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Journal of Inorganic Biochemistry 99 (2005) 2308–2321
Journal of Inorganic Biochemistry
www.elsevier.com/locate/jinorgbio

Voltammetry as a virtual potentiometric sensor in modelling of a metal–ligand system and refinement of stability constants. Part 4. An electrochemical study of Ni^{II} complexes with methylene diphosphonic acid

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Received 4 July 2005; received in revised form 27 August 2005; accepted 28 August 2005
Available online 6 October 2005

Abstract

The Ni^{II}–MDP–OH system (MDP = methylene diphosphonic acid) and stability constants of complexes formed at ionic strength 0.15 M at 298 K were established by direct current polarography (DCP) and glass electrode potentiometry (GEP). The final M–L–OH model could only be arrived to by employing recent concept of virtual potentiometry (VP). VP-data were generated from non-equilibrium and dynamic DC polarographic technique. The VP and GEP data were refined simultaneously by software dedicated to potentiometric studies of metal complexes. Species distribution diagrams that were generated for different experimental conditions employed in this work assisted in making the final choice regarding the metal–ligand model. The model established contains ML, ML_2, ML(OH) and $ML(OH)_2$ with stability constants, as $\log\beta$, 7.94 ± 0.02, 13.75 ± 0.02, 12.04 (fixed value), and 16.75 ± 0.05, respectively. It has been demonstrated that virtual potential must be used in modelling operations (predictions of species formed) when a polarographic signal decreases significantly due to the formation of polarographically inactive species (or formation of inert complexes). The linear free energy relationships that included stability constant $\log K_1$ for Ni^{II}–MDP established in this work together with other available data were used to predict $\log K_1$ values for Sm^{III} and Ho^{III} with MDP. The $\log K_1$ values for Sm^{III}–MDP and Ho^{III}–MDP were estimated to be 9.65 ± 0.10 and 9.85 ± 0.10, respectively.

Keywords: DC polarography; Potentiometry; Virtual potential; Linear free energy relationship; Bisphosphonates

1. Introduction

Bone metastases or secondary tumours are formed when cells from the primary tumour spread to other parts of the body. It is common for bone metastases to develop in breast, prostate and lung cancer patients endangering their long term survival. Bone tissue in adults is not dormant, but is constantly being remodelled through lifelong repeated cycles of destruction (resorption) and rebuilding (formation) [1]. Three kinds of bone cells exist on the surface of the bone matrix and take part in the remodelling process, i.e., osteoclasts, osteoblasts and osteocytes. The process starts with bone resorption carried out by osteoclasts creating an acidic environment where most of the secreted enzymes are able to solubilise hydroxyapatite crystals. This is followed by reversal phase in which a thin cement type layer is formed to which the osteoblasts adhere and rebuild the excavated area. Osteocytes are the most numerous cells and are imbedded in the bone matrix maintaining bone integrity and signal the start of a remodelling process when the bone is under mechanical stress.

The common pathway for the spread of malignancies is from the primary tumour that undergoes neovascularisation

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doi:10.1016/j.jinorgbio.2005.08.012

followed by the transport of malignant cells to other areas in the body via the vascular system and adherence to a distant capillary bed [1]. Metastasis to the bone occurs in 80% of the breast, lung and prostate cancer patients. Once the metastases cells have located to the bone, metastasis thereof occurs and spread of malignancies all over the bone follows by a large increase in bone resorption and loss of calcium from the bone. The increase in resorption is also a common phenomenon in osteoporosis. What causes pain in patients with skeletal metastasis is not fully understood. The disruption of the structural integrity of the bone might be a contributing factor therefore agents inhibiting the resorption process might be effective pain palliation therapies helping the patient to maintain a good quality of life.

Bisphosphonates are classified as drugs that are considered to be stable analogues of pyrophosphates. They are physiological regulators of calcification and bone resorption processes [2] and not metabolically active. Several bisphosphonates have been approved for clinical use in Paget's disease, hypercalcemia of malignancy and osteoporosis. The basic structure of a bisphosphonates (PO_3^{2-}–C(R)(R′)–PO_3^{2-}) allows for many variations by changing the R and R′ lateral chains on the carbon atom, hence the investigation of bisphosphonates for their effect on bone in humans. The affinity of bisphosphonates to bone hydroxyapatite is the basis for their use as inhibitors of calcification and bone resorption. Furthermore, they preferentially accumulate under the osteoclasts decreasing their activity by reducing their acid production, lysosomal enzymes and prostaglandin formation as well as to directly reduce the number of osteoclasts.

Because of their affinity for bone, ligands such as methylene diphosphonic acid (MDP) and 1-hydroxyethylenediphosphonic acid (HEDP) are being used extensively in combination with $^{99m}Tc^{III}$ as imaging modalities for bone. $^{99m}Tc^{III}$–MDP appears to offer significant advantages, although many of its characteristics are similar to those of the $^{99m}Tc^{III}$ bone-seeking complexes. $^{99m}Tc^{III}$–HEDP on the other hand has a slower blood clearance but gives a better contrast between regions of higher and lower calcification rates [3]. In order to improve the understanding of the underlying factors governing the behaviour of these ligands and therefore improving the future design for these ligands and radiopharmaceuticals (not only bisphosphonates labelled by $^{99m}Tc^{III}$ for imaging but also with $^{153}Sm^{III}$, $^{166}Ho^{III}$ and $^{117m}Sn^{II}$ for pain palliation and therapy), it was necessary to study the Ni^{II}–MDP–OH system and establish its model and stability constants of complexes formed. The formation constant of the Ni^{II}–MDP complex ($\log K_1$) together with values for other metal ions forming ML complexes with MDP are necessary for the estimation of the first formation constants for Sm^{III} and Ho^{III} complexed to MDP. This, in turn, makes it possible to establish a blood plasma model that is able to predict the in vivo behaviour of a proposed radionuclide (metal ion) in the form of bisphosphonate complex [4]. The estimation of those formation constants is achieved with the use of the linear free energy relationship (LFER) because direct investigation of interactions between Sm^{III} and Ho^{III} and the MDP ligand is impossible. Many relationships between the free energies or rates of complex formation of sets of complexes, and a variety of properties of the metal ions, ligands, or complexes have been discovered. No strict thermodynamics is required in the derivation of such regularities and hence they are called extra-thermodynamic relationships [5]. These correlations do provide understanding into the factors governing complex formation. These relationships also allow for the prediction of unknown formation or rate constants. The LFER has been known with correlations involving rates and proton basicity of many organic aromatic bases [5]. The first observations of LFER were correlations between the protonation constants of the ligand and $\log K_{ML}$ with a variety of metal ions [6].

Preliminary studies of the Ni^{II}–MDP–OH system were performed by GEP [7]. They indicated the formation of a ML complex but the overall results were considered unreliable due to the formation of precipitate, hence the need to study the system further. The electrochemical techniques employed in this work include direct current polarography (DCP) and glass electrode potentiometry (GEP). The metal–ligand system studied here was found to be fully irreversible. The final Ni^{II}–MDP–OH model reported in this work was consistent for both electrochemical techniques. Glass electrode (GE) is still regarded as the most valuable potentiometric sensor due to its wide linearity range. It has been extensively used in the study of metal–ligand equilibria [5]. Well-tested dedicated software ESTA, that has been developed for the treatment of potentiometric data [8–11] and allows any kind of metal–ligand complex to be studied, was employed in this work. Polarography was recently found to be very useful in ligand design strategies when used for speciation studies of labile and non-labile, as well as mono- and polynuclear complexes [12–15]. The evaluation of stability constants from this technique results from the interpretation of the shift along the potential scale and intensity of the polarographic signal. Until recently the experiments were performed at a fixed pH, which only allowed for the determination of a single complex by use of Lingane method [16]. It has been shown recently [13] that in the case where several metal complexes are formed simultaneously in solution at a particular pH, the extended Lingane equation cannot be used successfully for the evaluation of stability constants and prediction of metal species. This is because a shift in the half-wave potential as well as variation in the limiting diffusion current were attributed only to one metal complex for which the stability constant was calculated; the computed stability constant was always larger than expected. The Lingane [16], DeFord and Hume [17] (determination of ML_j-type of complexes formed in consecutive manner when studied by ligand titration), or Schaap and McMasters [18] methods (the latter one being an extension of the DeFord and Hume methodology to systems with two competing ligands) showed