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Metal ion interactions with drugs: Electrochemical study of complexation of various bivalent metal ions with nimesulide and ibuprofen

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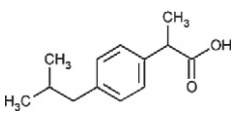
ABSTRACT

The present study reports the stability constants of complexes of two NSAIDs: nimesulide and ibuprofen with Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Sn^{2+}, Hg^{2+} and Pb^{2+} ions in water–ethanol medium 50% v/v at three different temperatures (298 K, 308 K and 318 K), keeping ionic strength constant (0.1 M KNO_3). Experiments were conducted in 1000 mL jacketed glass reaction vessels under nitrogen atmosphere. Hydrogen ion concentrations were measured and the stability constants were calculated from the pH-metric titration curves. The order of the stability constants of the formed complexes decreases in the sequence $Cu^{2+} > Co^{2+} > Cd^{2+} > Zn^{2+} > Ni^{2+} > Sn^{2+} > Pb^{2+} \approx Hg^{2+}$ for nimesulide (D_1) and $Cu^{2+} > Co^{2+} > Zn^{2+} > Ni^{2+} > Cd^{2+} > Sn^{2+} > Pb^{2+} > Hg^{2+}$ for ibuprofen (D_2). The effect of temperature was also studied and the corresponding thermodynamic functions ΔG, ΔH and ΔS were derived and discussed. The formation of metal complexes has been found to be spontaneous and entropically favorable. The method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to determine log K_1 values. This order is in good agreement with the Irving–Williams order of stability.

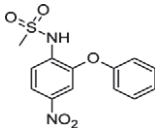
1. Introduction

The response of metal ions in our biological system ranges from deficiency to toxicity [1]. Thus for effective removal of toxic metals from our body, it is mandatory for these metal complexes to have high thermodynamic stability. However removal of the harmful/toxic metals from a biological system requires many other properties which are not completely understood and controlled [2]. Chelation therapy has been scientifically proven to remove excess toxic metals before they can damage the body, but at the same time chelation is not completely risk free. Henceforth the challenge of well-designed metal-based drugs is to minimize possible toxicity. Transition metals have a very good tendency to form coordination compounds. We have already reported ion-association, solvation behavior and compressibility studies of Cu(I) and Ag(I) in various organic solvents and even in mixtures of solvents [3–6]. A detailed knowledge of antibiotic binding sites can facilitate rational drug-design. To quote a few examples, the Cu(II) complexes of a few NSAIDs show better anti-cancer effects than bare drugs [7]; ligand therapy has significant antitumor effects in the case of ovarian tumor growth [8]. Chelation therapy is widely used in the cases of autism in which the molecules of heavy metals (lead, arsenic or mercury) or minerals are removed from the body by chelation using some chemical substances [9–11].

Drugs belonging to the non-steroidal anti-inflammatory drug group (NSAIDs) are not only used as anti-inflammatory and analgesic agents, but also show chemopreventive effects on various cancer cell lines. Useful information about the molecular mechanism of action of drugs can be derived by the study of the interaction of various antibiotics with biological metal ions [12–14]. This paper describes the potentiometric study on the ligand complex formation of Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Sn^{2+}, Hg^{2+} and Pb^{2+} with ibuprofen and nimesulide at a fixed ionic strength, I = 0.1 M (KNO_3). A mixed aqueous solvent system with 50% v/v ethanol–water medium is chosen. Both ibuprofen (IBU.); $C_{13}H_{18}O_2$; 206.3 g/mol; 2-(4-(2-methylpropyl) phenyl) propanoic acid and nimesulide (NIM.); $C_{13}H_{12}N_2O_5S$; 308.3 g/mol; N-(4-nitro-2-phenoxyphenyl)methane sulfonamide are non-steroidal anti-inflammatory drugs (NSAIDs).



Ibuprofen (IBU.); $C_{13}H_{18}O_2$



Nimesulide (NIM.); $C_{13}H_{12}N_2O_5S$

IBU. is believed to work through inhibition of cyclooxygenase (COX) i.e. inhibiting prostaglandin synthesis. There are at least two variants of COX (COX-1 and COX-2). IBU. inhibits both whereas NIM. is relatively COX-2 selective, having analgesic and antipyretic

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properties. Interaction of various antibiotics with a wide range of metal ions is also reported earlier in detail [15–23] but the stability constants and corresponding thermodynamic parameters of the above-mentioned NSAIDs with bivalent metal ions are not reported yet.

2. Experimental

All chemicals used were of A.R. grade. The potentiometric titrations were carried out in a jacketed cell. Ligand solutions were prepared in twice distilled deionized carbon dioxide free water. Metal salt solutions were prepared by dissolving the corresponding metal salts and standardized by standard volumetric methods. The free hydrogen ion concentrations were measured with a combined glass electrode attached to an EI pH meter model 112; the accuracy of the pH meter was ±0.01. 50% v/v ethanol–water medium was used at three temperatures (25 ± 0.1, 35 ± 0.1 and 45 ± 0.1 °C) and at an ionic strength of 0.1 mol L^{-1} (KNO_3). The pH meter was calibrated with suitable buffers before use. The three solutions (with a total volume of 50 mL in each case) were prepared and titration curves were obtained as follows: (a) mineral acid curve, (b) mineral acid + ligand curve and (c) mineral acid + ligand + metal ions (added one by one and separate curves were obtained).

An appropriate quantity of potassium nitrate solution (1.0 mol L^{-1}) was added to maintain the desired ionic strength (0.1 mol L^{-1}). The above three solutions were titrated against potassium hydroxide (0.05 mol L^{-1}). The three curves were obtained from the plots of pH versus volume of alkali required and are referred to as (i) acid, (ii) ligand and (iii) complex titration curves. The solution to be titrated was taken in a cell and immersed in the thermostat for half an hour before the titration so that it attained the required temperature. After the addition of each portion of alkali the highest pH reading which remained steady was recorded in all cases.

3. Results and discussion

The values of $\overline{n_A}$ (the degree of formation of the proton complex) were calculated by employing the following Eq. (1):

$$\overline{n_A} = Y + \frac{\left(V' - V''\right)\left(N + E^0\right)}{\left(V^0 + V'\right){T_L}^0} \tag{1}$$

where Y = number of replaceable hydrogen ions, V^0 = total volume: 50 ml, V′ = volume of alkali used by the acid, V″ = volume of alkali used by the acid and ligand, N = concentration of alkali, E^0 = total strength of acid, and T_L^0 = total concentration of ligand.

The proton ligand formation curves were obtained by plotting the degree of formation $\overline{n_A}$ of the proton–ligand complexes against pH values for nimesulide (Fig. 1) and ibuprofen (Fig. 2). The values of log K_1^H were obtained from the curves corresponding to $\overline{n_A}$ values of 0.5. The stability constants at three different temperatures were calculated by various computation methods [24–26] and are summarized in Tables 1 and 2 for nimesulide and ibuprofen respectively.

The respective value of $\overline{n}$ (average number of ligand molecules attached per metal ion) were calculated using Eq. (2)

$$\overline{n} = \frac{\left(V''' - V''\right)\left(N + E^0\right)}{\left(V^0 + V'\right)\overline{n_A}\,{T_M}^0} \tag{2}$$

where V‴ = volume of alkali used for acid + ligand + metal ion, ${T_M}^0$ = total concentration of the metal ion; the rest of term symbols are as given in Eq. (1). The free ligand exponent, pL was calculated using Eq. (3) as given below:

$$pL = \log_{10}\left[\frac{\sum_{n=0}^{n=j}\beta^H{}_n(1/\text{antilog}\beta)^n}{{T_L}^0 - \overline{n}\,{T_M}^0}\ \frac{V^0 + V'''}{V^0}\right]. \tag{3}$$

The stoichiometric metal–ligand stability constants have been calculated from the formation curves obtained by plotting $\overline{n}$ against pL. These plots indicate that the values of $\overline{n}$ are of the order of 1 for the complexes of these drugs with all the metal ions, indicating the formation of 1:1 complexes. Bjerrum's half integral method [27] of interpolating various $\overline{n}$ values and graphical method was used to calculate log k_1 values.

- *Effect of pH*: Only 1:1 complexes of all the metal ions Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Sn^{2+}, Hg^{2+} and Cd^{2+} are formed in the titration studies of these systems at 298 K, 308 K and 318 K. The complexation of different metal ions takes place almost in the same pH range at different temperatures. The following are the pH ranges for the complexation of metal ions with different ligands at 298 K, 308 K and 318 K: pH 4.5 to 5.3 for Cu^{2+}, pH 4.8 to 5.6 for Co^{2+}, pH 4.9 to 5.8 for Ni^{2+}, pH 5.1 to 5.8 for Zn^{2+}, pH 5.2 to 6.0 for Cd^{2+}, pH 4.3 to 5.2 for Pb^{2+}, pH 5.1 to 6.2 for Sn^{2+}, and pH 5.3 to 6.3 for Hg^{2+}.
- *Effect of temperature*: A perusal of data in Tables 1 and 2 shows that the pk_1^H values increase with an increase in temperature. Thus a higher temperature is not favorable for the replacement of proton from the carboxylic group of these ligands. The values of metal–ligand stability constant log k_1 decrease with an increase in temperature. Thus a higher temperature is not favorable for the complex formation in these systems.

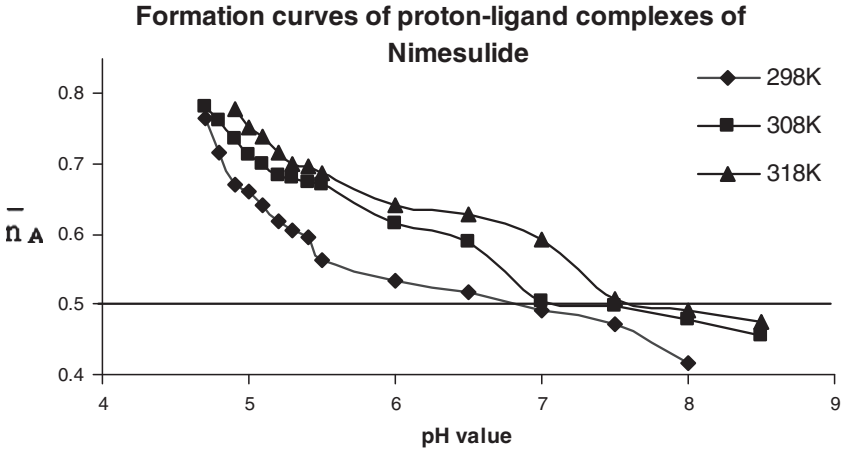

Fig. 1. Formation curves of proton–ligand complexes of nimesulide.