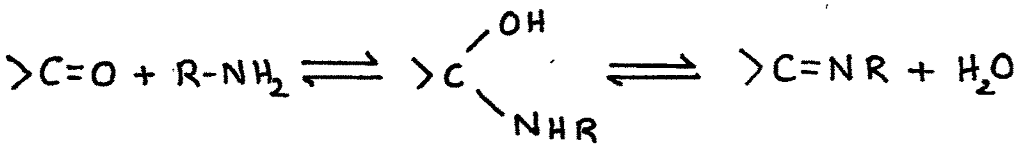
CHAPTER 1

INTRODUCTION

Schiffbases are the compounds characterized by the presence of the azomethine linkage=C=N-. They are formed by the condensation of primary amines with active carbonyl groups. Such compounds were first synthesized by Schiff and hence are known as Schiffbases[1]. They have general structure -RC:NR' where R and R' are alkyl, cycloalkyl, aryl or hetrocyclic radicals.

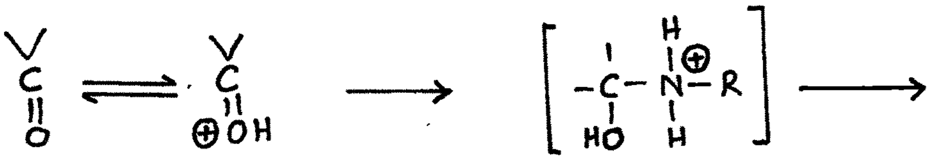
When compounds containing active carbonyl group react with amines, an addition product is first formed as an intermediate. This intermediate is unstable and it eliminates a molecule of water to form the Schiffbase[13].

The reaction can be represented as follows:



$$>C=O + R\text{-}NH_2 \rightleftharpoons >C\begin{smallmatrix} OH \\ NHR \end{smallmatrix} \rightleftharpoons >C=NR + H_2O$$

The addition involves a nucleophilic attack by the basic nitrogen compound on carbonyl carbon. At low pH the carbonyl oxygen gets protonated resulting in an increase of positive charge over the carbonyl carbon. This makes the carbonyl carbon more susceptible to nucleophilic attack. It can, therefore, be expected that as far as the carbonyl compound is concerned, addition of the primary amine should be favoured by high acidity. However, at high acidity the amines undergo protonation to form the ion, $H_3N^+\text{-}R$. The lone pair is used up in the binding of the proton and is no longer available for nucleophilic attack. Thus from the point of view of amines the addition should be favoured at low acidity.



$>C = N - R + H_2O + H^+$

$H_2N\text{-}R$	$H_3{}^{+}N\text{-}R$
Free base nucleophile	Salt not nucleophile

Hence these reactions are pH dependent. The optimum pH for the condensation reaction depends on the nature of the carbonyl compounds and the amine. The acidity of the solution should be such that a significant portion of the carbonyl compound should get protonated, but the protonation of the amine should not be high, so that an appreciable amount of the free nitrogen compound is available for condensation.

It is known that the reactivity of an organic molecule undergoes change on co-ordination with the metal ion. On co-ordination of a ligand (XY) through the atom 'X' to a metal ion, there is a drainage of electrons from 'X' leading to development of partial positive charge on 'X'. Stronger the co-ordination of the ligand atom, higher is the positive charge over 'X'.

Thus co-ordination of organic molecule with metal ion should result in an increase in the ease of attack by nucleophiles on the ligand and a decrease in the ease of attack by electrophiles.

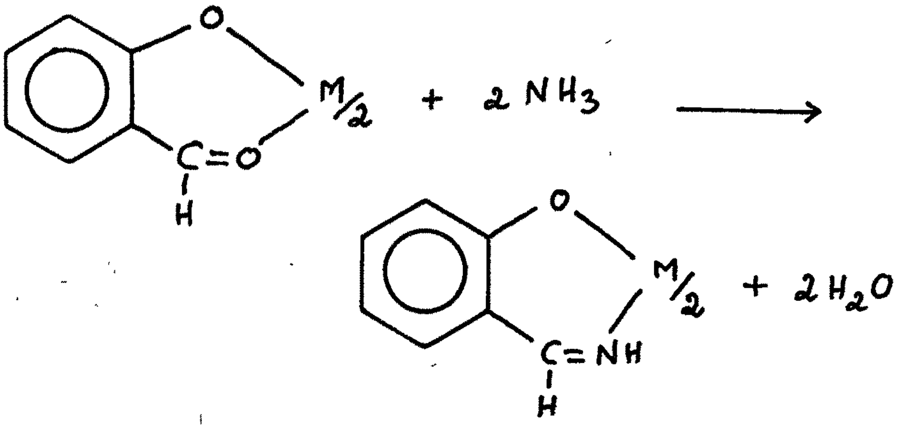
The increase in the reactivity of co-ordinated ligands is used to explain the role of metal ions in enzyme catalysed hydrolysis of amino acid esters, phosphates and peptides. In all these cases the nucleophilic attack of water molecule is favoured on co-ordination of the molecules with a metal ion. Transesterification is also a nucleophilic substitution of one alcohol by another and is facilitated if the ester is metal co-ordinated.

The role of metal ion in controlling the ligand activity in the complexes is also vividly illustrated in the formation of the Schiffbase complexes and the various reactions on co-ordinated Schiff bases. A carbonyl oxygen or N of azomethine has less tendency to donate electron pair to the metal ion and hence forms a weak complex. But if there is a co-ordinating group at the ortho position, a stable chelate is formed. The displacement of the ligand from the co-ordination sphere by the solvent molecule is very difficult.

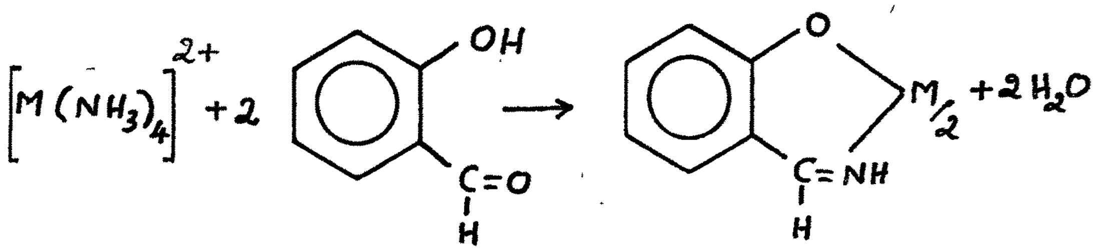
Mostly the Schiffbase complexes studied have bidentate ligand forming a chelate. Therein the ligand co-ordinates from the nitrogen of =C=N- group and another co-ordinating group, resulting in the formation of stable five or six membered ring. Pfeiffer[2], Layer[3], Dwyer and Mellor[4] studied the various aspects of the complexes of the Schiffbases derived from salicylaldehyde and amines. An excellent review on the chemistry of salicylaldimine, β-ketoimines and closely related ligands appeared in 1966[5]. Another article on the steriochemistry of the Schiffbase complexes, as well as some aspects of behaviour of such complexes in solution has also been published[6].

Besides the original method of preparing Schiffbase complexes by mixing the preformed Schiffbase with the metal salt, they can also be prepared by reactions in which the Schiffbase is formed in the presence of metal ion as follows:

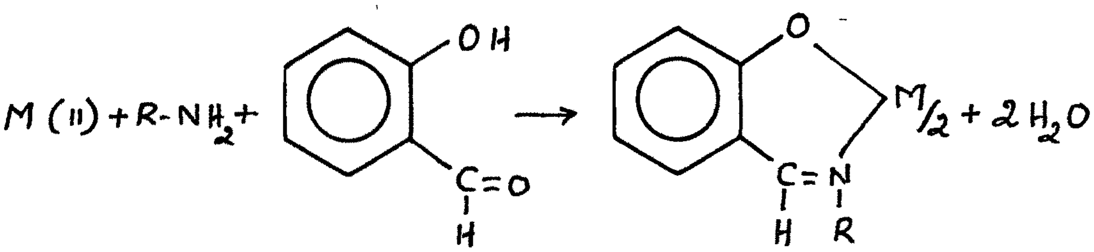
(a) The Schiffbase complexes can be prepared by the reaction of primary amines on the preformed metal complexes of aldehydes or ketones. This method was first suggested by Schiff[7] and developed by Pfeiffer[8,9]. The reaction can be shown as follows:



(b) Schiffbase complexes can also be prepared by the reaction of metal amine complexes with aldehydes or ketones. This method has been widely used for the synthesis of planar quadridentate complexes. A very interesting series of cationic complexes, containing macrocyclic ligands, have been prepared by Curtis and co-workers[10-12] by reacting metal amine complexes with aliphatic aldehydes and ketones. A general Schiffbase formation reaction can be shown as follows:

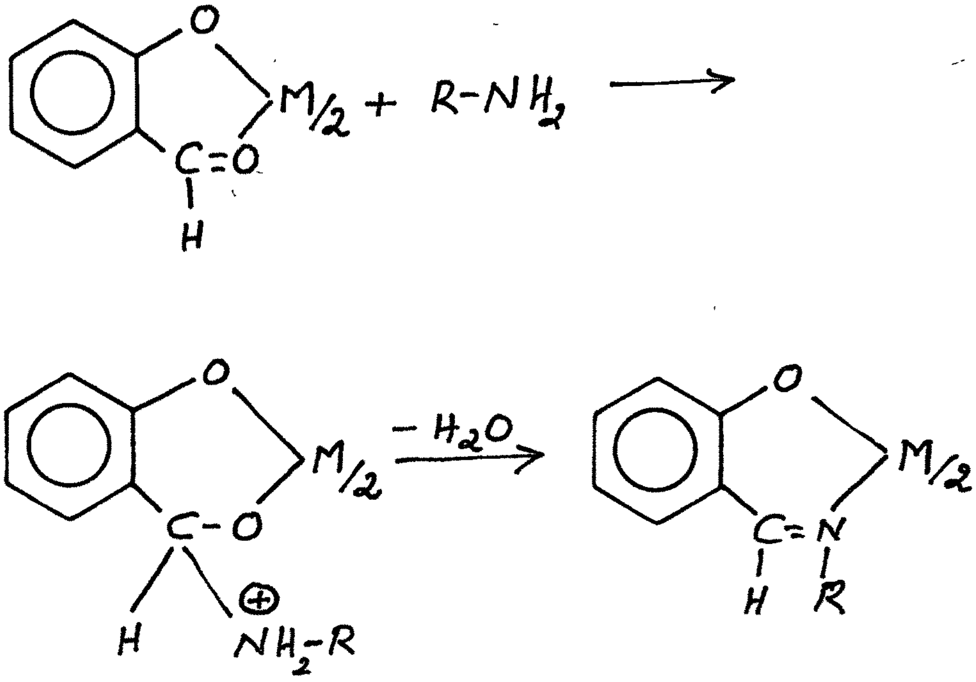


(c) The third method of preparation of the Schiffbase complex is by mixing the metal salt solution, a compound containing an active carbonyl group and the amine together and refulxing the mixture to get the complex. A typical reaction can be shown as follows:

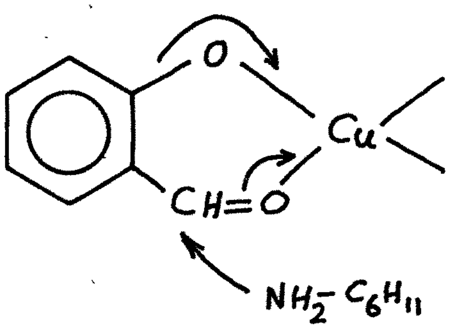


In the method (a) the co-ordination of the carbonyl group to the positive metal ion is supposed to result in polarization of the C=0 bond. The oxygen atom becomes more electronegative and pulls the electrons from the carbon atom. Thus the carbon atom becomes more susceptible to nucleophilic attack by the amine and Schiffbase formation is facilitated. It can be expected that Schiffbase formation is facilitated by strongly co-ordinating metal ions because there is a stronger metal ligand bond which causes an increase in the polarization of the carbonyl group.

The mechanistic course of the reaction is similar to the reactions of carbonyl compounds with amines near neutral pH. Schiffbase formation must be taking place in two distinct steps. A rapid nucleophilic attack of the carbonyl carbon by the amine first occurs yielding an intermediate carbinolamine complex, followed by the dehydration of the carbinolamine to yield the Schiffbase complex as shown below.



The study of the reaction of bis(salicylaldehydato)Cu(II) with cyclohexylamine has established the first order rate dependence of Schiffbase complex formation on both copper complex and amine[14]. The rate was much faster than between salicylaldehyde and the amine alone. This suggests strongly that the reaction involved a direct attack by the amine on the carbon atom of a co-ordinated carbonyl group rather than requiring complete dissociation of a salicylaldehyde anion from the copper as a first step as shown in the following figure.



Co-ordination of a metal ion also increases the tendency of the Schiffbase to undergo hydrolysis. However, if the Schiffbase is bidentate and forms a stable chelate, the hydrolysis effect is not predominent. For example, the reaction of salicyladehyde with glycine in the presence of copper ion leads to the formation of corresponding Schiffbase even at low pH, whereas the free ligand is easily hydrolysed[15]. This is due to the formation of stable chelate by the tridentate ligand. It appears that the overall stability is more than sufficient to counteract the susceptibility of the metal co-ordinated =C=N- group to undergo hydrolysis.

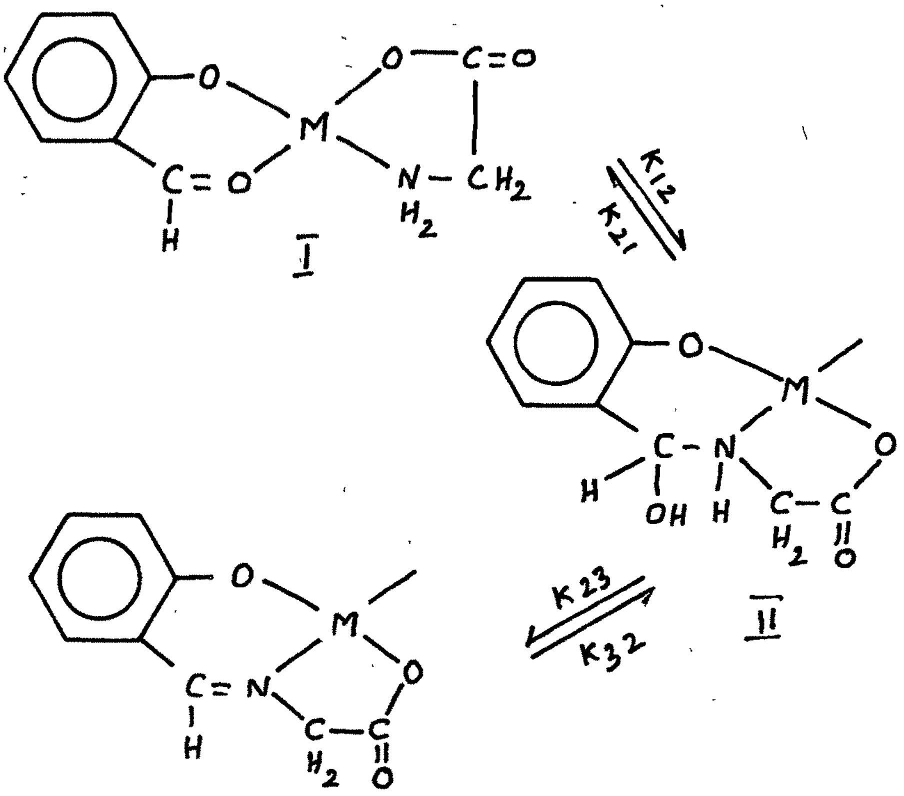
Further, if the ion has filled $d\pi$ orbitals suitable for back donation to π- acceptor orbitals on imine then this will help to reduce the effective positive charge on the imine carbon and it is less susceptible to hydrolysis. This explains the stability of transition metal Schiffbase complexes.

In the method (b) and (c) the presence of metal ion is supposed to promote the formation of metal Schiffbase complex due to template effect as termed by Busch[16]. "Metal template reactions may be defined as reactions involving ligands which require, or can be significantly enhanced by, a particular geometrical orientation imposed by co-ordination to a metal"[17]. Two types of template effects can regulate the formation of Schiffbase in situ. Firstly, the metal ion can bring the carbonyl group and the amine group in the close vicinity by the formation of mixed ligand complex. This facilitates the interaction of the carbonyl group with amines and more of the Schiffbase is formed. This is called sterically directed kinetic template effect. Secondly the metal ion may also be useful to remove the Schiffbase from an equilibrium by forming the complex and thus favours the forward reaction leading to the formation of more of the Schiffbase. This is termed thermodynamic template effect.

Kinetic and equilibrium studies on the formation of zinc(II) salicylaldehyde Schiffbases derived from ethylenediamines and 1,3-diaminopropane have been reported by Leussing and McQuate[18]. A quantitative study of the kinetic activity associated with metal ions in Schiffbase formation was first reported in 1966 and 1967[19,20]. These workers established that Pb(II), Cd(II), Mn(II), Mg(II) and Zn(II) were kinetically active, while Co(II), Ni(II) and Cu(II), with partially filled d orbitals, were inactive in bringing Schiffbase formation reactions. Hopgood and Leussing[21] established the function of metal ion in forming a mixed ligand complex with the amine donar and carbonyl compound in a preequilibrium step. This is followed by Schiffbase formation.

On the basis of their kinetic and equilibrium studies[21] on formation of N-salicylaldimine glycinato complexes, they have ruled out the possibility of amine attacking the co-ordinated salicylaldehyde. This is because both Cu(II) and Ni(II) form more stable complexes with salicylaldehyde than Zn(II) and therefore should catalyse the Schiffbase formation reaction if the above mechanism is operative. The other possibility of salicylaldehyde attacking co-ordinated glycine has also been found implausible by Leussing[21] because the co-ordinated amine does not have the lone pair to react with carbonyl carbon. The possibility of preequilibrium between salicylaldehyde and glycine to give the carbinolamine has also been found unlikely because Cu(II) and Ni(II) should have catalysed the reaction in that case.

Thus the Schiffbase formation proceeds through the ternary complex Zn(sal)(aminoacid) (I). This forms the Schiffbase by either of the two schemes.



There may be an equilibrium between the intermediate carbinolamine complex (II) with the initial complex (I) followed by rate determining dehydration to give the Schiffbase or a rate determining formation of the intermediate (II) followed by rapid dehydration.

The first mechanism is unlikely because that will require the existence of sufficient concentration of carbinolamine complex in solution for sometime and should be detectable spectrophotometrically. Further the dehydration of the carbinolamine complex should be catalysed by all the metal ions even Cu(II), Ni(II), Co(II) etc. Thus the metal ion is considered to function effectively reducing the condensation reaction from a second order to a first order process and thus catalyses the reaction.

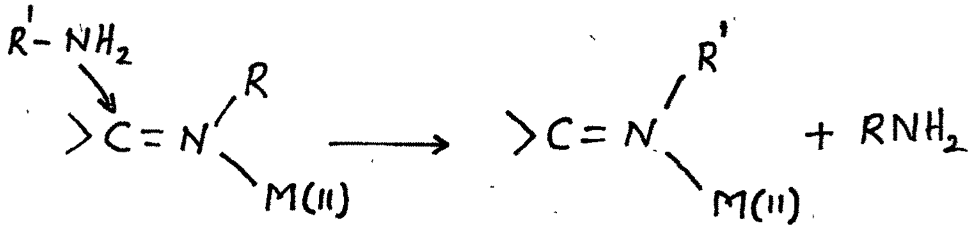
A metal ion which catalyses a bimolecular reaction by forming a ternary complex intermediate with the reactants was previously considered to act as a template.

However, the template mechanism cannot account for the inactivity of Cu(II), Ni(II) and Co(II) metal ions. The inactivity has now been explained by Leussing and co-workers[20,21] to be due to the rigid metal ligand geometries imposed by the ligand field splitting of the 3d orbitals in case of transition metal complexes. This does not allow the reaction of the amine and the aldehyde in the mixed ligand complex (I). In case of Zn(II), Pb(II), Cd(II), Mn(II) and Mg(II) ions CFSE being low, the metal ligand bonds are less rigid and hence the formation of the Schiffbase complex through a mixed complex is facilitated. Thus the requirement of the catalysing metal ion is that it should form a ternary complex with two reactants but should impose a minimum steric requirement on them. Leussing and co-workers[20,21] preferred to term the role of the metal ion as promnastic effect (match maker) rather than template effect.

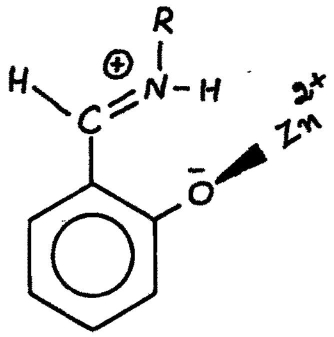
The inactivity of the metal ions Co(II), Ni(II) and Cu(II) also ruled out a mechanism in which polarization of the carbonyl group plays an important role. This implies that the increase in the Schiffbase complex formation in reaction (a) i.e. reaction of amines on the preformed complex of salicylaldehyde or ketones may also be due to the promnastic effect rather than due to the polarization of C=O bond. This remains to be confirmed by kinetic studies.

Amine exchange reactions

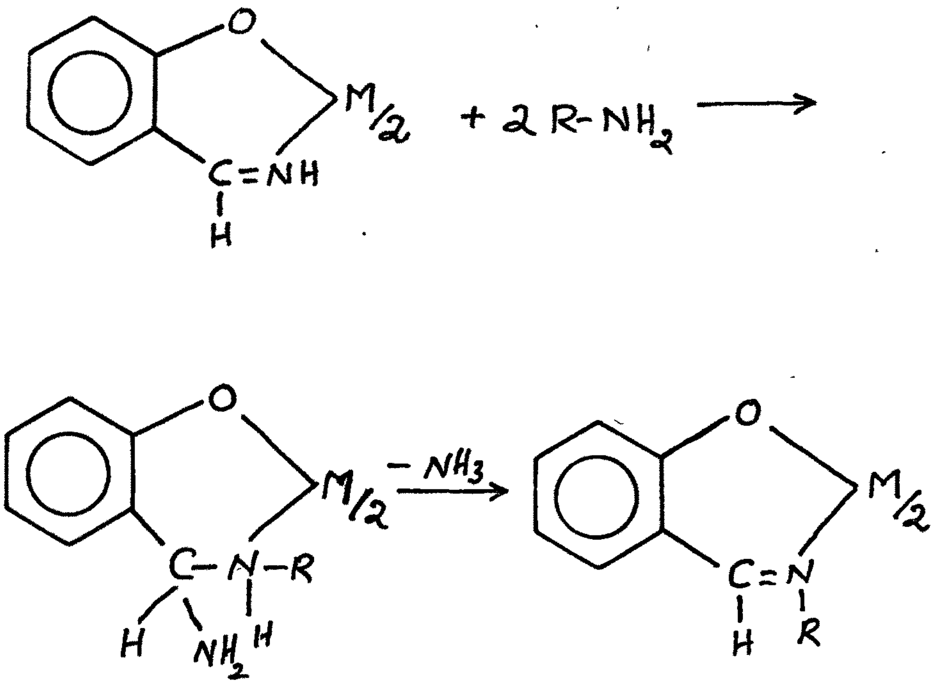
The replacement of the imine group in the Schiffbase complexes by another amine is called amine exchange or transamination reaction. This reaction is also comparable with Schiffbase formation from the co-ordinated aldehydes or ketones. This reaction is of interest because of its preparative significance[22-24] and because of its relation to the biological processes of transamination and deamination[25,26]. The general reaction can be illustrated as follows:



Molecular orbital calculations[27] show that the carbon atom of the $=C=\overset{+}{N}H$ group is more susceptible to nucleophilic attack than that of the $=C=\overset{+}{O}H$. The higher zwitterion constant of the protonated salicylidenes compared to H(sal), together with the above, must account to a large extent for the greater reactivities of the Schiffbases than the original aldehyde or ketone. Stabilities, rate of formation and rates in transimination in aqueous solution of some Zn(II) Schiffbase complexes derived from salicylaldehyde has been found out by Leach and Leussing[28]. These workers showed that the Zn(II) mediated paths is faster in transimination than in Schiffbase formation. The electronegativity of the imine carbon atom is increased due to withdrawal of electrons by the co-ordinating metal ions. Models show that protonation of the imine nitrogen atom should cause the Zn(II) ion to be forced out of plane of the aromatic ring[28].



In such a position the Zn(II) would be suitably located to interact with the nitrogen π electrons and would thereby tend to induce a still greater positive charge on the 7-carbon atom. Further with co-ordination sites still available to accept the entering amine, the metal ion can also serve to aid the reaction through the promnastic effect[28] i.e. rapidly forming in a preequilibrium step a mixed complex which contain both reactants. This results in the formation of the Schiffbase in two steps, a slow reaction leading to the formation of a gemdiamine complex analogous to carbinolamine complex. This undergoes a rapid deamination to form the complex of the Schiffbase of the entering amine. By reducing the overall reaction from second order to first order a more favourable entropy of activation would be obtained.



A less basic amine is expected to be replaced by a more basic amine. Amine exchange reaction is, however, concentration dependent. A more basic amine can be replaced by a less basic amine provided a large amount of it is added to the complex.

It is observed that amongst the Schiffbase complexes, those derived from salicylaldehyde have been most thoroughly studied[7,23]. Binary and ternary complexes of 2-hydroxyacetophenone have been reported from our laboratory[29,30]. Complexes of 2-hydroxybenzophenone and substituted 2-hydroxybenzophenones have been prepared earlier[31-34]. Not much work has, however, been done on the reactions of co-ordinated 2-hydroxybenzophenone and its methyl derivatives. In the present thesis reactions of ammonia and hydroxylamine have been attempted on bis 2-hydroxybenzophenone or its methyl derivative complexes of Cu(II) and Ni(II). Mixed ligand complexes of the type MLL', where M = Cu(II) or Ni(II); L = 2-hydroxybenzophenone or its methyl derivatives and L' = salicylaldehyde or 2-hydroxy-1-naphthaldehyde, have been prepared and the reactions with ammonia and hydroxylamine have been undertaken.

Amine exchange reactions and the reactions of hydroxyalkylamines have been carried out on the bis and mixed Schiffbase complexes.

Nitration and bromination reactions on co-ordinated Schiffbase complexes have also been attempted.

References

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