Journal of Organometallic Chemistry 568 (1998) 143–147

The determination of stability constants of *N*-acetyl-L-cysteine chrome, nickel, cobalt and iron complexes by potentiometric method

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Received 2 April 1998

Abstract

The stability constants of the complexes which were formed *N*-acetyl-L-cysteine (NAC) with chrome(III), nickel(II), cobalt(II), iron(III) were determined using Irwing–Rossotti method, in this work. The protonation constants and dissociation constants of the ligand were found as $\log k_1 = pk_2 = 9.60$; $\log k_2 = pk_1 = 2.70$ at 25°C and for $I = 0.12$ and $\log k_1 = pk_2 = 9.30$; $\log k_2 = pk_1 = 2.70$ at 37°C and for $I = 0.12$. Also the overall formation constants of complexes were found as $\log \beta_2 = 7.80$ for cobalt(II); as $\log \beta_2 = 15.00$ for chrome(III); as $\log \beta_2 = 9.34$ for nickel(II); and as $\log \beta_2 = 18.80$ for iron(III); at 37°C and $I = 0.12$. The conditional formation constants and the formation pH ranges of complexes were determined. Relative abundance was plotted using conditional formation constant and the steps of the formation of the complexes were shown in graphs. As can be seen from the results, the formation constants of the complexes of Cr(III) and Fe(III) with NAC are considerably higher than those of Ni(II) and Co(II) complexes.

Keywords: Stability constants; Potentiometric titration; *N*-acetyl-L-cysteine; Cobalt(II); Chrome(III); Iron(III); Nickel(II)

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1. Introduction

N-acetyl-L-cysteine (NAC) is being used for the treatment of congestive and obstructive heart diseases and in the treatment of paracetamol intoxication [1,2].

To prevent the development of nitrate tolerance and use as an immunomodulating agent are the potential usages of the drug [3]. It has also been shown to inhibit HIV-1 replication in infected cells [4], thus treatment with NAC may be considered for HIV-1-infected patients [5]. The mechanism of action of NAC is as a supplier of cysteine for glutathione, acting as an antioxidant or scavenger of electrophiles [6].

On the other hand, it has been previously reported that cysteine residues and some derivatives of it are very effective ligands for many heavy metals like Cd(II), Zn(II) and Ni(II) [7–9].

It is also reported that NAC is incompatible with some metals like copper, nickel and iron [10]. We consider it would be worthwhile illuminating the interaction of NAC which has a potent therapeutic importance for the future, with some metals which exist as trace elements in the organism. To achieve this, the stability constants of the complexes of NAC with Ni(II), Co(II), Cr(III) and Fe(III) were determined using the Irwing–Rossotti method.

2. Experimental

2.1. Materials

The stock solution of metal ions were prepared from nitrate salts. Other chemicals used were sodium hydroxide, sodium perchlorate and perchloric acid.

All chemicals were analytical reagent grade from Merck. Metrohm 654 digital pH-meter with a combined

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PII S0022-328X(98)00719-0

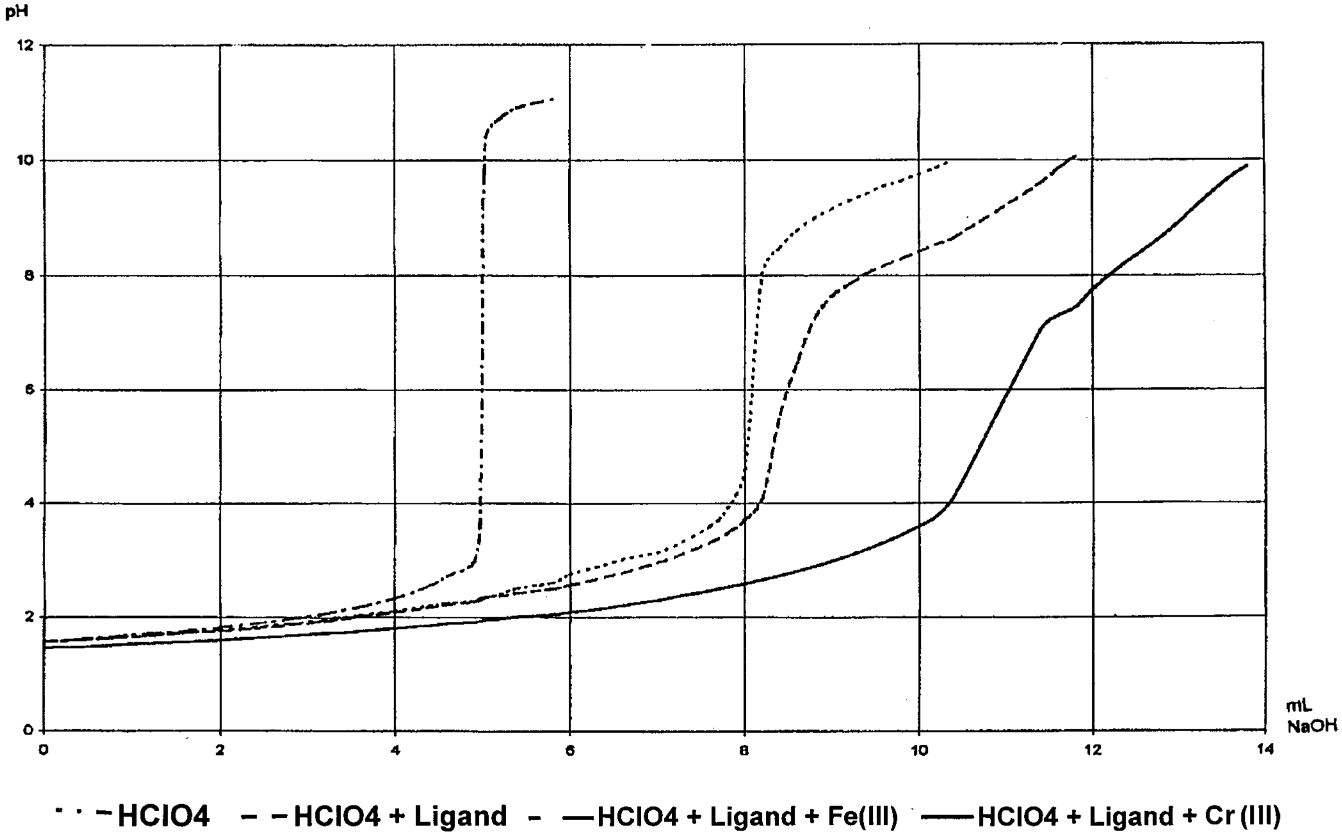

Fig. 1. Potentiometric titration curves of Cr(III) and Fe(III) at 37°C.

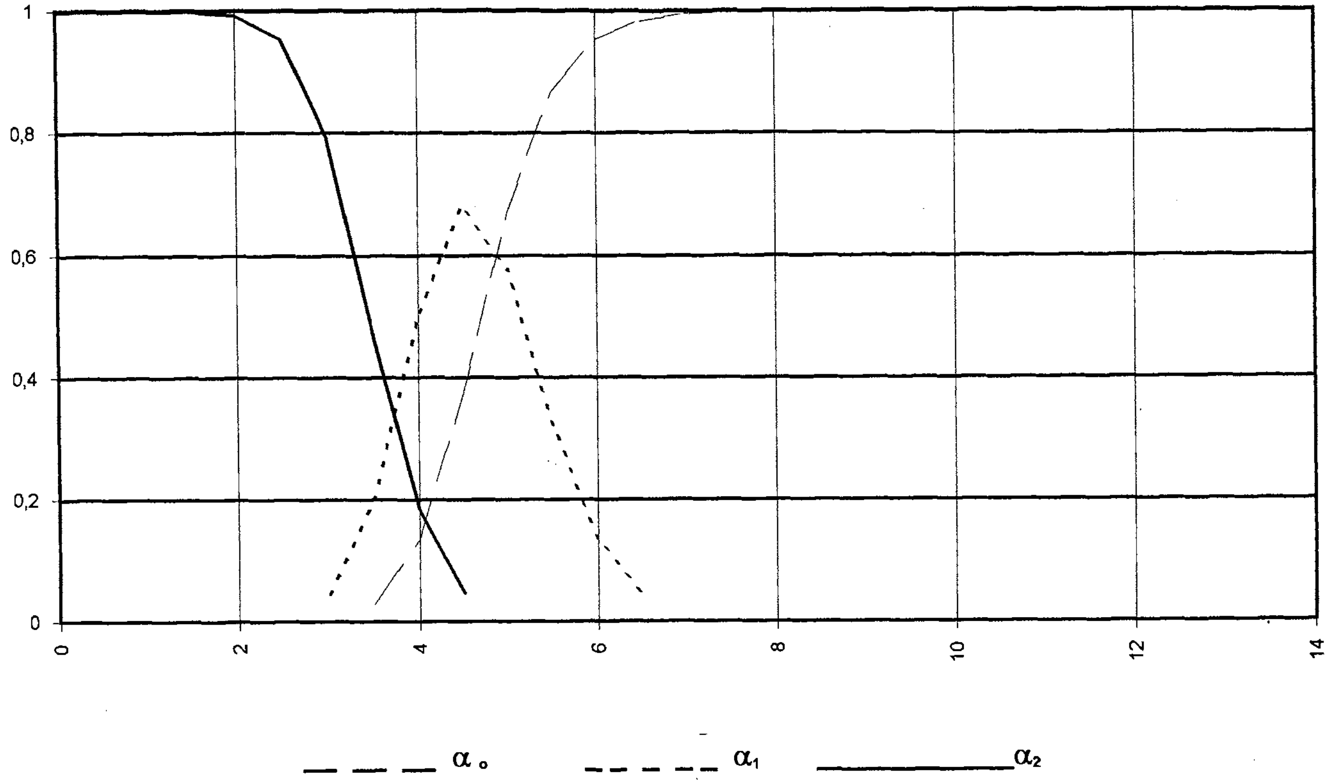

Fig. 2. Mole fraction diagram of Cr(III) at 37°C.

glass electrode assembly was used for pH measurements. ‘Metrohm Multi-Burette E-485’ was used as the burette. The temperature was fixed at 37°C with IKA-TRON ETS D2, H-37. The calculations on the pH-metric data were carried out by a computer.

2.2. Procedure

NAC has dissolved in water. The ionic strength was kept at $I=0.12$ using $NaClO_4$ during the experiment. Solutions were made up under a N_2 atmosphere in H_2O which was decarbonated and triply distilled. The standard solutions of 0.100 M NaOH and 0.100 M $HClO_4$ were kept for no longer than 3 weeks. Stock solutions of the ligands (0.006 M) were prepared prior to use.

The end of the burette was always dipped into the titration solutions. The exact calibration was done daily by using commercial buffer solutions (Merck) of pH 4 and 7. Exact concentrations of the Fe(III), Co(II), and Ni(II) salt solutions were determined titrimetrically by standard EDTA solutions. The concentration of Cr(III) salt solution was determined titrimetrically by standard Fe(II) and $K_2Cr_2O_7$ solutions.

In order to determine the protonation constants, each of the solutions including 0.010 M $HClO_4$ and 0.006 M ligand + 0.010 M $HClO_4$ were titrated potentiometrically with 0.100 M NaOH solution at 37 and 25°C. Average $\tilde{n}_A$ values were calculated from the titration curves. For this, the following equation was used:

$$\tilde{n}_A = y + \frac{(V_1 - V_2)(N + E^\circ)}{(V_0 + V_1)T_L^\circ}$$

where V_0 is volume at the beginning (50.0 ml), M is molarity of base (0.100 M), T_L° is concentration of total ligand (0.006 M), E° is concentration of acid (0.010 M) and y is the number of protons given (2). The mixtures which also contain metal ions were titrated with 0.100 M NaOH potentiometrically and the titration curves were plotted in Fig. 1.

Table 1
Constants of NAC protonation ($I=0.12$, $NaClO_4$, 25 and 37°C)

Ligand	pk_1	pk_2
NAC	3.08 (COOH)	9.62 (SH)

Table 2
β-values ($I=0.12$)

25°C	37°C
$\beta_1 = k_1 = 3.98\times10^9$ $\beta_2 = k_1 \times k_2$ $= (3.98\times10^9)\times(5.01\times10^2)$ $= 1.99\times10^{12}$	$\beta_1 = k_1 = 1.99\times10^9$ $\beta_2 = k_1 \times k_2$ $= (1.99\times10^9)\times(5.01\times10^2)$ $= 1.00\times10^{11}$

The $\tilde{n}_A$ values corresponding to several pH values for NAC by the use of V_1 and V_2 volumes from Fig. 1 were calculated. The figure of $\tilde{n}_A = f(\mathrm{pH})$ was plotted by using the values obtained. The protonation constants' corresponding acid constants were found. The results are given in Tables 1 and 2. The stability constants of the complexes were determined potentiometrically using the Irwing–Rossotti method.

$\tilde{n}_L$ values were calculated using $\tilde{n}_A$ values, pL values were calculated using $\tilde{n}_L$ values to calculate the stability constants of metal complexes.

The following equation was used to calculate $\tilde{n}_L$ values:

$$\mathrm{pL} = \log \frac{1 + \beta_1[H^+] + \beta_2[H^+]^2}{T_L^\circ - \tilde{n}_L \times T_M^\circ}$$

Where V_0 is volume at the beginning (50.0 ml); M is molarity of base (0.100 M); T_L° is concentration of total ligand (0.006 M); E° is concentration of acid (0.100 M); Y is the number of protons given (2); and T_M° is concentration of total metal (0.005 M).

pL values were calculated using β-values (Table 2). $\tilde{n}_L = f(\mathrm{pL})$ Graphs were plotted using $\tilde{n}_L$ and pL values which were calculated for each metal ligand complex. The formation constants of complexes were found from pL values which corresponded to $\tilde{n}_L = 0.5$ and $\tilde{n}_L = 1.5$ values. In addition, the changes in mole fractions of the molecular and ionic species derived from complexes with the pH of solution were calculated (Figs. 2 and 3).

3. Results and discussion

The solution which has a final NAC concentration of 0.006 mol l^{-1} and $HClO_4$ concentration of 0.010 mol l^{-1} and an ionic strength of 0.120 was titrated with 0.100 mol l^{-1} NaOH solution. The protonation constants of NAC were found graphically by using the Irwing–Rossotti method. The results are shown in Fig. 1. Acid constants of NAC which were calculated from the protonation constants are in accordance with the ones reported in the previous studies [7,8]. For finding the stability constants of the complexes of metals with NAC, the solutions which contain Ni(II), Co(II), Cr(III) and Fe(III) salts in certain concentrations were titrated with NaOH solution potentiometrically in 25 and 37°C. Titration curves were obtained by plotting the pH changes versus the 0.100 mol l^{-1} NaOH volumes. The resulting titration curves, belonging to Cr(III) and Fe(III), are shown in Fig. 1. The graphs of $\tilde{n} = f(\mathrm{pL})$ are plotted by using these titration curves for 25 and 37°C. The formation constants for the metal complexes which were found from the related $\tilde{n} = f(\mathrm{pL})$ graphs for 25 and 37°C are shown in Tables 3 and 4. The conditional formation constants of the complexes are calculated and they were plotted versus the related

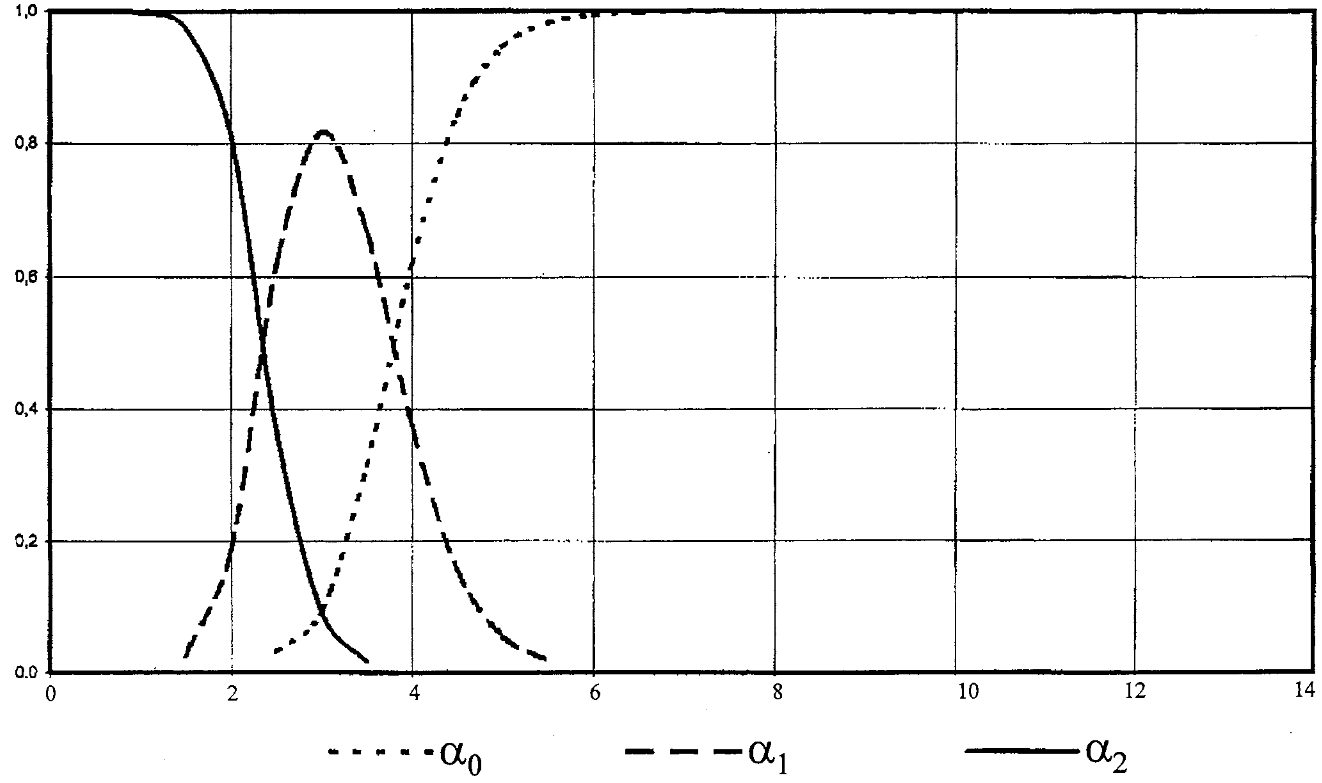

Fig. 3. Mole fraction diagram of Fe(III) at 37°C.

pH changes. In calculating the conditional formation constants, it is accepted that the only competitive ligand is the hydronium ion in the reaction medium. The pH ranges in which the complexation occurs, the maximum values of conditional formation constants and the pH values related to these conditional formation constants for 25 and 37°C are shown in Tables 5 and 6.

Table 3
The formation constants for the metal complexes ($I = 0.12$, $t = 25$°C)

Metal	log k_1	log k_2	log β_2
Chrome(III)	8.26	6.74	15.00
Cobalt(II)	4.18	3.62	7.80
Nickel(II)	5.02	4.32	9.34
Iron(III)	10.58	8.22	18.80

Table 4
The formation constants for the metal complexes ($I = 0.12$, $t = 37$°C)

Metal	log k_1	log k_2	log β_2
Chrome(III)	8.11	6.84	14.95
Cobalt(II)	4.22	3.72	7.94
Nickel(II)	4.84	4.38	9.22
Iron(III)	9.66	7.76	17.42

As it can be seen from the results, the formation constants of the complexes of Cr(III) and Fe(III) with NAC are quite high with the values log $\beta_2 = 14.95$ and log $\beta_2 = 17.42$. On the other hand, the ones for Ni(II) and Co(II) complexes are low with the values log $\beta_2 = 9.22$ and log $\beta_2 = 7.94$ for 37°C.

Table 5
The conditional formation constants for the metal complexes ($I = 0.12$, $t = 25$°C)

Metal	pH range of the metal complexes	pH (Kc is max)	max Kc
Chrome(III)	6–8	7.00	8.10^5
Cobalt(II)	9–11	10.00	9.10^6
Nickel(II)	8.5–10.5	9.50	1.10^8
Iron(III)	5–9	7.00	2.5×10^6

Table 6
The conditional formation constants for the metal complexes ($I = 0.12$, $t = 37$°C)

Metal	pH range of the metal complexes	pH (Kc is max)	max Kc
Chrome(III)	6–8	7.00	3.10^6
Cobalt(II)	8.5–11	9.50	2.10^7
Nickel(II)	8.5–10.5	9.50	1.5×10^8
Iron(III)	5–8.5	7.00	4.5×10^5

It is reported that NAC itself reacts with Zn(II) in the organism and also its metabolite cysteine, so its uriner excretion is enhanced when NAC is administrated in high doses in paracetamol intoxication [11].

Taking into consideration that the uriner excretion of Zn(II) is enhanced by forming NAC and cysteine complex with it which has a quite low log β_2 value 11.48 (7), one must be careful about the interaction of NAC with Cr(III) and Fe(III), because of their high stability constants.

References

[1] L.F. Prescott, R.N. Illingworth, J.A.J.H. Critchley, M.J. Steward, R.D. Adam, A.T. Proudfoot, Br. Med. J. 2 (1979) 1097.

[2] M. Aylward, J. Maddock, P.M. Dewland, Evr. J. Respir. Dis. 61 (III) (1980) 81.

[3] J. Abrams, Am. J. Med. 91 (1991) 106.

[4] M. Reoderer, P.A. Raju, F.J. Staal, L.A. Herzenberg, AIDS Res. Hum. Retrovir. 7 (1991) 563.

[5] M. Reoderer, S.W. Ela, F.J. Stall, L.A. Herzenberg, AIDS Res. Hum. Retrovir. 8 (1992) 209.

[6] P. Moldeus, Ian A. Catgreare, Methods Enzymol. 234 (1994) 483.

[7] P. Gockel, H. Vahrenkamp, Helv. Chim. Acta 76 (1993) 511.

[8] H. Kozlowski, I. Urbanska, I. Sovago, Polyhedron 9 (1990) 831.

[9] L. Wagner-Ross, H. Zahn, Toxicol. Environ. Chem. 22 (1989) 77.

[10] U.S.P., Drug Information for the Health Care Professional, 15th ed., vol. 1, 1995.

[11] H. Brumas, B. Filella, M.G. Berthon, Agents Action 36 (1992) 278.