

Stability Constants of Complexes of Divalent and Rare Earth Metals with Substituted Salicylnals

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Summary. 5-Chloro-4-6-dimethyl-salicylaldehyde was synthesized from 4-chloro-3,5-dimethyl-phenol. A series of substituted salicylnals were obtained by condensation of 5-chloro-4,6-dimethyl-salicylaldehyde with several amines. The amines were chosen such as to vary the basicity of salicylnals by changing the substituents at one of the coordination sites. The stability constants of complexes of bivalent (Mg^{2+} , Ca^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Cd^{2+}) and trivalent (Y^{3+} , La^{3+} , Pr^{3+} , Nd^{3+} , Sm^{3+} , Eu^{3+} , Gd^{3+} , Tb^{3+} , Er^{3+} , Yb^{3+}) metal ions with these salicylnals and the pK values corresponding to the dissociation of the phenolic proton and the association of a proton to the azomethine nitrogen were determined potentiometrically using the *Calvin-Bjerrum* technique as adopted by *Irving* and *Rossotti* at 303 K and a constant ionic strength of 0.1 M in a 75:25 (v/v) dioxan-water mixture in an inert atmosphere. The influence of substituents on the proton affinity of the ligands was examined on the basis of inductive and mesomeric effects. It is also shown that some of the complexes possess antibacterial, antitubercular, antifungal, and anticoagulant activity.

Keywords. Metal chelates; *Schiff* bases; Divalent metals; Rare earth metals; 5-Chloro-4,6-dimethyl-salicylaldehyde; Antibacterial activity.

Introduction

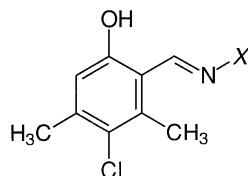
The elegance and variety of many coordination compounds and the intriguing range of concepts required to interpret their behaviour have attracted much interest with respect to the study of their synthesis and an understanding of their reactions. *Schiff* bases play a central role as chelating agents for a large number of metal ions, as they form a stable five- or six-membered ring after complexation with the metal ion and can also be used as analytical reagents. It has been observed that compounds with $\text{C}=\text{N}$ groups are of considerable biological importance, as they show antimicrobial activities. It is also accepted that the knowledge of the stability constants of such *Schiff* bases and their metal complexes may eventually help to throw some light on the inactivation of essential trace metals in biological systems.

Many investigators have reported the determination of the proton acid dissociation constants of some salicylaldehydes and the stability constants of their

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complexes with Cu(II) in 50% dioxan-water [1] and the mechanism of the antibacterial action of phenols and salicylaldehydes [2–4]. A survey of the literature shows that no research on the stability constants of metal chelates of the series of ligands reported herein as well as on their antibacterial, antitubercular, antifungal, and anticoagulant activity has been reported so far. The present study was therefore undertaken to add valuable information to that already existing in the literature.

Results and Discussion



In general, the configuration of all compounds under investigation may be represented by the above formula where X represents the substituents listed in Table 1. Figures 1 and 2 show acid, ligand, and metal titration curves. It can be seen that for the same volume of alkali added the ligand titration curves had a lower pH value than the acid titration curve. The displacement of a ligand titration curve along the volume axis with respect to the acid titration curve is an indication of proton dissociation. The proton-ligand stability constants were calculated using the method of *Irving and Rossotti* [12].

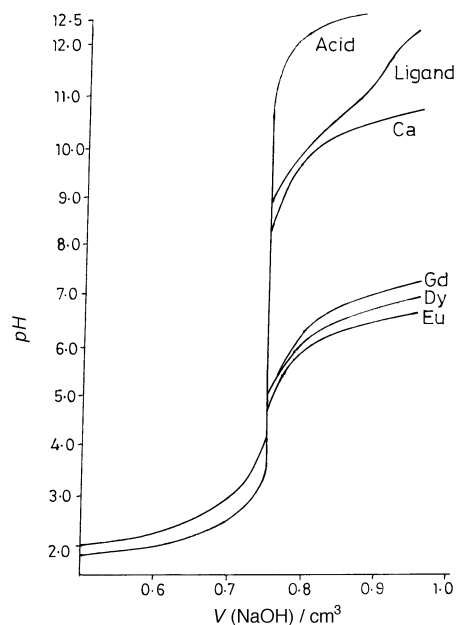


Fig. 1. Representative titration curves for acid, ligand, and metal titration for complexes of Ca^{2+} and some rare earth metal ions with N-(5-chloro 4,6-dimethyl-salicylidene)-4-bromo-5-methyl-aniline

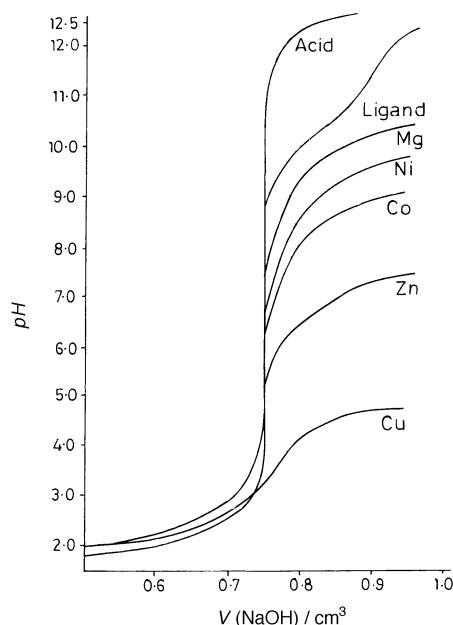


Fig. 2. Representative titration curves for acid, ligand, and metal titration for complexes of some transition metal ions with N-(5-chloro-4,6-dimethyl-salicylidene)-4-bromo-5-methyl-aniline

Due to the liberation of protons, the metal titration curve gives still lower pH values for the \bar{n} values which indicate the difference in the volume of alkali required to produce the identical pH in the metal and the ligand titrations. With this method it is not necessary to know the actual hydrogen ion concentration of the system.

In the present work, metal-ligand stability constants have been calculated using the following methods [13]: (i) half integral method (plot of \bar{n} vs. pL), (ii) graphical method (plot of $\log(n/1 - \bar{n})$ vs. pL and $\log(2 - \bar{n}/\bar{n} - 1)$ vs. pL), and (iii) least squares method.

In the half integral method (HI), pL values at $\bar{n} = 0.5$ and 1.5 were taken as $\log K_1$ and $\log K_2$, respectively, from the formation curves extending over the range of $0 < \bar{n} < 1.9$. These values correspond to 1:1 and 1:2 metal-ligand stability constants. The $\log K$ values were accurate to ± 0.02 log units, and a maximum standard deviation of $\Delta \bar{n} = \pm 0.229$ [13] was obtained for the complex of Eu with N-(5-chloro-4,6-dimethyl salicylidene)-4-bromo-5-methyl-aniline.

In addition, the possibility of hydrolysis of the ligands was tested spectrophotometrically. It was observed that λ_{\max} for most of the ligands remained unchanged at 300 nm for a period of 3 h, thus ruling out the possibility of hydrolysis. The metal ion solution used in the present study was very dilute, hence there was no possibility of formation of polynuclear complexes.

Formation of complexes in the solution was confirmed by the following observations:

- (1) The metal titration curves were displaced to the right-hand side of the ligand titration curves along the volume axis, indicating proton release upon complex

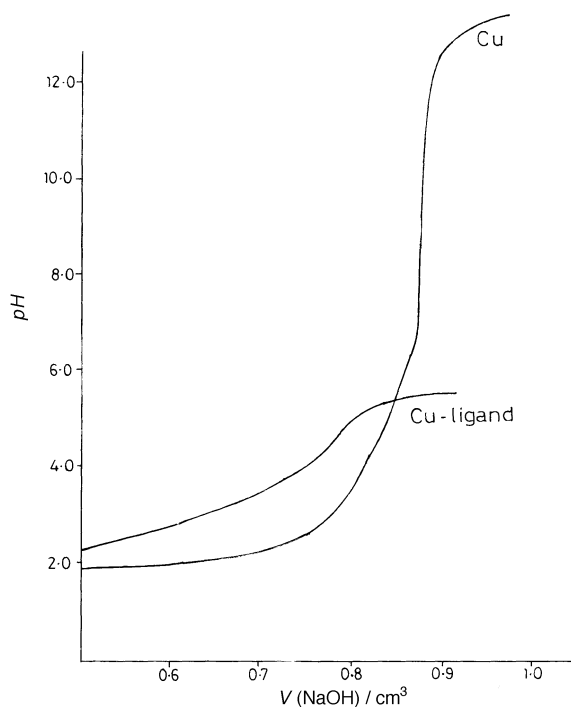


Fig. 3. Representative titration curves of pure metal and metal-ligand for copper ions

formation of the metal ion with the ligand. The large decrease in pH for the metal titration curves relative to ligand titration curves point to the formation of strong metal complexes [14].

- (2) In most cases, the colour of the solution after complex formation was observed to be different from the colour of the ligand at the same pH .
- (3) The metal curves depart from the ligand curves at pH values lower than the pH values of the hydrolysis of the corresponding metal ions.
- (4) Figures 3 and 4 show representative titration curves of pure metal in absence (pure metal titration) and presence of ligand (ligand titration) (Table 3). Note that the pure metal titration curve resembles the acid titration curve, thus ruling out the possibility of formation of aqua complexes of the corresponding metal. At the same time, a large shift was observed above $pH = 3$ in case of ligand titration relative to pure metal titration, again suggesting the formation of strong metal chelates [15].

The phenolic $-OH$ group is known to be weakly acidic, indicating a stronger bonding between the proton and the oxygen donor. This means that the proton-ligand stability constants of the ligands containing a phenolic $-OH$ group should be high. The pK_1^H values for all ligands correspond to the dissociation of this $-OH$ group. It would thus follow that the pK_2^H values represent the proton affinity of the basic groups where such are involved.

The pK_1^H values of the derivatives of 5-chloro-4,6-dimethyl-salicylaldehyde were compared with each other. The acidity order of these compounds is influenced by the inductive or mesomeric effect of the substituents. Substituents showing a

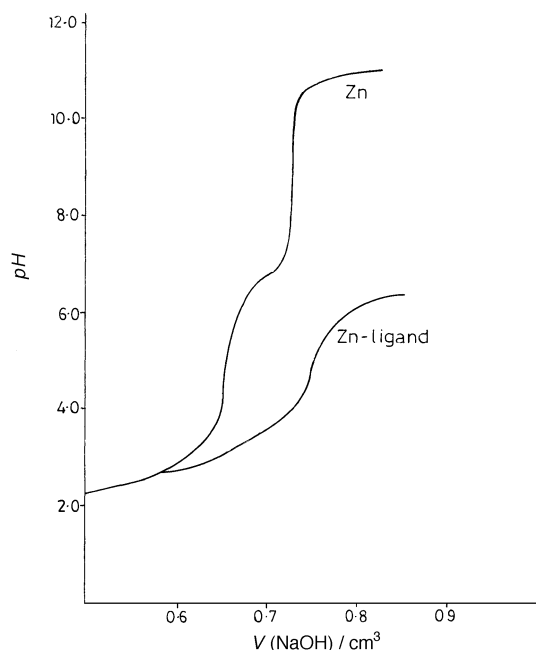


Fig. 4. Representative titration curves of pure metal and metal-ligand for zinc ions

positive inductive or mesomeric effect (*i.e.* an electron donating effect) decrease the acidity of the compounds, whereas substituents with negative inductive or mesomeric effects (*i.e.* electron withdrawing effect) increase the acidity of the compounds [16, 17]. It can be seen that N-(5-chloro-4,6-dimethyl salicylidene)-aniline has a pK_1^H value of 10.45 (Table 1). It was observed that when a bromo group was introduced at the *para* position of the aniline ring, the corresponding compound (N-(5-chloro-4,6-dimethyl salicylidene)-4-bromoaniline) has a pK_1^H value of 10.14. This was evident from the fact that the bromo group in the *para* position exerts a negative inductive effect, thus resulting in the lower pK_1^H value.

On the basis of inductive and hyper conjugative effects, N-(5-chloro-4,6-dimethyl salicylidene)-2,4-dimethyl-aniline would be expected to possess a higher pK_1^H value. However, the results obtained contradicted these expectations. This is probably due to the fact that the location of the additional $-\text{CH}_3$ group in the *ortho* position of the aniline ring is likely to disturb the planarity of the molecule, thereby decreasing its pK_1^H value. The results are also in accordance with *Hammett's para* substituent constant values for $-\text{H}$ and $-\text{CH}_3$ (0.00 and -0.17 , respectively).

N-(5-Chloro-4,6-dimethyl-salicylidene)-4-acetylamino-aniline has a pK_1^H value almost equal to that of N-(5-chloro-4,6-dimethyl-salicylidene)-aniline. This can be probably attributed to the fact that the electron withdrawing effect of the $-\text{COCH}_3$ group is almost exactly counterbalanced by the electron donating tendency of the $-\text{NH}$ nitrogen, thus leading to almost identical pK_1^H values. The results are also in accordance with *Hammett's para* substituent constant values [18]. In the present investigation it was observed that most of the ligands follow the *Irving-Williams* order of stability constants [19].

Table 1. pK_1^H values for various substituents in the salicynals

Substituent	Method ^a	pK_1^H	pK_2^H
Aniline	HI	10.45	3.15
	GRA	10.45	3.21
4-Bromo-aniline	HI	10.15	–
	GRA	10.14	–
4-Bromo-5-methyl-aniline	HI	10.30	2.45
	GRA	10.29	2.40
4-Methyl-aniline	HI	10.50	3.80
	GRA	10.54	3.95
2,4-Dimethyl-aniline	HI	10.40	3.80
	GRA	10.38	3.77
4-Acetyl-aniline	HI	10.04	–
	GRA	10.02	–
4-Acetylamino-aniline	HI	10.45	3.60
	GRA	10.44	3.62
4-Phenoxy-aniline	HI	10.55	3.40
	GRA	10.52	3.42
4-Carboxy-aniline	HI	10.11	–
	GRA	10.08	–
4-Phenylazo-aniline	HI	10.29	–
	GRA	10.29	–

^a HI: half integral; GRA: graphical

The $\log K_1$ values for rare earth metal ions were found to be higher than the $\log K_1$ values for transition metal ions except Cu^{2+} (Table 2). This can be attributed to the fact that rare earth metal ions have vacant orbitals for hybridization and hence readily form inner orbital complexes. The transition metal ions lack vacant orbitals, and the energy required to pair the unshared d-electrons does not allow the formation of inner orbital complexes. Copper is capable of forming square planer complexes involving strong dsp^2 bonds; thus, the copper complex was found to be most stable one.

The stability of the metal complexes decreases with increasing basicity of the metals. Thus, the weakly basic copper and the lanthanide ions form strong complexes, whereas strongly basic metals such as Ca^{2+} or Mg^{2+} form weaker complexes. The strength of bonding in these chelates depends on the ability of the metals to form homopolar bonds. The metals with the strongest homopolar bonds form the most stable chelates. A complete discussion of the trends in the formation constant data for rare earth metal complexes is severely limited by the fact that only few ligands have been studied with all rare earth ions so far.

In the present study, a correlation between the atomic number of metal and its tendency to form a chelate has been studied by plotting $\log K_1$ vs. the atomic number (Fig. 5). There was a monotonic rise to a maximum for copper, followed by a lower value for zinc [19]. This confirms that the stability decreases with increasing basicity of the metal.

Calvin and *Melchior* [20] have shown a linear correlation between the second ionization potential and the stability of the complexes. The $\log K_1$ values show an

Table 2. Metal-ligand stability constants of various complexes of derivatives of N-(5-chloro-4,6-dimethyl-salicylidene) at $I_c = 0.10 \text{ mol/dm}^3$ and 303 K

	Aniline	4-Bromo-aniline	4-Bromo-5-methyl-aniline	4-Methyl-aniline	2,4-Dimethyl-aniline	4-Acetyl-aniline	4-Acetyl-amino-aniline	4-Phenoxy-aniline	4-Carboxy-aniline	4-Phenylazo-aniline
Mg ²⁺	4.61	4.35	4.19	4.87	5.36	4.29	5.97	5.13	4.79	4.02
Ca ²⁺	4.48	3.65	3.02	4.16	4.88	–	4.40	4.75	4.21	3.25
Co ²⁺	5.34	5.32	5.47	5.62	5.63	5.53	6.88	6.20	5.57	5.24
Ni ²⁺	6.51	5.47	5.05	6.20	5.91	5.30	7.16	6.36	5.53	6.20
Cu ²⁺	9.16	8.43	10.81	9.57	9.41	8.80	10.01	8.86	9.16	8.24
							7.87 ^a	8.16 ^a		
Zn ²⁺	7.29	6.54	6.69	6.78	6.58	6.33	6.74	7.22	6.17	6.64
Cd ²⁺	5.79	5.00	5.72	5.99	5.71	5.48	6.22	5.81	5.84	5.86
Y ³⁺	7.42	7.30	7.28	7.32	6.94	6.79	6.98	7.47	7.45	7.09
								7.04 ^a		
La ³⁺	6.65	6.11	6.67	6.37	6.41	6.35	6.78	7.34	6.48	6.44
				5.66 ^a						
Pr ³⁺	7.12	6.38	6.92	7.22	6.98	6.58	6.86	6.67	6.71	6.58
Nd ³⁺	7.05	7.04	7.49	7.43	7.39	6.71	6.92	7.29	6.80	6.78
								6.54 ^a		
Sm ³⁺	7.45	6.97	7.36	7.55	7.23	7.06	7.90	7.46	7.10	6.97
Eu ³⁺	7.18	6.85	7.46	7.80	7.44	7.04	6.97	7.10	7.55	7.33
			6.68 ^a							
Gd ³⁺	7.00	7.08	7.18	6.87	7.08	6.59	6.69	7.39	7.11	7.10
Tb ³⁺	7.62	7.36	7.58	7.54	7.68	6.96	7.87	7.27	7.27	7.42
	7.11 ^a									
Dy ³⁺	7.20	7.11	7.29	7.11	7.96	7.03	7.36	7.28	7.35	7.34
Er ³⁺	7.34	7.25	7.25	7.39	7.32	7.17	7.79	7.81	7.26	7.37
										6.61 ^a
Yb ³⁺	7.76	7.48	7.65	7.10	7.56	7.41	7.97	7.56	7.08	7.49

^a log K_2 values

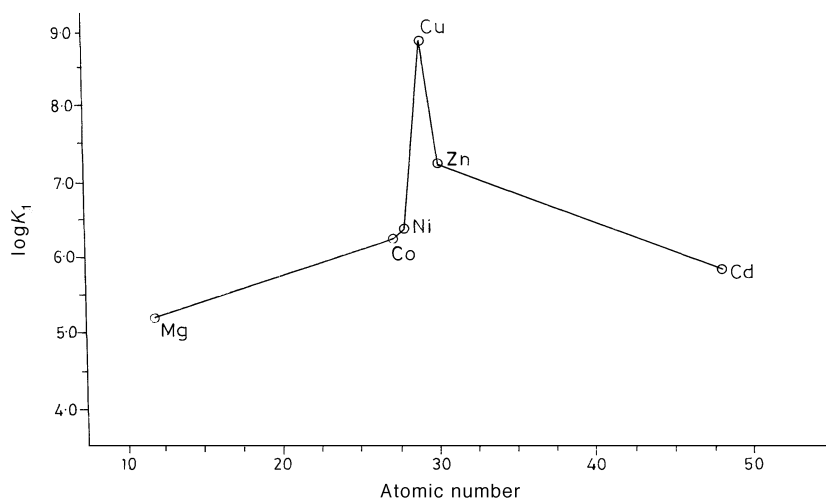


Fig. 5. $\log K_1$ vs. atomic number for some transition metals

order of $\text{Co} < \text{Ni} < \text{Cu} > \text{Zn}$ as expected from the respective second ionization potential values of these metals. This trend can be ascribed to the continuously increasing number of d-electrons until zinc. Then a discontinuity due to the absence of vacant d-orbitals occurs, thus explaining the low value of the stability constants in the case of Zn^{2+} , Cd^{2+} , and Mg^{2+} (Table 2). More electronegative (less basic) metals like Cu form stronger complexes compared to less electronegative metals like Mg. The first formation constants were found to increase somewhat informally with decreasing ionic radii, irrespective of the ligands, as would be expected from a predominantly electrostatic interaction.

The IR spectra of the ligands and their copper and lanthanum complexes revealed that the lowering of the C=N stretching frequency in free *Schiff* bases might be due to the coordination of the nitrogen donor atom to the metal ion and the involvement of the nitrogen atom of the azomethine group in the coordination process. Thus, the coordination *via* the nitrogen atom of the azomethine group to the central metal atom reduces the electron density on the nitrogen, resulting in a reduction of the C=N frequency.

The ESR spectra (303 K) afforded g_{\parallel} , g_{\perp} , and g_{av} as 2.1092, 2.1772, and 2.1545 in the case of the copper complex with aniline and 2.1092, 2.1191, and 2.1158 for copper complexes with *p*-aminoethyl benzoate.

The *Schiff* bases synthesized were tested for their antibacterial activity using the 'ditch-plate' techniques. The tests were carried out using gram-positive and gram-negative bacteria. The activity of the reagents indicates that the introduction of bromo, methyl, phenoxy, or azo groups increases the antibacterial activity; however, the improvement is not significant.

Antitubercular activity was tested using the *Löwenstein-Jenson* medium. The tests were carried out against *mycobacterium tubercule bacilli*. It was observed that compounds containing an additional nitrogen atom exerted less activity. Compounds containing carboethoxy, phenoxy, *etc.* groups at the *para*-position exhibited less activity, but the decrease was not significant.

Antifungal activity was studied by the test tube dilution method. The fungi used were *candida albicans* and *aspergillus niger*. The presence or absence of growth was noted after 7 days for *candida albicans* and after 15 days for *aspergillus niger*. It was found that the bromo and methyl substituted derivatives were inactive against the fungal strains utilized in the present investigation.

Anticoagulant activity was probed using the *Dale-Laidlaw* and *Sabraze* techniques [21, 22]. The tests were carried out using rabbit's whole blood. It was found that the compounds with bromo, acetyl, and acetylamino substituents at the *para*-position in the aniline ring imparted anticoagulant activity.

Experimental

Materials and solutions

All solutions were prepared from Analar grade reagents in CO₂-free doubly distilled water on a mass by volume basis. Metal perchlorates were prepared by dissolving metal carbonates or oxides (Indian Rare Earth Ltd.) in perchloric acid and concentrating the solution to give 0.008 M in 0.16 M perchloric acid of G.R. grade (E. Merck, India). Solutions were standardized by titration with EDTA [5]. Dioxan (1:4) of G.R. grade (E. Merck, India) was purified by the method described by Vogel [6].

The ligands were obtained by condensation of 5-chloro-4,6-dimethyl-salicylaldehyde [7,8] with a series of amines in equimolar proportions. Since all ligands and their metal chelates were found to be either insoluble or sparingly soluble in water, a reaction medium consisting of 75:25 (v/v) dioxan-water was used. Further, dioxane has the advantage of a very low dielectric constant (2.209 as compared to 78.30 for water at 25°C), thus preventing decomposition of the metal chelates. A fresh ligand solution (0.004 M) was prepared just before use. Sodium perchlorate solution (Analar grade, Thomas Baker, USA) of exactly 0.64 mol/dm³ was used to maintain constant ionic strength throughout each titration. A carbonate-free sodium hydroxide solution (1.075 M) was purified by the method described by Vogel [9].

pH Measurements

A precision research pH-meter (Elico LI-120, sensitivity: ±0.01) was used for pH determinations. The pH-meter was calibrated using potassium hydrogen phthalate (0.05 mol/dm³) in the acidic range and borax solution (0.01 mol/dm³) in the basic range before each titration.

The *Bjerrum-Calvin* pH titration technique [10,11] as modified by *Irving* and *Rossotti* [12] was used in the present study. All three types of titrations (Table 3) were carried out under the same conditions (0.10 mol/dm³ ionic strength, 303 K). Each titration was performed in triplicate to test the reproducibility of the results. After completion of each titration, the electrodes were washed with

Table 3. Details of titrations

Titrations	I_c mol/dm ³	HClO ₄ (0.16 mol/dm ³)	NaClO ₄ (0.64 mol/dm ³)	Ligand (0.004 mol/dm ³)	Metal (0.008 mol/dm ³)	Dioxan
Acid	0.10	5 cm ³	5 cm ³	–	–	30 cm ³
Ligand	0.10	5 cm ³	5 cm ³	W ^a	–	30 cm ³
Metal	0.10	–	5 cm ³	W ^a	5 cm ³	30 cm ³
Pure metal	0.10	–	5 cm ³	–	5 cm ³	30 cm ³

^a W is the amount of ligand weighed to give a concentration of 0.004 mol/dm³ of the final solution

water, 0.10 M HCl, and distilled water and allowed to remain in distilled water for about 3 to 4 h. The *pH* titration data were collected, and plots of *pH* values against the volume of alkali added were generated.

Electron spin resonance spectra

The ESR spectra of two representative complexes of copper were recorded on a Varian E-112 spectrometer (X-bands) at room temperature (303 K) in toluene (liquid phase). A minute polycrystalline sample of tetracyanoethylene (TCNE) free radical was used as *g*-marker. From these spectra, g_{\parallel} , g_{\perp} , and g_{av} were evaluated.

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