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Mixed ligand complexes of cadmium(II) involving nitrilotriacetic acid

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Abstract. Formation and equilibria of mixed ligand cadmium(II) complexes involving nitrilotriacetic acid (NTA) and other ligands (L) have been investigated. Results of pH-titration measurements have shown the formation of 1:1:1 mixed ligand complexes. Equilibrium constants of the complexes formed have been calculated. The mode of chelation has been deduced.

Keywords. Cadmium(II); nitrilotriacetic acid; mixed ligand complex; potentiometric studies.

1. Introduction

There is much evidence of the carcinogenic effects of cadmium(II) compounds (Sunderman 1978). Cadmium(II) compounds are also notorious for their toxic effect on bones, as in *itai-itai byo* disease in Japan (Hughes 1981). Most treatments for metal poisoning use chelating agents, which are expected to form soluble, stable and non-toxic complexes that are readily excreted (Cerijones *et al* 1984). At present, only a few chelating agents have found clinical use, and a number of problems have been encountered with these (Peters *et al* 1945).

Because of the great affinity of cadmium(II) toward nitrilotriacetic acid (NTA) (Perrin 1979), it would be of interest to study the mixed ligand complexes of cadmium(II) with NTA and some selected ligands. This interest stems from the resemblance of NTA coordination sites to those of some proteins (e.g. concanavalin) (Hardman 1973). The selected ligands studied may represent models for effective metal ion binding sites in biological systems. As a continuation of our research on amino acids (Shoukry *et al* 1987, 1988) and peptides (Rabenstein *et al* 1982, 1985; Shoukry *et al* 1986, 1988; Shoukry and Abdel Hadi 1989), we present a study of some mixed ligand complexes of cadmium(II) involving NTA and selected ligands such as homocysteine, 2-mercaptoethylamine, N-acetylcysteine, N-acetylpenicillamine, glycine, 2-alanine, valine, 2-aminobutyric acid and serine.

2. Experimental

2.1 *Materials and reagents*

The ligands used were homocysteine (Nutritional Biochemicals), N-acetylcysteine, N-

acetylpenicillamine, 2-mercaptoethylamine hydrochloride, glycine, 2-alanine, valine, 2-aminobutyric acid, serine (Sigma) and nitrilotriacetic acid disodium salt (Aldrich). Reagent grade cadmium nitrate was used.

The Cd-content of solutions was estimated complexometrically (Welcher 1965). The thiol-contents of the stock solutions of homocysteine, N-acetylpenicillamine, N-acetylcysteine and 2-mercaptoethylamine hydrochloride were determined by reaction of thiol with iodoacetamide, followed by reaction of the protons displaced from the thiol group with strong base (Reid and Rabenstein 1981).

2.2 *Procedure and measuring techniques*

All pH measurements were made with an Orion Model 701 digital pH meter, equipped with either a standard glass electrode–porous ceramic junction reference electrode pair or a combination electrode. Fisher-certified buffers of nominal pH values 4·00, 7·00 and 10·00 were used for calibration of the pH meter. The exact pH of each of these buffers was established, and periodically checked, by comparison with freshly prepared NBS pH standard buffer solutions (Bates 1973). The titrations were performed using a Mettler DV10 autotitrator and titration vessel described previously (Shoukry *et al* 1986b), at 25°C in a purified nitrogen atmosphere. The following mixtures (A)–(C) were prepared and titrated potentiometrically against 0·20 M NaOH solution for determination of the equilibrium constants:

(A) 10·0 ml of 0·02 M secondary ligand (L) + 30·0 ml of 0·13 M KNO_3;
(B) 10·0 ml of 0·02 M Cd(II) + 10·0 ml of 0·02 M NTA + 20·0 ml of 0·20 M KNO_3;
(C) 10·0 ml of 0·02 M Cd(II) + 10·0 ml of 0·02 M NTA + 10·0 ml of 0·02 M secondary ligand (L) + 10·0 ml of 0·40 M KNO_3.

The stepwise nature of the reaction of formation of the mixed ligand complexes of NTA as well as EDTA has been reported previously (Iyer *et al* 1966; Sathe *et al* 1968; Panchal and Bhattacharya 1972; Chidambaram and Bhattacharya 1973). The formation of the mixed ligand complexes studied is assumed to involve the following equilibria

$$Cd^{2+} + NTA^{3-} \rightleftharpoons [Cd(NTA)]^{-}, \tag{1}$$

$$HL \rightleftharpoons H^{+} + L^{-}, \tag{2}$$

$$[Cd(NTA)]^{-} + L^{-} \rightleftharpoons [Cd(NTA)L]^{2-}. \tag{3}$$

The acid dissociation constants of the ligands were determined by titrating mixture (A) of each. The stability constants, $K^{Cd(NTA)}_{Cd(NTA)L}$, of the mixed ligand complexes were determined by titrating mixture (C), utilizing the data obtained within the pH range corresponding to complete formation of $[Cd(NTA)]^{-}$ complex. The data used for calculation of stability constants of the mixed ligand complexes is in the range $a = 1$ to $a = 3$ for mercaptoethylamine and homocysteine, and in the range $a = 2$ to $a = 3$ for N-acetylpenicillamine and N-acetylcysteine. The data in the range $a = 1$ to $a = 2$, on the other hand, is used for the other ligands (a = number of moles of base added per mole of ligand). The calculations were performed using the computer program (Gans *et al* 1976) MINIQUAD-75 on the TEKTRONEX 4025 IBM computer. Various models were tested and that selected which gave the best statistical fit, consistent with

Table 1. Acid dissociation constants of the secondary ligands and stability constants of their mixed ligand complexes.

Ligand	$\log K_1^H$	$\log K_2^H$	$\log K_{Cd(NTA)L}^{Cd(NTA)}$	$\log K_{Cd(NTA)(L)(H)}^{Cd(NTA)}$
Homocysteine	10·35(0·02)*	8·83(0·02)	5·72(0·08)	14·76(0·05)
Mercaptoethylamine	10·61(0·02)	8·22(0·02)	7·12(0·07)	15·46(0·05)
N-acetylcysteine	9·61(0·03)	3·24(0·02)	5·03(0·02)	
N-acetylpenicillamine	10·06(0·02)	3·38(0·03)	5·48(0·03)	
2-Aminobutyric acid	9·75(0·01)		2·56(0·05)	
Glycine	9·54(0·01)		2·93(0·03)	
2-Alanine	9·81(0·01)		2·67(0·03)	
Valine	9·65(0·01)		2·52(0·02)	
Serine	9·15(0·02)		3·22(0·08)	

* Values in parentheses are standard deviations.

chemical logic, to the titration data without any systematic drifts in the magnitudes of various residuals as described previously (Gans *et al* 1976). The results are listed in table 1.

3. Results and discussion

The acid dissociation constants of the secondary ligands (L) have been determined previously (Perrin 1979). These constants were redetermined under the experimental conditions used in this work for investigating the mixed ligand complexes. Potentiometric equilibrium titration curves of the mixed ligand complex of homocysteine, taken as being representative, are depicted in figure 1. The Cd(II)–NTA (1:1) mixture titration curve starts at pH 2·9 and there is a low pH buffer region followed by a sharp inflection at $a = 1$, corresponding to complete formation of the 1:1 complex. The titration curve of the mixed Cd(II)–NTA–secondary ligand (1:1:1) solution does not show the sharp inflection at $a = 1$. The formation of a mixed ligand complex is ascertained by comparison of the mixed ligand titration curve with the composite curve obtained by graphical addition of the secondary ligand (L) titration curve to the 1:1 Cd(II)–NTA titration curve. The experimental titration curve of the mixed ligand system is found to deviate from the composite curve, indicating the formation of a stable mixed ligand complex. The homocysteine and mercaptoethylamine mixed ligand complex curves deviate from the composite curve in the region $a = 1$ to $a = 3$ indicating the release of two protons in the mixed ligand complex formation and the species $[Cd(NTA)(HL)]^{2-}$ and $[Cd(NTA)(L)]^{3-}$ are possibly formed. In case of N-acetylpenicillamine and N-acetylcysteine, the mixed ligand titration curve coincides in the range $a = 0$ to $a = 2$ with the composite curve. The region is indicative of the titration of a hydrogen ion released from the Cd–NTA complex formation and an easily replaceable carboxylic proton of N-acetylpenicillamine and N-acetylcysteine, the deviation from the composite curve is in the region $a = 2$ to $a = 3$ revealing the release of one proton in the mixed ligand complex formation. The curves of mixed ligand complexes involving the amino acids glycine, alanine, 2-aminobutyric acid and serine deviate in the region $a = 1$ to $a = 2$ indicating the formation of the complex through the release of one proton.

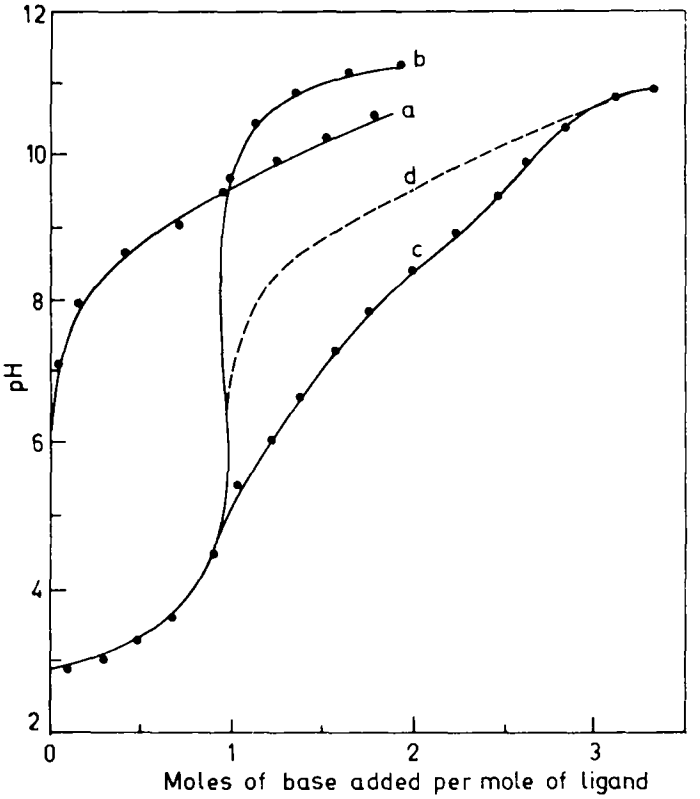

Figure 1. Potentiometric titration curves of Cd(II)–NTA–homocysteine system. (**a**) Homocysteine, (**b**) Cd(II)–NTA, (**c**) Cd(II)–NTA–homocysteine, and (**d**) composite curve.

Based on the above findings and the fact that the 1:1 Cd(II)–NTA complex is appreciably more stable than the 1:1 Cd(II)–secondary ligand (L) complex (Perrin 1979), one molecule of NTA is ligated to the cadmium(II) ion, with subsequent ligation of the secondary ligand (L).

The relative stability of the mixed ligand complex as compared to that of the corresponding binary complex can be quantitatively expressed in different ways. A review (Martin and Prados 1974) of these methods has shown that for a variety of reasons the most suitable comparison is in terms of $\Delta \log K$, given by

$$\Delta \log K = \log K^{Cd(NTA)}_{Cd(NTA)L} - \log K^{Cd}_{CdL}. \quad (4)$$

The $\log K^{Cd}_{CdL}$ for glycine, as a representative, is 3·95 (Munze *et al* 1969), the $\Delta \log K$ value is $-1{\cdot}02$. This means that glycine forms a more stable complex with the free Cd(II) ion than with the Cd–NTA complex. This may be chiefly due to an electrostatic repulsion between the negatively charged $[Cd(NTA)]^-$ complex and the incoming secondary ligand (also negatively charged) during the mixed ligand complex formation.

In a previous study (Shoukry 1989), the zinc(II) mixed ligand complexes of NTA and selected ligands used in this study were investigated. It is found that the Cd(II) complexes are more stable than the corresponding Zn(II) complexes, as previously reported (Cotton and Wilkinson 1980).

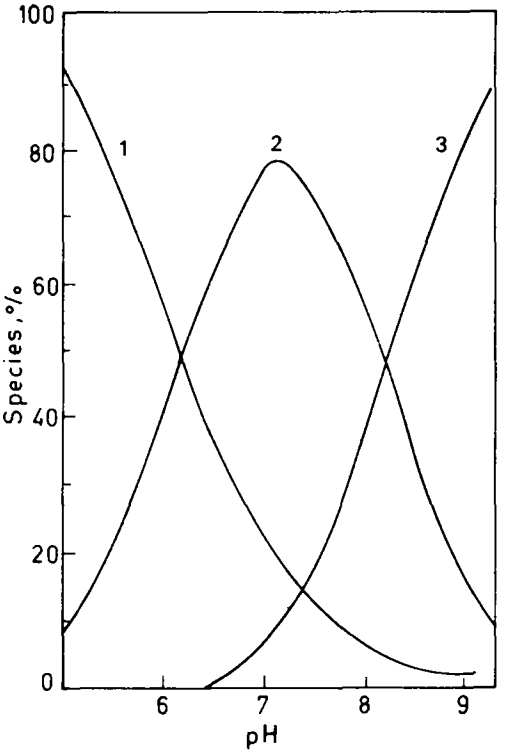

Figure 2. Distribution of various species (%) as a function of pH in the Cd–NTA–mercaptoethylamine system. (1)$[Cd(NTA)]^-$, (2)$[Cd(NTA)HL]^{-2}$, (3)$[Cd(NTA)L]^{-3}$.

The concentration distribution of various complex species as a function of pH was obtained by means of the MINIQUAD-75 computer program. The distribution curves of 2-mercaptoethylamine complexes, taken as representative, are shown in figure 2. Under the experimental conditions used, the different magnitudes of stability constants of the formed complex species are manifested unequivocally in different concentrations of those species. It has been found that the formation percentage of the Cd(II) protonated mixed ligand complex reaches a maximum of 73% at pH 7·9 and 79% at pH 7·1 for homocysteine and mercaptoethylamine, respectively. The unprotonated mixed ligand complexes of Cd(II) seem to prevail with a formation percentage of about 50 at pH values 9·6, 9·1, 8·9, 8·4, 7·7 and 7·3 for glycine, serine, homocysteine, mercaptoethylamine, N-acetylpenicillamine and N-acetylcysteine respectively. On the other hand, this value reaches the maximum of 44% at pH 10·2, 42% at pH 10·1 and 38% at pH 9·9 for alanine, 2-aminobutyric acid and valine respectively.

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