in which the polarization resistance is determined typically by scanning the potential from a value slightly below the corrosion potential to one slightly above the corrosion potential. It is an extremely easy technique that has been put to considerable use in corrosion monitoring. The polarization resistance can be determined by a simple two-point measurement at values above and below the OCP. These simplified analyses assume that the polarization response is perfectly linear, and an error will result if there is any deviation from linearity. The linear polarization technique is considered to be ‘‘nondestructive’’ relative to potential scanning over a wide range because the electrode is barely disturbed from the open circuit condition. Larger

polarization in either the anodic or cathodic direction can affect the electrode surface, and therefore might be ‘‘destructive’’. A typical linear polarization graph is given in Fig.1C.2.

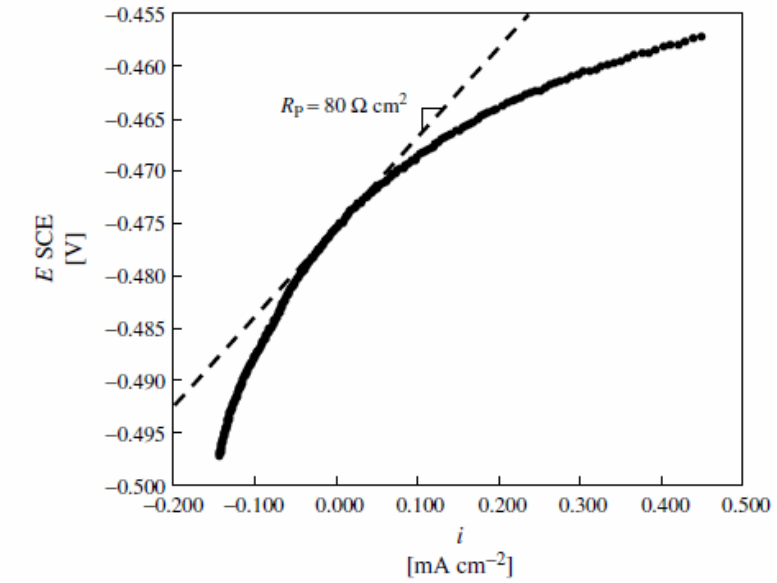

Fig.1C. 2 Linear polarization graph

1C.9.3 Electrochemical Impedance Spectroscopic method

Electrochemical impedance spectroscopy (EIS) is a convenient and effective method of assessing the properties and performance of organic-coated metal systems. The a.c impedance of an electrochemical cell can be determined by applying a sine wave of potential (V) of a certain frequency (ω*)* and measuring the corresponding current (I) flowing across the cell. The ratio of potential and current is the impedance of the cell (Z) at the chosen frequency, according to Ohm’s law:

$$Z=\frac{V}{I}=\frac{V_0 \sin\omega i}{I_0 \sin(\omega i - \Psi)} \qquad (15)$$

A spectrum can be obtained by varying the frequency of the applied signal, in which case the technique is called EIS. When compared to other techniques for corrosion evaluation, EIS has several advantages. It gives kinetic information on the corrosion processes. The use of a.c signals allows the

separation between the resistances of charge transfer, of the coating itself and of the solution. With polarization curves only the polarization resistance is measured, which is the sum of all the resistances in the system. The possibility of separation of each of those components is of great importance, particularly in highly resistive systems, such as organic coatings. It gives mechanistic information. This is based upon the use of 'equivalent circuits', which are electronic circuits whose response is identical to that of the cell under study. It provides information on the properties of the coating itself, namely its resistance and capacitance. The changes in these properties have been associated with the loss of protective properties. The technique is non destructive, in contrast with dc polarization curves, and it provides immediate information on the systems, in contrast to exposure of samples in natural environments or even in climatic chambers. The greater disadvantages are the difficulty of interpreting the spectra in an unknown system, and also the need to control the area under measurement, since all the values determined are affected by the extension of the surface. In the EIS technique, a small ac signal (typically a sine wave of amplitude) is applied over a wide range of frequency, and the current response is measured at each frequency, ω. The impedance is determined by

$$Z(\omega)=V(\omega)/I(\omega) \tag{16}$$

The low magnitude of the applied voltage signal means that EIS, like the linear polarization technique, does not polarize a system far from its steady state condition and it may be considered to be a nondestructive technique. For a linear system, the current response will be a sine wave of the same frequency as the excitation signal, but shifted in phase. Since the impedance is the ratio of two sine waves, it is a complex number that can be represented by amplitude and a phase shift or as the sum of real and imaginary components,

$$Z(\omega)=Z'(\omega)+jZ''(\omega) \tag{17}$$

The discontinuity generated by an electrode surface in an electrolyte results in separation of charge to create parallel planes of charge as is found in a capacitor. However, the electrode–electrolyte interface does not behave as a

perfect capacitor. If it did, the current would cease flowing when the capacitor became fully charged. The interface behaves instead like a leaky capacitor, or like a circuit composed of a capacitor and resistor in parallel. Fig.1C.3 shows a circuit that represents the behavior of many electrochemical interfaces. The resistor in parallel with the capacitor is labeled as R_P, the polarization resistance. For a simple electrochemical reaction under activation control, the polarization resistance can be considered to be a charge transfer resistance, and is sometimes labeled as R_{ct}. The capacitor is labeled in Fig.1C.3 as C_{dl}, the double layer capacitance, which is associated with the separation of charge at the electrode/electrolyte interface. Many corroding interfaces have a surface film (e.g. a surface oxide) and still exhibit behavior that is represented well by the circuit shown in Fig.1C.3. The capacitance in that case can be associated with the capacitance of the film. In the field of corrosion, impedance data are usually reported in one of two formats. Fig.1C.4 shows the impedance spectrum presented in the format of a Bode plot. Both the log of the impedance magnitude and the phase angle are plotted as a function of the log of the frequency of the excitation signal in this format. It is very close to that of a perfect RC circuit. Modern EIS analysis software allows fitting of the data to the behavior expected for a given equivalent circuit, such as the RC circuit shown in Fig.1C.3. Such fitting provides best values for all of the circuit components. The other common plot for impedance data in corrosion is the complex plane plot or Nyquist plot, in which the imaginary component is plotted as a function of the real component at each frequency. Low frequency data are on the right side of the plot and higher frequencies are on the left. A perfect RC circuit such as is given in Fig.1C.3 will form a semicircle in the complex plane, which intercepts the real axis twice. The high-frequency intercept is the ohmic resistance, and the low-frequency intercept is the sum of the ohmic and polarization resistances. Since this plot is on linear axes, the low ohmic resistance is difficult to resolve in Fig.1C.5. As mentioned, most data are analyzed nowadays by computer fitting. However, the double layer capacitance also can be determined for a system exhibiting behavior similar to a perfect RC circuit from the polarization

resistance and ∫max, the frequency for the point at which the imaginary component has a maximum value:

$$C_{dl}=\frac{1}{2\pi \int \max Rp} \tag{18}$$

An electrochemical interface must behave as a collection of perfect electrical components. In particular, as shown above, the capacitance is often non ideal. Nonideal capacitors can be represented by constant phase elements with impedance given by:

$$Z=A(j\omega)^{-\alpha} \tag{19}$$

where A is a constant and the exponent α is less than or equal to 1. When α = 1, this expression represents the impedance of a perfect capacitor. When α = 0, the impedance is a constant, independent of frequency, which is the behavior of a resistor. Electrochemical interfaces often exhibit behavior that can be modeled by a constant phase element as shown in Eq. (18), with α less than 1. EIS allows for identification of components in complex equivalent circuits, and such as is exhibited by electrodes coated by an organic layer.

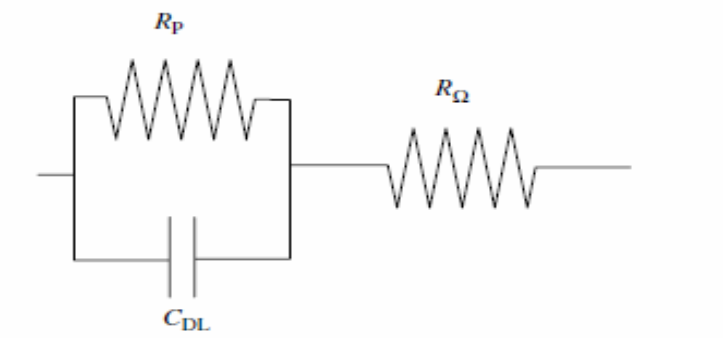

Fig.1C.3 Circuit describing the behaviour of a simple electrochemical interface.

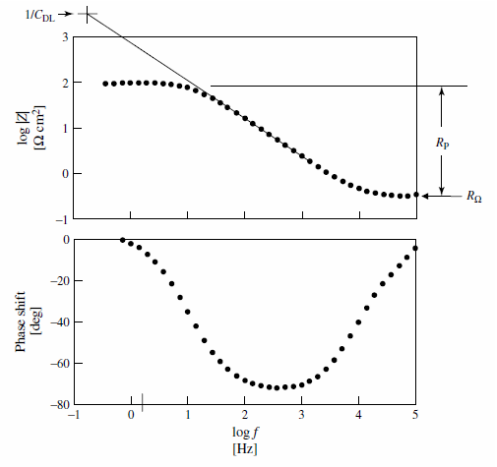

Fig.1C.4 Bode plots of EIS

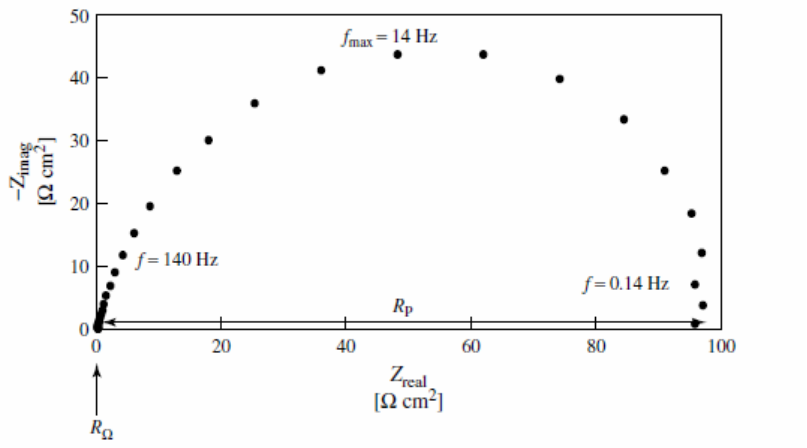

Fig .1C.5 Nyquist plot of EIS

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1C.10 COMPUTATIONAL METHODS

1C.10.1 Gaussian 03 package

Gaussian is the most widely used computational chemistry program. Actually it is a suite of programs with MM, ab initio, semi empirical and DFT, and all the usual high-level correlated ab initio methods. The common high-accuracy methods are available simply by key-words. There is a large number of basis sets and functionals. Electronically excited states can be calculated.

GAUSSIAN has appeared in improved versions every few years from 1970 (...G92, G94, G98, ..G03.). Gauss View is a graphics programs designed to help us prepare input for submission to Gaussian and to examine graphically the output that Gaussian produces. Gauss View provides advanced visualization facility, allows us to rapidly sketch in even very large molecules, then rotate, translate and zoom in on these molecules through simple mouse operations. It can also import standard molecule file formats such as PDB files. Gauss View makes it easy to set up many types of Gaussian calculations and finally examine the results of these calculations using a variety of graphical techniques. Gaussian provides Optimized molecular structures, Molecular orbitals, Electron density surfaces from any computed density, Electrostatic potential surfaces, Surfaces for magnetic properties, Atomic charges, Animation of the normal modes corresponding to vibrational frequencies, IR, Raman, NMR, and other spectra, Animation of geometry optimizations and potential energy surface scans. We use Ab initio and Density functional theory for calculations. Ab initio calculations based on solving the Schrödinger equation; the nature of the necessary approximations determines the level of the calculation. In the simplest approach, the HF method, the total molecular wavefunction is approximated as a Slater determinant composed of occupied spin orbitals. To use these in practical calculations the spatial orbitals are approximated as a linear combination (a weighted sum) of basis functions. These are usually identified with atomic orbitals, but can really be any mathematical functions that give a reasonable wavefunction. The main uses of the ab initio method are calculating molecular geometries, energies, vibrational frequencies, spectra (IR, UV, NMR), ionization potentials and electron affinities, and properties like dipole moments which are directly connected with electron distribution. These calculations find theoretical and practical applications. The visualization of calculated phenomena, such as molecular vibrations, charge distributions, and molecular orbitals, can be very important in interpreting the results of calculations.

Density functional theory is based on the two Hohenberg-Kohn theorems, which state that the ground-state properties of an atom or molecule are

determined by its electron density function, and that a trial electron density must give energy greater than or equal to the true energy. Actually, the latter theorem is true only if the exact functional is used; with the approximate functionals in use today, DFT is not variational - it can give an energy below the true energy. In the Kohn-Sham (KS) approach the energy of a system is formulated as a deviation from the energy of an idealized system with non interacting electrons. The energy of the idealized system can be calculated exactly since its wavefunction (in the Kohn-Sham approach wavefunctions and orbitals were introduced as a mathematical convenience to get at the electron density) can be represented exactly by a Slater determinant. From the energy equation, by minimizing the energy with respect to the Kohn-Sham orbitals the Kohn-Sham equations can be derived, analogously to the HF equations. The molecular orbitals of the KS equations are expanded with basis functions and matrix methods are used to find the energy, and to get a set of molecular orbitals, the KS orbitals, which are qualitatively similar to the orbitals of wavefunction theory. The most popular current DFT method is the LSDA gradient-corrected hybrid method which uses the B3LYP (Becke three-parameter Lee-Yang-Parr) functional. Gradient-corrected and, especially, hybrid functionals, give well to excellent geometries. The mutually related concepts of electronic chemical potential, electronegativity, hardness, softness, and the Fukui function are usually discussed within the context of DFT. They are readily calculated from ionization energy, electron affinity, and atom charges.

1C.10.2 Material Studio

Materials Studio is a flexible software environment that brings some of the world's most advanced materials simulation and modeling technology. Materials Studio draws on well-validated and widely applied simulation methods from the leader in high quality materials simulation software. Among the various tools used in this package we use Adsorption locator, compass and Forcite model. Adsorption - A tool that allows you to find low energy adsorption sites on both periodic and non periodic substrates. Compass - A powerful all-atom forcefield supporting simulations of condensed-phase

materials. Forcite - A collection of molecular mechanics tools that allow to investigate a wide range of systems, in which the key approximation is that, the potential energy surface on which the atomic nuclei move is represented by a classical forcefield. Adsorption Locator enables us to simulate a substrate loaded with an adsorbate or an adsorbate mixture of a fixed composition. Adsorption Locator is designed for the study of individual systems, allowing to find low energy adsorption sites on both periodic and non periodic substrates or to investigate the preferential adsorption of mixtures of adsorbate components. Adsorption Locator identifies possible adsorption configurations by carrying out Monte Carlo searches of the configurational space of the substrate-adsorbate system as the temperature is slowly decreased. Simulated annealing is a metaheuristic algorithm for locating a good approximation to the global minimum of a given function in a large search space. The concept is drawn from the process of annealing in metallurgy, where microcrystalline materials are heated and then slowly cooled in a controlled manner to increase crystallite size and reduce the number of defects in the crystal lattice. At high temperatures, the molten material is disordered because the kinetic energy forces atoms to explore higher energy states, such as substitution or defect sites. The system is cooled very slowly such that, at any given time, it is approximately in thermodynamic equilibrium. A slow rate of cooling increases the probability that the atoms will find configurations with lower energy, corresponding to more regular positions in the crystal lattice. As cooling proceeds, the system becomes more ordered and finally freezes into a ground state. If the system is not heated to a sufficiently high temperature or if it is cooled too quickly, lattice defects may become trapped and the system becomes quenched in metastable states, corresponding to local energy minima.

1C.11 SCANNING ELECTRON MICROSCOPY (SEM)

A scanning electron microscopy (SEM) is a type of electron microscopic technique that images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals that contain information about the

sample's surface topography, composition, and other properties such as electrical conductivity. There are many advantages to using the SEM instead of an optical microscopy. The SEM has a large depth of field, which allows a large amount of the sample to be in focus at one time. The SEM also produces images of high resolution, which means that closely spaced features can be examined at a high magnification. Preparation of the sample is relatively easy since most SEMs only require the sample to be conductive. The combination of higher magnification, larger depth of focus, greater resolution, and ease of sample observation makes the SEM one of the most widely used instruments in research areas today.

1C.12 ORGANIC COMPOUNDS AS INHIBITORS

The main advantage of an organic inhibitor is that they have no limitation on the range of concentration at which they lose inhibitive action and accelerate attack or become dangerous [129]. Various types of organic inhibitors have found use in numerous industries to prevent corrosion in boilers and water-cooling systems and in the primary and secondary extraction of oil. A different method for preventing corrosion in steam condensing systems is based on the use of film forming substances. They act by forming a hydrophobic film on the surface in contact with the condensate. This film acts as a barrier between the metal and the condensate [130].

The use of reaction products of fatty acids and polyamines [131] and of imidazolines or pyrimidines with side chains containing a large number of carbon atoms has also been suggested. These compounds generally contain a long hydrocarbon chain and at least one polar functional group. Maximum inhibition is obtained by using straight chain saturated derivatives of amines. Primary amines are found to be more effective than tertiary amines. The mechanism of their action has been assumed to be the formation of a compact monomolecular layer by adsorption of the compounds on the metallic surface through the polar functional group, with the hydrocarbon chain turned away from the metal surface. The protection against corrosion is ensured by the covering and the water-repellent characteristics of the film. Saturated long chain compounds give a maximum coverage density as compared to those

having branched chains because of their lateral orientations away from the surface. Tertiary amines give a smaller coverage and therefore a lower degree of inhibition because of their spatial arrangements.

The inhibition of the acid corrosion of stainless steels has been studied by Carassiti [132] using decylamine, quinoline, and phenylthiourea and dibenzyl sulphoxide [133]. The passivating effect of organic inhibitors on steel in acid solutions has also been studied. Machu and Gouda [134] have obtained interesting results using gelatin and di-o-tolyl thiourea for inhibiting the corrosion of Zn, Cd, and Pb. They have shown that these inhibitors are first chemically bonded to the metal surface before they are physically adsorbed to it. Chemical bonding has been found to be more effective than mere physical adsorption. The potential value of the adsorbing metal has an important bearing on the bonding of the inhibitor. The more electropositive the metal is, the poorer is its chemical bonding. The adsorption is exclusively physical for silver and platinum as reported by Machu and Gouda [135].

Some report [135] suggests that many organic inhibitors affect the anodic as much as or even more than the cathodic processes. The inhibition is brought about by the adsorption of the substance over the entire surface of the metal. This mechanism suggests the inclusion of many inhibitors like polyhydric substances which neither possesses any positively charged neither grouping nor the ones useful in inhibition, under this category [136].

Acid inhibitors are mainly organic molecules containing nitrogen and sulfur in polar groups. They are also called 'pickling inhibitors' or 'restrainers' and are used where acids are likely to attack metals as in acid pickling for removing scale. Hydrochloric and sulphuric acids being used, the inhibitors reduce the loss of metal, the loss of acid and the unpleasantness of the working conditions. They are adsorbed on the bare surface of the metal and shield it from acid attack. They neither prevent attack by oxidising agents nor reduce the rate of pickling where it occurs [137].

1C.13 PRESENT INVESTIGATION

Chapter 1V deals with materials and methods used for corrosion studies. Chapter V deals with corrosion inhibition studies of copper in 1M HNO_3 using MBATD by electrochemical,thermodynamic,quantum mechanical and surface morphological studies.Chapter VI present corrosion inhibition studies of mild steel in IM HCl using Ethylene thiourea by electrochemical, thermodynamic and fukuii indices studies.Chapter VII deals with corrosion inhibition studies of mild steel in IM HCl using MBATD by electrochemical, thermodynamic, quantum mechanical and surface morphological studies.In chapter VIII ,the corrosion inhibition studies of mild steel in IM HCl by using CBMTDT as inhibitor by gravimetric and electrochemical studies.

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