

ORIGINAL ARTICLE

POTENTIOMETRIC STUDY ON TERNARY COMPLEX INVOLVING DIVALENT TRANSITION METAL ION

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ABSTRACT

An investigation was made into the experimental conditions for the formation of poorly soluble complexes of the divalent nickel(II) combined with the selected amino acid Proline in the form of suspensions for parenteral administration. The number of Ni(II)-binding sites in the amino acid (n) as well as the amino acid affinity to Ni(II) (K_a), were determined. Proline was found to have the highest number of Ni(II)-binding sites. In this conditions described here in, Ni(II) – amino acid complexes of diverse stability (durability) were obtained. The analysis of the kinetics of the binding revealed that the most stable complexes were those formed by Ni(II) in combination with Proline ($K_a=405.78 \text{ M}^{-1}\cdot 12.17$). The stability of the Ni(II) – amino acid complexes obtained was conditioned by both the molecular weight of the amino acid and its isoelectric point.

.Keywords MDPT, IR, Microanalyser, Proline, Potentiometric technique .

1.INTRODUCTION

One of the well-known methods of sustaining the action of a parenterally administered in clinical practice is to form a poorly soluble complex of the drug substance combined with a Group 2 metal, in the form of a suspension. Examples of such a formulation of a medicine are the suspensions of insulin, corticotropin, and hirudin, in combination with divalent transition metal¹⁻³. These polypeptides combine with transition metal to form the solid Zn(II) – hormone complexes. The above method was used to develop such a formulation also with reference to other protein – peptide hormones⁴⁻⁸.The mechanism by which suspensions of hormones combined with metal in the form of poorly soluble complexes are obtained, is not, however, completely clear. For the above reason, the purpose of the present study was to determine the power to form complexes with Ni(II) for selected amino acids, and to establish the influence of the amino acid chemical structure upon the properties of the divalent metal ion – amino acid complexes obtained. The most frequently encountered amino acid components of protein – peptide hormones were used as the model substances in the study suspensions. In the case of metal – amino acid complexes, the process of their formation is

conditioned by the temperature applied, the concentration of the complex-forming factor, and the acidity of the solution. Various complex forms may dominate a wide range of pH⁹.

2.Materials and Methods

E. Merck sample of sodium hydroxide was dissolved in double distilled water in a Pyrex flask. The layer of carbon dioxide on the sodium hydroxide pellets was washed away previously. The solution was standardized potentiometrically against a standard oxalic acid solution. The stock solution of perchloric acid was prepared by diluting AR, BDH sample to required sample to required concentration and this was titrated potentiometrically against standard alkali solution. 1,4-Dioxan was purified by standard method¹⁰. An AR, BDH sample of sodium perchlorate was dissolved in double distilled water to make the stock solution of strength 1 mol dm^{-3} .

Preparation of 3-methyl-2,6-diphenyl piperidin-4-thiocarbohydrazone(MDPT)

An equimolar (0.05 mol dm^{-3}) mixture of 3-methyl-2,6-diphenylpiperidine-4-one¹¹ and thiocarbohydrazone¹² was treated with 1g of anhydrous sodium acetate in 150 ml of rectified spirit. This mixture was refluxed for 12 to 16 hrs. The insoluble product was filtered off and the volume of the

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filtrate was reduced by heating over a steam bath and poured into de-ionized water. The pale yellow colored product formed was filtered in a bucker funnel, dried and was recrystallized from benzene-petroleum ether (40-60°C) fraction. Yield was 40% (m.p.79°C). The purity of the product was checked by TLC method.

Calibration of pH meter in dioxan-water medium

A mixture of 50% (v/v) dioxan-water medium was used since the chelates formed are relatively insoluble in water. Therefore, it was necessary to calibrate the pH meter in dioxan-water medium. To accomplish this the following concentrations of perchloric acid in 50% (v/v) dioxan-water medium were prepared (total volume 50 ml) and the pH meter readings (B values) were measured in all cases.

Characterization of ligands

Microanalyser, UV and IR techniques characterized the ligand MDPT. IR spectra were recorded on a JASCO 700 spectrophotometer in KBr pellets and UV spectrum was recorded on a UVIDEC-340 spectrophotometer, using a quartz cell, 1 cm in dioxan medium. Microanalysis of the ligand MDPT was determined by standard method nitrogen¹³ and sulphur¹³; Ni:19.40 (19.83), S: 9.00 (9.06), for MDPT.

Result and Discussion

The acid dissociation constants of the ligands and the formation constants of their binary complexes were previously reported¹⁴. We have redetermined these constants under the prevailing experimental conditions as those utilized for determining the stability constants of the mixed-ligand complexes. The results obtained are in good agreement with the literature data²⁵.

UV spectral analysis

Condensation of the reactants is confirmed after comparing the ligands spectra with those of starting materials. The ketochromophores of 3-methyl-2,6-diphenylpiperidin-4-ones (MDPT) exhibit a band around 35087 and 43478 cm⁻¹ for MDPT in 1,4-dioxan medium. These bands are disappeared and instead of these, two new bands are observed in the ligands, 28571 and 39215 cm⁻¹ for MDPT.

The ligand bands are at totally different wave numbers and have different molar extinction coefficient compared to the starting materials in the same medium. All the absorption bands observed in the ligand spectra can be attributed on n → n* and π → π* transition¹⁵.

IR spectral studies

A comparison of IR spectra of the ligands with starting compounds is also done to confirm the condensation between the starting compounds. The ligands spectra show a broad band around 3410-3390 cm⁻¹¹⁶ which is attributed to the presence of secondary amine of piperidine ring nitrogen and thiocarbohydrazideazine group (-NH - NH₂). The band due to NH₂ wagging vibrations appear in the region 750-756 cm⁻¹¹⁷.

The disappearance of the bands pertains to the ketocarbonyl at 1705-1700 cm⁻¹ of 3-methyl-2,6-diphenylpiperidin-4-one, and new band appeared at 1625 cm⁻¹ of MDPT is attributed to the formation of azomethine (C=N)¹⁸⁻²⁰ group. The absence of any band in the region 2500-2600 cm⁻¹ confirms the presence of thioamide(N-C-N) group in the thione form exclusively^{12,21}. The other stretching vibrational frequencies are unaltered.

Nickel(II) complex formation equilibria with Proline

Proline was titrated in the presence and absence of Ni(II) ion. The titration curve of the Ni(II) complex is lowered from that of the free glycine curve. This indicates a complex formation associated with release of hydrogen ions. The formation constants were determined by fitting potentiometric data on the basis of possible composition models. The selected model with the best statistical fit was found to consist of Ni(A) and Ni(A)H complexes.

The association constant of MDPT, Proline, and its stability constant of binary and ternary Ni(II) determined in 50% (v/v) 1-4-dioxane water mixture at 35°C and data are given in Tables (1-3) and Figs. (1).

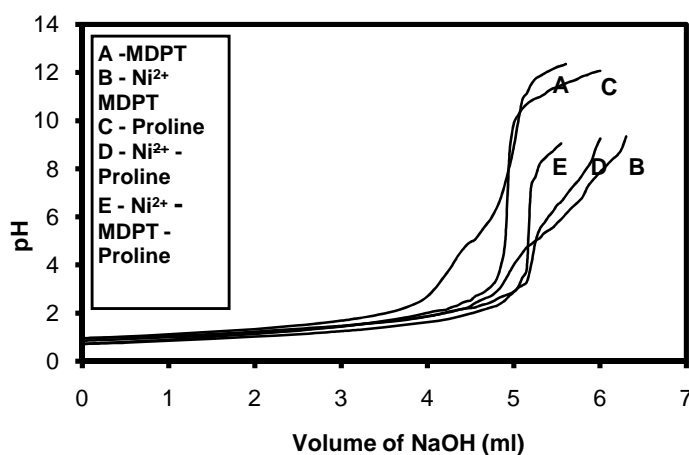


Fig. 2. pH metric titration curve for Ni²⁺-MDPT-Proline system

Table 1 pH titration data of Ni²⁺ with MDPT at 35 ± 0.1°C in dioxan-water (50 % v/v)

Ionic strength [I] = 0.1 mol dm⁻³ [MDPT] = 0.00517 mol dm⁻³
 [HClO₄] = 0.010442 mol dm⁻³ [Ni²⁺] = 0.0015 mol dm⁻³

Volume of NaOH ml	pH meter reading	
	MDPT	Ni ²⁺
0.00	0.95	0.96
0.50	1.03	1.00
1.0	1.12	1.07
1.50	1.23	1.13
2.00	1.34	1.23
2.50	1.49	1.35

3.00	1.69	1.47
3.25	1.82	1.54
3.50	1.99	1.63
3.75	2.24	1.72
4.00	2.70	1.87
4.25	3.80	2.04
4.35	4.37	2.13
4.45	4.82	2.21
4.50	4.96	2.30
4.55	5.06	2.42
4.65	5.54	2.59
4.75	6.02	2.75
4.85	6.81	3.10

Table 2 pH titration data of Pro and MDPT with Ni²⁺ at 35 ± 0.1°C in dioxan-water (50 % v/v)

Ionic strength [I] = 0.10 mol dm⁻³ [HClO₄]
 = 0.010442 mol dm⁻³
 [Pro] = 0.0043 mol dm⁻³ Initial volume = 30 ml

Volume of NaOH ml	pH meter Reading
	Ni:[MDPT]:[Pro]
0.00	0.72
0.50	0.77
1.00	0.85
1.50	0.93
2.00	1.02
2.50	1.12
3.00	1.25
3.25	1.32
3.50	1.41
3.75	1.52
4.00	1.62
4.25	1.76
4.50	1.98
4.75	2.25
4.80	2.30
4.85	2.40
4.90	2.53
4.95	2.72
5.00	2.87
5.05	3.07

Table 3 pH titration data of Pro and MDPT with Ni²⁺ at 35 ± 0.1°C in dioxan-water (50 % v/v)

Ionic strength [I] = 0.10 mol dm⁻³ [HClO₄]
 = 0.010442 mol dm⁻³
 [Pro] = 0.0043 mol dm⁻³ Initial volume = 30 ml

Volume of NaOH ml	pH meter Reading
	Ni:[MDPT]:[Pro]
0.00	0.72
0.50	0.77
1.00	0.85
1.50	0.93
2.00	1.02
2.50	1.12
3.00	1.25
3.25	1.32
3.50	1.41
3.75	1.52
4.00	1.62
4.25	1.76
4.50	1.98
4.75	2.25
4.80	2.30
4.85	2.40
4.90	2.53
4.95	2.72
5.00	2.87
5.05	3.07

The association constant of Proline, assigned as ligands (B) and the stability constants of the parent binary complex of Ni(II) at 35°C in I = 0.1 mol dm⁻³ (NaClO₄) used for the computation of mixed ligand complex system is reported. The data of Ni-MDPT binary system estimated under identically experimental conditions are reported. logβ values obtained for 1:1, 1:2 Ni(II)-MDPT complex compared favourably with values expected for glycine likes mode of binding of MDPT . The Ni-A/Proline system showed the presence of one mixed complex of NiAB.

It appears that complex formation between MDPT and Ni(II). In the NiAB species involves the formation of chelate ring the comparison of log K_{NiAB}^{NiA} (Table 4) and log K_{NiB}^{Ni} clearly indicate that all the ligands form five membered chelate ring in the NiAB complex species.

Thus, NiAB species would contain five membered chelate ring since more coordination positions are available for binding the first ligand to metal ion than for second ligand, negative values for ΔlogK_{NiAB} are expected.

Table 4Complex formation constants for the ternary complexes of MDPT-nickel with some normally bidentate L-amino acids at 35°C (NaClO₄) standard deviation are given in parentheses

Parameters	L-Gly
$\log K_{HB}$	9.61
$\log K_{H_2B}$	11.89
$\log K_{H_3B}$	-
$\log K_{NiB}$	9.50 (2)
$\log K_{NiB_2}$	11.62
$\log K_{NiAB}$	19.00 (9)
$\log K_{NiAB}$	1.6
$\log X_{NiAB}$	7.6

The existence of member of species in equilibrium of all pH values in ternary system where is certain pH regions. The concentration of one complex strongly predominant (Figs. 2)

Table 5Data for charge distribution of Ni- Proline system pH versus percentage of complex

pH	Percentage of complex
1.51	1.25
1.61	1.91
1.7	2.75
1.8	4.09
1.92	6.52
2.12	13.04
2.27	20
2.53	35.4
2.95	59.9
3.11	67.1
5.03	85.4
5.55	84.8
5.8	84.8
6.06	84.8
6.54	84.8
6.93	84.2
7.38	84.2
7.58	84.2
7.84	83.5
8.10	83.5
8.92	83.5

However, the maximum amount of total Ni(II) present in the Ni_{AB} complex is only about maximum 40%, the lesser percentage of complex formation attributed to steric faster associated with five membered chelating ring in the species. Distribution of various species as a function of pH of various ternary system in Tables (5&6) and Figs. (2).

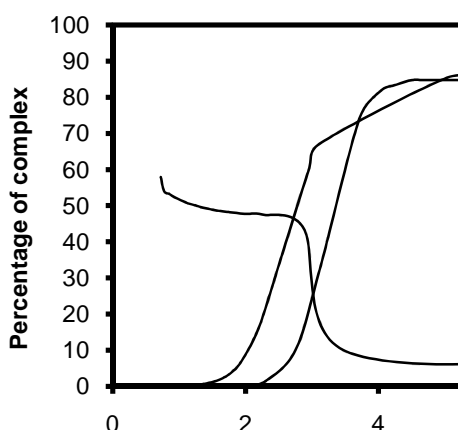


Fig. 2. Charge distribution curve for between pH Vs percentage

Distribution diagram obtained in terms of percentage found Ni(II) as a function of pH in all four binary and ternary systems in the study, show the same quality features of formation of ternary complex species other binary complex species.

Table 6Data for charge distribution of Ni-MDPT- Proline system pH versus percentage of complex

pH	Percentage of complex
0.72	57.9
0.77	54.0
0.85	53.2
0.93	52.3
1.02	51.5
1.12	50.7
1.25	50.0

1.32	49.6
1.41	49.2
1.52	48.8
1.62	48.48
1.76	48.2
1.98	47.7
2.25	47.5
2.87	43.8
3.47	10.0
6.75	8.6
7.23	26.2
7.65	9.8
8.18	9.2

3. CONCLUSION

This study offers an intensive investigation on stoichiometries and stabilities associated with binary and ternary complex systems studied in aqueous solutions. The complexation behavior of Ni^{2+} with proline and the biologically abundant aliphatic dicarboxylic acids shows the formation of ternary complexes in a stepwise manner in aqueous media. The complex formation equilibria were investigated to ascertain the composition and to determine the stability constants of the formed binary and ternary complexes. The concentration distribution diagrams of ligands and binary and ternary complex formed were evaluated. The potentiometric technique was used to obtain reliable formation constant values for different complexes formed and to validate the speciation models for both the ligands and complexes studied. The mode of chelation of the ternary complexes was ascertained by potentiometric titration technique. The ternary complexes formed may have interesting biological activity and more research work need to be conducted by biologists.

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