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Solution equilibria studies of complexes of divalent metal ions with 2-aminophenol and 3,4-dihydroxybenzoic acid

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ABSTRACT

The chelation abilities of 2-aminophenol and 3,4-dihydroxybenzoic acid with divalent metal ions (Cu^{2+}, Be^{2+}, Zn^{2+}, Ni^{2+}, Co^{2+} and Mn^{2+}) in binary and ternary systems at 37 ± 0.1 °C and an ionic strength of 0.15 mol dm^{-3} NaCl were systematically investigated by using the potentiometric titration method. The chelating abilities of these complexes were obtained by processing the titration data using the Hyperquad2008 program and the results are presented as stability constants. In a binary system, it was shown that metal complexation involving 3,4-dihydroxybenzoic acid (ligand D) is more stable than the one with 2-aminophenol (ligand A). The stability of the formed metal complexes, both in binary and ternary systems, decreases in the following order: $Cu^{2+} > Be^{2+} > Zn^{2+} > Ni^{2+} > Co^{2+} > Mn^{2+}$. The tendency of these metals and ligands to form binary or ternary complexes was also evaluated and discussed by calculating their $\Delta \log K_M$ and $\log X$ values. In addition, the distribution of complex species in these systems was graphically presented using the HySS2009 program. UV–Vis spectrophotometry was also performed to qualitatively verify the protonation of these ligands and to confirm the model of the complex formed.

1. Introduction

The earth is rich in various metals which are distinguished by their electronic distributions, that in turn affect their physiological and pathological characteristics. Several metals, which are part of dietary minerals, are found in every living organism and they take part in the functionality of body systems; in particular as stabilizers of biological structures, components of control mechanism (in nerves and muscles) and activators or components of redox systems [1,2]. In other words, some metals are categorized as essential elements, meaning the lack of them will affect the biological functions of the human body. In contrast, their presence in excess levels is toxic and may have adverse effects on human health.

Chelation therapy has been known as one of the medical treatments that is able to reduce excess metal levels in the human body and indirectly prevent carcinogenesis and cancer development. This therapy has been applied historically and it commonly employs certain chelating agents to reduce the body's burden towards metal toxicity [3–5]. However, commercial chelators still bring some adverse effects and it sometimes leads to death [1,6–9]. Several new potential chelators, including vitamin, phenolic compounds and amino acids, are found to increase metal mobilization, which means they could minimize the possibility of the interaction of the metal ions with important bio-substances [10–12]. Several studies have reported that combining a chelating agent and an antioxidant may be beneficial for metal poisoning antidote therapy, by protecting the human body from reactive oxygen species and oxidative stress [1,12,13].

In this study, two phenolic compounds (2-aminophenol and 3,4-dihydroxybenzoic acid) were investigated for their potential as chelating agents. Both phenolics are known to possess different binding sites that may play important roles in their chelating activity. 2-Aminophenol contains neighboring N and O donor atoms in the aromatic ring, which allow the compound to form stable five-membered-ring complexes with metal ions [14]. The compound was also found to have antibacterial activity against gram-negative *Bacillus* [15,16]. Its administration into animals also showed no toxic effects and the compound was excreted in conjugation with both sulfuric acid and glucuronic acid [17]. Another potential chelator, 3,4-dihydroxybenzoic acid, was reported to have chemoprevention activity against carcinogenesis [18–20]. This compound

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was found to be effective in inhibiting colon, skin and liver cancers, either in the initiation phase or in the promotion/progression of carcinogenesis. It also shows antioxidant activity due to the occurrence of a carboxylic group and two adjacent hydroxyl groups. These functional groups may act as inhibitors of free radical reactions by forming complexes with transition metal ions (Cu^{2+} and Fe^{2+}) and thus may lower the activity of enzymes that catalyze the reactions of free radical formation [21,22].

In order to gain an initial understanding and basic information on metal chelation for further research in chelation therapy, this study investigated the complexation of 2-aminophenol and 3,4-dihydroxybenzoic acid with divalent metal ions (Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and Be^{2+}) in binary and ternary systems. While many stability constants of metal ions and 3,4-dihydroxybenzoic acid have been reported before, only very limited information can be found regarding the metal complexing abilities of the 2-aminophenol ligand. In addition, the usefulness of these chelating agents to reduce excess metal ions in ternary system with both ligands has never been investigated before. Therefore, it is necessary to understand the possible chelation processes and stable complexes formed between these chelators and certain metal ions. While most reported works were carried out at 25 °C and with an ionic strength 0–0.2 mol dm^{-3} NaCl, all the experimental studies in this work were carried out at physiological conditions which mimic body fluids (37 ± 0.1 °C and 0.15 mol dm^{-3} NaCl) to gain reliable results for further research in drug development for chelation therapy. The stability constant study helps to understand the interaction strength between the chelating agent and metal ion in forming complexes. The complexing abilities were investigated using a potentiometric method and the Hyperquad2008 program. The speciation model was determined using the HySS2009 program. UV–Vis spectrophotometry was performed to determine the first protonation constant of the 3,4-dihydroxybenzoic acid, to qualitatively verify the protonation of the ligands and to confirm the model of the complexes formed.

2. Materials and methods

2.1. Materials

The chemicals used in this study and their suppliers are as follows: 2-aminophenol (MW = 109.1; 0.99 purity) and 3,4-dihydroxybenzoic acid (MW = 154.1, 0.97 purity), Alfa Aesar (Lancashire, UK); nickel chloride hexahydrate (MW = 237.7, 0.98 purity) and beryllium sulfate tetrahydrate (MW = 177.1, 0.98 purity), Alfa Aesar (Lancashire, UK); zinc nitrate hexahydrate (MW = 297.5, 0.98 purity) and manganese chloride tetrahydrate (MW = 197.9, 0.998 purity), Acros Organics (Morris Plains, NJ); cobalt nitrate hexahydrate (MW = 291.0, 0.98 purity), copper chloride dihydrate (MW = 170.5, 0.99 purity), potassium hydrogen phthalate (MW = 58.45, 0.99 purity), Sigma Aldrich (Steinheim, Germany); sodium hydroxide (MW = 40, 0.96 purity), Yakuri Pure Chemicals (Kyoto, Japan); sodium chloride (MW = 58.44, 0.995 purity), Showa (Tokyo, Japan); hydrochloric acid (MW = 63.01, 0.376 purity), Fisher Scientific (Hampton, NH). All chemicals were directly used without further purification. Solutions were prepared daily in distilled deionized water (resistance >18 M Ω). In particular, solutions of metal salts, NaOH and HCl were standardized before used.

2.2. Potentiometric measurement

The following solutions, each with a total volume of 50 cm^3, were prepared in a 100 cm^3 double walled equilibrium cell for pH-potentiometric measurements and each was titrated against standard carbonate-free NaOH (0.10 mol dm^{-3}).

(a) 3×10^{-3} mol dm^{-3} HCl + 1.5×10^{-1} mol dm^{-3} NaCl.
(b) Solution a + 1×10^{-3} mol dm^{-3} 2-aminophenol (A) or 3,4-dihydroxybenzoic acid (D).
(c) Solution a + 1×10^{-3} – 1.2×10^{-3} mol dm^{-3} A or D + 4×10^{-4} – 1×10^{-3} mol dm^{-3} metal salt.
(d) Solution a + 5×10^{-4} – 1×10^{-3} mol dm^{-3} A + 4×10^{-4} – 1×10^{-3} mol dm^{-3} D + 4×10^{-4} – 1×10^{-3} mol dm^{-3} metal salt.

Prior to titration, each solution was kept at 37 ± 0.1 °C for 15 min by connecting the equilibrium cell to a refrigerated circulating bath equipped with a thermocouple to closely monitor the reaction temperature. During potentiometric measurements, the temperature and ionic strength of the system were maintained at a constant 37 ± 0.1 °C and 0.15 mol dm^{-3} NaCl, respectively. At least three repetitions for the pH-potentiometry procedure were carried out for each experiment, with a reproducibility of ±0.02 in pH units.

The potentiometric titrations were performed using a meterohm 888-Titrando Autotitrator equipped with a Dosimat model 805, 802 rod stirrer and 804 Ti stand, and an Ecotrode Plus pH glass electrode was used for potentiometric measurements. The instrument was connected to a personal computer equipped with Tiamo 2.3 computer software to control the titration conditions and record the experimental data. The glass electrode response was able to give a pH reading with a precision of ±0.001. Prior to use, the electrode was calibrated with standard buffer solutions (pH 4.00, 7.00 and 10.00) at the same temperature used for the main experimental work (37 ± 0.1 °C). Since the determination of metal–ligand stability constants was carried out at high ionic strength (0.15 mol dm^{-3} NaCl), it was necessary to carry out a strong acid-strong base titration for the glass electrode calibration. For this purpose, the titration curve of solution a was processed using the Glass Electrode Evaluation (GLEE) program to evaluate the calibration of the glass electrode and to estimate carbonate contaminant for each investigation [23].

The titration curve of solution b was later processed by the Hyperquad2008 program in order to determine the protonation constant of the ligands. In contrast, the investigations of metal ligand stability constants in the binary and ternary systems were carried out by processing the titration curves of solutions c and d, respectively. As shown in Table 1, the metal ligand complexation studies in the binary system were done at four different metal-to-ligand ratios, while ternary studies were done at three different metal:ligand A:ligand D ratios, to cover all possible complex species that may occur in the system.

Table 1
Concentrations of metal and ligand in solution c that were used to determine the overall formation constants of binary complexes.

Ratios	Concentration (mol dm^{-3})		
	Metal	Ligand A	Ligand D
Binary [M]:[L]			
1:1	1.0×10^{-3}	1.0×10^{-3}	
1:2	5.0×10^{-4}	1.0×10^{-3}	
1:2.5	4.0×10^{-4}	1.0×10^{-3}	
1:3	4.0×10^{-4}	1.2×10^{-3}	
Ternary [M]:[A]:[D]			
1:1:1	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}
1:1:2	5.0×10^{-4}	5.0×10^{-4}	1.0×10^{-3}
1:2:1	5.0×10^{-4}	1.0×10^{-3}	5.0×10^{-4}