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Stability and Antimicrobial Studies of Mixed Ligand Complexes of Nickel(II) with Some Reactive Methylene Compounds and Carboxylic Acids

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The stability of simple and mixed complexes of Ni(II) with oxalic acid (Ox^{2-}), N-(2-ethoxy) phenyl malonamic acid (EPM^-) and N-(4-methyl) phenyl malonamic acid (MPM^-) have been studied polarographically. Lingane's method DeFord and Hume's method have been used to determine the composition and stability constants of simple complexes and Schaap and McMaster's method for the mixed systems in aqueous media. Antimicrobial studies of ligands and their simple and mixed metal complexes were carried out by screening them *in vitro* against bacterial species *Escherichia coli* (gram –ve) and *Staphylococcus aureus* (gram +ve).

INTRODUCTION

Much attention has been paid to the studies of mixed ligand complexes[1–3] of metals in recent years because of their wide applications in various fields of chemical activity and more particularly because of their presence in biological systems. In fact, many naturally occurring metal complexes are mixed ligand complexes[4]. Such complexes are found to be of favoured formation and stability. Polarography is being more widely used in complexometry of mixed ligand complexes which aims at probing the competitive behaviour of pairs of biologically active ligands for complexation with a metal[5]. It has also been established that biological activity of a ligand is altered many-folds on its coordination with metal ions[6]. Reactive methylene compounds have been found to be excellent starting materials for synthesis of various types of chemotherapeutic agents and analytical reagents both for organic and inorganic qualitative and quantitative analyses[7, 8]. An attempt has been made to furnish knowledge about the formation and stability of the complexes of Ni(II) and their antibacterial activity in aqueous media.

EXPERIMENTAL

(a) *Polarographic studies*: All the chemicals used were of analytical reagent grade and their stock solutions were prepared in conductivity water. Potassium oxalate and sodium salts of N-(2-ethoxy) phenyl malonamic acid and N-(4-

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methyl) phenyl malonamic acid were the source of Ox^{2-}, EPM^- and MPM^- respectively. KCl was used as a supporting electrolyte and also to maintain a constant ionic strength. The concentration of each depolariser was maintained constant at 4.0×10^{-3} M. Polarograms of the solutions were obtained by means of a manual polarograph (Toshniwal CL 02 A) in conjunction with Toshniwal polyflex gavanometer (PL 50). Purified nitrogen was used for removing the dissolved oxygen. All the measurements were made at 25 ± 0.1°C. A saturated calomel electrode (SCE) was used as a reference electrode. The d.m.e. had the following characteristics: $m = 2.40$ mg sec^{-1}, $t = 3.4$ sec, $m^{2/3}t^{1/6} = 2.2$ $mg^{2/3}$ $sec^{-1/2}$ (in 2.0 M KCl, open-circuit), $h_{corr} = 55.6$ cm.

(b) *Antimicrobial studies*: Ligands under study and their metal complexes were screened *in vitro* for their antibacterial activity by serial dilution method against two bacteria, *viz.*, *Escherichia coli* (gram negative) and *Staphylococcus aureus* (gram positive) [incubation period 24 h at 37°C]. The test solutions of all the compounds were prepared in aqueous medium.

RESULTS AND DISCUSSION

(a) *Stability constants*: The polarographic reduction of Ni(II) in Ox^{2-}, EPM^- and MPM^- separately were found to be irreversible and diffusion-controlled. The plots of log $i/i_d - i$ *vs.* $E_{d.e.}$ were linear with slopes more than 80 mV, which showed that the reductions were irreversible with a value of n = 2. Stability constants of simple complexes of Ni(II) with Ox^{2-}, EPM^- and MPM^- were determined prior to the study of mixed ligand systems. Identical conditions were maintained in both the simple and mixed systems.

Simple systems

A series of polarograms were obtained at constant ionic strength $\mu = 2.0$ (KCl) and pH = 4.0. The value of $E^r_{1/2}$ has been obtained by Gelling's method[10]. With Ox^{2-} and MPM^- the plot of $E^r_{1/2}$ *vs.* log $[Ox^{2-}]$ and log $[MPM^-]$ is a straight line which shows the formation of a single complex. However, the plot of $E^r_{1/2}$ *vs.* log $[EPM^-]$ is a smooth curve showing the formation of successive complexes. The composition and stability constant of the former systems have been determined by the Lingane's[11] method while that of the latter by DeFord and hume's[12] method. The composition and stability constants of various complex species are given in Table-1 (a).

TABLE-1 (a)
COMPOSITION AND STABILITY CONSTANTS OF COMPLEXES OF Ni(II) WITH Ox^{2-}, EPM^- AND MPM^- IONS

Systems	Complex species	Stability constants
Ni(II)-Ox^{2-}	$[Ni(Ox)_3]^{4-}$	log $\beta_3 = 7.51$
Ni(II)-MPM^-	$[Ni(MPM)_3]^-$	log $\beta_3 = 12.25$
Ni(II)-EPM^-	$[Ni(EPM)]^{4}-$	log $\beta_1 = 5.77$
	$[Ni(EPM)_2]$	log $\beta_2 = 9.36$
	$[Ni(EPM)_3]^-$	log $\beta_3 = 12.16$

Mixed systems

In both the systems concentration of oxalate was varied keeping the concentration of reactive methylene ligand constant. $E_{1/2}$ values were more negative than those obtained in the absence of Ox^{2-} thereby showing the formation of mixed complexes. Schaap and McMaster's[13] method has been used to determine the composition and stability constants of mixed systems which is shown in Table-1 (b).

TABLE-1 (b)
COMPOSITION AND STABILITY CONSTANTS OF COMPLEXES OF Ni(II) WITH Ox^-, EPM^-/CPM^- IONS

Systems	Complex species	Stability constants
$Ni\text{-}Ox^{2-}\text{-}EPM^-$	$[Ni(Ox)(EPM)]^-$ $[Ni(Ox)(EPM)_2]^{2-}$ $[Ni(Ox)_2(MPM)]^{3-}$	$\log \beta_{11} = 7.87$ $\log \beta_{12} = 11.39$ $\log \beta_{21} = 10.86$
$Ni\text{-}Ox^{2-}\text{-}MPM^-$	$[Ni(Ox)(MPM)_2]^{2-}$ $[Ni(Ox)_2(MPM)]^{3-}$	$\log \beta_{12} = 12.53$ $\log \beta_{21} = 11.47$

(b) *Antibacterial activity*: The observation shows that the ligands are practically inactive antimicrobially against the two bacterial species. On the other hand, their metal complexes in simple as well as mixed systems show considerable activity against the microorganisms. This leads to the conclusion that the introduction of the metal and its coordination with ligand induces biological activity, thus making the complexes antimicrobially active.

TABLE-2
MINIMUM INHIBITORY CONCENTRATION (MIC) VALUES OF ANTIBACTERIAL ACTIVITY OF LIGANDS AND Ni(II) COMPLEXES

S. No.	Compound	MIC value in μg/mL bacteria		MIC values in molar conc.	
		E. coli	*S. aureus*	*E. coli*	*S. aureus*
1.	Ox^{2-}	—	—	—	—
2.	MPM^-	—	—	—	—
3.	EPM^-	—	—	—	—
4.	$Ni\text{-}Ox^{2-}$	100	100	4.080	4.080
5.	$Ni\text{-}MPM^-$	25	25	0.514	0.514
6.	$Ni\text{-}EPM^-$	50	50	0.750	0.750
7.	$Ni\text{-}Ox^{2-}\text{-}MPM^-$	75	100	1.486	1.981
8.	$Ni\text{-}Ox^{2-}\text{-}EPM^-$	50	75	0.885	1.328

The ligands under study (*i.e.*, Ox^{2-}, EPM^- and MPM^-) were found to be inactive against the ~~tested~~ bacterial species, *viz.*, *E. coli* and *S. aureus* as shown in Table-2. Simple complexes of Ni(II) with MPM^-, EPM^- and Ox^{2-} exhibited profound biological activity against both the bacteria. Ni(II)-MPM^- complex was found to be most active followed by Ni(II)-EPM^- and Ni(II)-Ox^{2-} complexes. Mixed complexes of Ni(II) with Ox^{2-} and MPM^-/EPM^- ions showed comparatively lower biocidal activity than simple complexes. The Ni(II)-Ox^{2-}-EPM^- complex was found to be more active for both the bacteria than Ni(II)-Ox^{2-}-MPM^- complex. The results ae presented in Table-2.

Thus we arrive at the conclusion that though the ligands under study are inactive antimicrobially, their metal complexes in case of simple and mixed systems show definite biocidal activity. These results can be attributed to the following probable reasons:

1. More liposolubility of the metal complexes might have induced the biological activity in them.
2. Metal ion present in biological systems of the enzymes of bacterial cell might have been replaced by the invading metal ion of the more liposoluble metal complexes.
3. The mixed Ni(II) complexes being more heavy and bulky are slower to rupture and destroy the microbial cell membrane as compared to simple complexes even though they are more stable in aqueous media.

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