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Binary and ternary complexes of hydroxamic acids

Mohamed Taha*[1], Mohamed M.Khalil[1], Alaa T.Ahmed[3]

[1]Department of Chemistry, Faculty of Science, Cairo University, Beni-Suef Branch, Beni-Suef, (EGYPT)

[2]Geochemistry department, Faculty of Science, Al-Azhar University, Nasr City, Cairo, (EGYPT)

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ABSTRACT

Formation of binary and ternary complexes of some transition metal ions (M^{+2}=Cu^{+2}, Co^{+2}, and Ni^{+2}) with some selected aromatic hydroxamic acids (benzohydroxamic acid and salicylhydroxamic acid) and some biologically relevant aliphatic carboxylic acids (succinic acid, maleic acid, and tartaric acid) or dipicolinic acid was studied pH-metrically at 25°C and I=0.1mol dm^{-3} $NaNO_3$ in aqueous solution. The acid-base properties of ligands were investigated and discussed. The formation of the different 1:1, and 1:1:1 ternary complexes is inferred from the corresponding titration curves. The ternary complexes are formed in a stepwise mechanism. The stability constants of the binary and ternary systems were evaluated. The order of stability of the ternary complexes in terms of the nature of hydroxamic acid, aliphatic carboxylic acid, and dipicolinic acid is investigated and discussed. The stability of the ternary complexes is also discussed in relative to that of the binary complexes of secondary ligands.

INDRODUCTION

Hydroxamic acids, agroup of naturally occurring and synthetic weak organic acids of general formula RC(=O)N(R/)OH, are widespread in tissues of plants, in metabolites of bacteria and fungi, including complex compounds. They have been found as constituents of therapeutics, mostly related with the microbial transport of iron and the iron-overload chelating therapy[1]. Recently, hydroxamic acids have also been extensively studied as metal binding complexing agents in the field of zinc and nickel metalloenzyme inhibition, namely as inhibitors of matrix metalloproteinase(MMP)[2,3] and urease[4,5], respectively. Most of them have even advanced into human clinical trials for the treatment of diseases such as cancer and arthritis. However, patients treated with hydroxamic acid drugs such as siderphore desferrioxamine B(DF) trihydroxamic acid, frequently experienced problems during clinical treatment. These problems include agranurocytosis, joint pains, lupus-like syndromes as well as gastric intolerance[6]. More recently, a new oral iron chelator, salicylhydroxamic acid (Sham) is developed and found to have a promising advantage, since no toxicity has, as yet, been recorded[7]. The iron chelating property is due to presence of the hydroxamic acid moiety (-CO-NOH), which it shares with desferrioxamine B and another lower molecular weight iron chelator, acetohydroxamic acid (Aha), which may also have potential as iron chelator[8]. A detailed knowledge of the complexation behavior of hydroxamic acids with metal ions, often existing in biological fluids, has confirmed the importance of these analytical reagents in medicine.

The present work concerns a study of the solution equilibria involved in the formation of binary and ternary complexes of divalent metal ions containing some selected aromatic hydroxamic acids (benzohydroxamic acid (Bha), and salicylhydroxamic acid (Sham)) and other biologically relevant ligands (succinic acid, maleic acid, tartaric acid, and dipicolinic acid), to investigate the complexation behavior of these systems and to determine the stability constants of the complexes formed

in solution, using the pH-metric titrations, as these systems mimic many biological reactions. The present investigation is an extension of our earlier work on solution studies on the Hydroxamic acids[9,10,13].

EXPERIMENTAL

Materials and solutions

Benzohydroxamic acid (Bha) was obtained from Sigma products. Salicylhydroxamic acid (Sham) was purchased in pure form from Nasr Pharmaceutical Chemicals Co., Egypt. Dipicolinic acid was provided by Fluka. The reagent was repeatedly recrystallized from water, dried at 115°C, and checked by its melting point (250°C). The metal salts were provided also by BDH as nitrates or chlorides. All solutions were prepared in bidistilled water. A stock solution of tricine was prepared by dissolving an accurate amount by mass in the appropriate volume of bidistilled water. The metal ion solutions were standardized by EDTA using suitable indicators[11]. Carbonate-free sodium hydroxide solution was prepared by dissolving the Analar pellets in bidistilled water, and the solution was standardized potentiometrically with potassium hydrogen phthalate (Merck AG). Aliphatic acid, nitric acid, sodium hydroxide and sodium nitrate were from Merck p.a.

Apparatus and procedure

The pH titrations were performed using a Metrohm 702 titroprocessor equipped with a 665 dosimat (Switzerland). The titroprocessor and electrode were calibrated with standard buffer solutions; based on the scale of the U. S. National Bureau of Standards[12]. The pH-metric titrations were carried out at the desired temperature in a purified nitrogen atmosphere.

The following solutions were prepared (total volume 50cm^3) and titrated potentiometrically against standard carbonate-free NaOH (0.10mol dm^{-3}) solution:

a. HNO_3 (0.003mol dm^{-3}) + $NaNO_3$(0.10mol dm^{-3})
b. Solution a+(0.001mol dm^{-3}) hydroxamic acids
c. Solution b+(0.001mol dm^{-3}) metal ion
d. Solution a+(0.001mol dm^{-3}) aliphatic carboxylic acids or dipicolinic acid
e. Solution d+(0.001mol dm^{-3}) metal ion
f. Solution a+(0.001mol dm^{-3}) metal ion+(0.001mol dm^{-3}) hydroxamic acids+(0.001mol dm^{-3}) aliphatic carboxylic acids or dipicolinic acid

Each of the above solutions was thermostated at the required temperature with an accuracy of ± 0.1^{0}C, where the solutions were left to stand for about 15 min before titration. Magnetic stirrer was used during all titrations. Multiple titrations were carried out for each system. All calculations were performed using a computer program based on unweighted linear least-squares fits.

RESULTS AND DISCUSSION

Figures 1 and 2 display representative set of experimental titration curves obtained according to the sequence mentioned in the experimental section, for Cu^{2+}- benzohydroxamic acid-succinic acid and Cu^{2+}- dipicolnic acid-salicylhydroxamic acid systems, respectively.

The dissociation constants of hydroxamic acids investigated (benzohydroxamic acid and salicylhydro

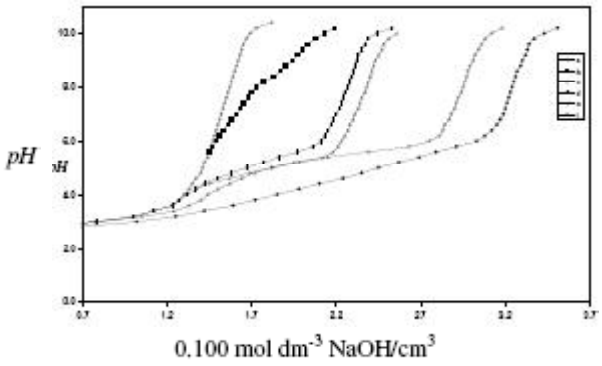

Figure 1 : Potentiometric titration curves for the Cu^{2+} – benzohydroxamic acid - succinic acid system at 25^{o}C and I=0.1mol dm^{-3} $NaNO_3$

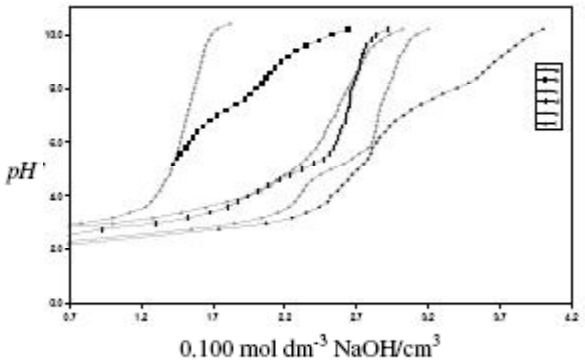

Figure 2: Potentiometric titration curves for the Cu^{II} - dipicolinic acid-salicyhydroxamic acid system at 25^{o}C and I=0.1mol dm^{-3} $NaNO_3$

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TABLE 1 : Dissociation constants of the ligands studied at (25 ± 0.1)°C and I=0.10mol dm^{-3} $NaNO_3$

Ligand	pK_1	pK_2
Bha	8.63 ± 0.03	--
Sham	7.40 ± 0.02	9.75 ± 0.07
Succinic acid	4.20 ± 0.04	5.65 ± 0.06
Maleic acid	1.80*	6.22 ± 0.05
Tartaric acid	3.00 ± 0.03	4.35 ± 0.03
Dipicolinic acid	2.32 ± 0.02	4.53 ± 0.04

*from ref[16]

xamic acid) have been determined from titration curves (a) and (b).

Benzohydroxamic acid (Bha) can release one proton in the measurable pH-range. The pK_a value for benzohydroxamic acid =8.63±0.03.

Salicylhydroxamic acid (Sham) contains two hydroxyl groups, so that the potentiometric titration curve (b) shows two buffer regions (see figure 2).

The first one extends up to the neutralization of the hydroxamic proton, and the second region is most likely associated with the neutralization of the phenolic hydroxyl group of sham. The stepwise protonation constants amount to $pK_{a1=}$7.40 ±0.02 for the hydroxamic hydroxyl group and $pK_{a2=}$9.75 ± 0.07 for the phenolic group. The greater acidity of the hydroxamic acid OH group in sham relative to that of Bha is due to stabilization of the conjugate base by intermolecular hydrogen bonding with the phenolic OH group. The results obtained are in good agreement with literature values[13,14,15].

The acidity constants of aliphatic carboxylic acids and dipicolonic acid (DPA) have been determined from titration curves (a) and (d) under the same experimental conditions.

Potentiometric pH titrations of Cu^{2+}, Co^{+2} and Ni^{+2} were performed at both 1:1 metal/ligand molar ratio. Analysis of the complexed ligands curves (c) and (e) as shown in figures 1 and 2, indicates that the addition of metal ion to the free ligand solutions shifts the buffer region of the ligand to lower pH values. This show that complex formation reactions proceed by releasing of protons from such ligands.

Generally, it is observed that the binary metal complexes of hydroxamic acids begin to form in the pH range 2.8-4.8 with respect to the titration curves of the binary metal-aliphatic carboxylic acid complexes; one may deduce that these complexes start to form in the pH range 3.2 -5.2. The complexes are quite stable up to high pH values. In all cases, no calculations have been performed beyond the precipitation point, hence, the hydroxyl species likely to be formed after this point could not be studied.

With respect to the titration curves of the different metal-dipicolonic acid (DPA) investigated, it is observed that the metal ions Cu^{II}, Co^{II} and Ni^{II} show high tendency to form binary complexes with DPA where complete complex formation takes place at very low pH values. Accordingly, determination of the formation con-

TABLE 2 : Stability constants for Cu^{2+} binary and ternary complexes at (25 ± 0.1)°C and I=0.1mol dm^{-3} $NaNO_3$

Ligands	$\log K_1$	$\log K^{MA}_{MAL}$		$\log \beta^{M}_{MAL}$		$\Delta \log K$		R.S. (%)	
		Bha	Sham	Bha	Sham	Bha	Sham	Bha	Sham
Bha	7.63 ± 0.04								
Sham	13.06 ± 0.06								
Succinic acid	3.20 ± 0.03	6.06 ± 0.02	6.65 ± 0.02	19.12	19.71	2.86	3.45	89.37	107.81
Maleic acid	4.07 ± 0.05	5.97 ± 0.02	6.38 ± 0.05	19.03	19.44	1.90	2.31	46.68	56.76
Tartaric acid	5.16 ± 0.02	5.52 ± 0.04	6.22 ± 0.02	18.58	19.28	0.36	1.06	6.98	20.54
Dipicolinic acid	9.14*	4.40 ± 0.02	5.68 ± 0.06	13.54	14.82	-3.23	-7.38	-42.33	-56.51

*From ref[17]

TABLE 3 : Stability constants for Co^{2+} binary and ternary complexes at (25 ± 0.1)°C and I=0.1mol dm^{-3} $NaNO_3$

Ligands	$\log K_1$	$\log K^{MA}_{MAL}$		$\log \beta^{M}_{MAL}$		$\Delta \log K$		R.S. (%)	
		Bha	Sham	Bha	Sham	Bha	Sham	Bha	Sham
Bha	4.74 ± 0.04								
Sham	6.59 ± 0.03								
Succinic acid	2.96 ± 0.04	5.49±0.06	6.12 ± 0.04	10.23	12.97	2.53	3.16	85.47	106.76
Maleic acid	3.02 ± 0.05	4.88±0.04	5.10 ± 0.05	9.62	11.69	1.86	2.08	61.59	68.87
Tartaric acid	3.17 ± 0.02	3.31±0.03	3.93 ± 0.02	8.05	11.56	0.14	0.76	4.42	23.97
Dipicolinic acid	6.65*	3.72±0.04	3.84 ± 0.03	10.37	11.09	-2.87	-2.75	-60.55	-41.73

*From ref[17]

TABLE 4 : Stability constants for Ni^{2+} binary and ternary complexes at (25 ± 0.1)°C and I=0.1mol dm^{-3} $NaNO_3$

Ligands	$\log K_1$	$\log K^{MA}_{MAL}$		$\log \beta^{M}_{MAL}$		$\Delta \log K$		R.S. (%)	
		Bha	Sham	Bha	Sham	Bha	Sham	Bha	Sham
Bha	5.05 ± 0.07								
Sham	6.02 ± 0.03								
Succinic acid	3.12 ± 0.04	5.88 ± 0.06	6.38 ± 0.04	11.9	12.40	2.76	3.26	88.46	104.49
Maleic acid	3.70 ± 0.05	5.59 ± 0.04	5.94 ± 0.05	10.64	11.96	1.89	2.24	51.08	60.54
Tartaric acid	4.68 ± 0.02	4.83 ± 0.03	5.46 ± 0.02	9.88	11.48	0.15	0.78	3.21	16.67
Dipicolinic acid	6.95*	4.21 ± 0.04	5.11 ± 0.03	11.16	12.06	-1.81	-0.91	-35.84	-15.12

*From ref[17]

stant values of such complexes could not be possible. The values of stability constants are taken from the work of Anderegg[17] using a copper amalgam electrode (P^{Cu}-method) as shown in TABLES 2-4.

The stability constants of 1:1 binary complexes of the ligands studied, except those containing DPA, have been determined at 25°C and I=0.10mol dm^{-3} $NaNO_3$. The formation of the mixed-ligand complex is ascertained by comparison of the mixed ligand titration curve with the additive curve, obtained from the linear addition of the secondary ligand titration data to that of the 1:1 metal-primary ligand titration curve. Therefore, it is assumed that, the hydroxamic acid (A) interacts first with the metal ion forming a 1:1 MA binary complex then followed by ligation of aliphatic carboxylic acid (L); i.e. , the ternary complex formation could be considered in stepwise equilibria (Eqs 1 and 2):

$$M + A \rightleftharpoons MA \quad (1)$$

$$MA + L \rightleftharpoons MAL \quad (2)$$

$$K^{MA}_{MAL} = \frac{[MAL]}{[MA][L]} \quad (3)$$

However, in the case of ternary systems involving M^{2+}, dipicolinic acid (DPA) and hydroxamic acids (Bha and Sham), it is observed from the titration curves the dipicolinic acid (DPA) acts as a primary ligand (A) whereas hydroxamic acids act as secondary ligand (L). The overall stability constant β^{M}_{MAL} may be represented by Eq. (4)

$$M + A + L \rightleftharpoons MAL \quad (4)$$

$$\beta^{M}_{MAL} = \frac{[MAL]}{[M][A][L]} = K^{MA}_{MAL} \times K^{M}_{MA}$$

One approach, commonly used to quantify the stability of a ternary complex, is by comparison with the stability of the binary complex, and can be expressed in terms of $\Delta \log K$, which represents the difference in stabilities for the addition of ligand (L) to the 1:1 MA binary complex and to the aquated metal ion as shown in equation (5).

$$\Delta \log K = \log K^{MA}_{MAL} = -\log K^{M}_{ML} \quad (5)$$

The value of $\log K$ is the logarithm of the equilibrium constant derived from equation (6).

$$MAL + MA \rightleftharpoons MAL + M \quad (6)$$

In the ternary systems studied, the values of $\log K^{MA}_{MAL}$ were found to lie in the sequence: succinic>maleic>tartaric>dipicolnic acid. This can de explained in accord with basicities($pK_{a1} + pK_{a2}$) of the ligands. It is well known that the increases in basicity of a ligand increases the stability of its metal complexes. The observed order of stability with respect to the ligand hydroxamic acid is Sham>Bha. This may be ascribed to an additional interaction of the phenolic group (sham) with the metal ion.

The observance of statistically unexpected positive $\Delta \log K$ values for the majority of the ternary systems involving aliphatic carboxylic acid indicates that ligands form more stable ternary complexes.

It is observed, that in ternary complexes involving DPA, $\Delta \log K$ is negative as expected from the statistical considerations. There is π acidic character in the primary Ligand (DPA), due to the possibility of $M \rightarrow N\pi$ bond formation. This behaviour is similar to that observed previously in[M-dipyridyl-L] complexes[18,19].

Another parameter, percent Relative Stabilization (%R.S.) to quantify stability of a ternary complex may be defined[20] as

$$\%\,R.S. = [(\log K^{MA}_{MAL} - \log K^{M}_{ML}) / \log K^{M}_{ML}] * 100$$

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The values of % R.S. have been calculated (TABLES 2-4). For some ternary systems, The parameter % R.S. is negative. This may be attributed to the higher stability of binary M^{2+}-L complexes involving secondary ligands than those corresponding the ternary systems MAL. Negative values of % R.S. agree with the $\Delta \log K$ values as shown in TABLES 2-4 .

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