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Comparative study of stability constants and thermodynamic properties of complexation of Aspirin and Paracetamol with divalent metal ions by potentiometry

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ABSTRACT : The equilibrium constants for metal complex formation have been employed from long as an effective measure and parameter of the affinity of a ligand for a metal ion in solution. Potentiometry is one of the most convenient and successful technique employed for metal complex equilibrium measurements. Potentiometric measurement of hydrogen ion concentration may be employed when the degree of complex formation is sensitive to the hydrogen ion concentration thus the degree of complex formation undergoes increase/ decrease with change in pH. In the present work, we investigate the stability constants of Aspirin and Paracetamol complexes with Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Sn^{2+} and Pb^{2+}potentiometrically using pH metric technique in 50% v/v ethanol - water medium 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 method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to determine log K_1 values. The thermodynamic parameters ΔG, ΔH and ΔS are calculated. System tend to progress in the direction of increasing entropy as entropy is a measure of a system's tendency towards spontaneous change.

Keywords : Potentiometry, Stability constant, Thermodynamic parameters, Entropy.

INTRODUCTION

Aspirin; 2-(acetyloxy) benzoic acid;$C_9H_8O_4$;180.160 g/mol is a salicylate drug, often used an analgesic to relieve minor aches and pains, as an antipyretic to reduce fever and as an anti-inflammatory medication. It also has an antiplatelet or "anti-clotting" effect and is used in long term low doses to prevent heart attacks, strokes and blood clot formation in people at high risk for developing blood clots. Paracetamol; para-acetylaminophenol; $C_8H_9NO_2$; 151.169 g/ mol. Unlike aspirin it is not a very effective anti inflammatory agent. It is well tolerated, lacks many of the side effects of aspirin. Paracetamol is also useful in the management of more severe pain, where it allows lower dosages of additional non - steroidal anti-inflammatory drugs (NSAIDs) to be used, thereby minimizing overall side effects.It is considered safe for human use at recommended doses; however, acute overdose can cause potentially fatal liver damage.

There are many methods that can be employed for providing the information which reach to the determination of the concentration of at least-one of the species in equilibrium and analytical composition of experimental solution such as Paper Electrophoretic method, Potentiometry, High pressure liquid chromatography, spectrophotometry, Calorimetry, Polarography, Colorimetry, H-point standard addition method and other methods have been analysed and interpreted in detail [1-6]. It is well established fact that the simplest electroanalytical technique is potetiometric titration system using the glass electrode. Recently a number of studies have been reported on stability contants of ligands / acids of medicinal and environmental importance.

A very simple and selective spectrophotometric method for simultaneous kinetic determination of paracetamol and caffeine using H-point standard addition method (HPSAM) was described [7]. The proposed method was successfully applied to the simultaneous determination of paracetamol and caffeine in pharmaceutical samples and satisfactory results were obtained. Paracetamol is a sparingly soluble bitter tasting drug. It is widely used as an analgesic and antipyretic. Complexation of drug with different cyclodextrins was attempted to improve solubility of Paracetamol. During the drug excipient interaction studies, α, β cyclodextrins elicited analytical interference and showed considerable absorbance at λ max of (243.5 nm) of Paracetamol while the ones constituting of hydroxypropyl-beta-cyclodextrin (HP-β-CD) did not show any such interference [8]. Another paper reports the simultaneous determination of Paracetamol, Chlorzoxazone, and related impurities 4-Aminophenol, 4'-Chloroacetanilide, and p-Chlorophenol in pharmaceutical preparations by High- Performance Liquid Chromatography. The mobile phase consisted of water- methanol-glacial acetic acid (60 + 40 + 2, v/v/v) [9]. Fukushima *et al* carried out the determination of the Intrinsic Stability Constants of Toxic divalent metal ions to Alginic Acid [10]. Such a character has been utilized for removing toxic heavy-metal ions from waste water. The binary complexes of 5-amino-3, 5-dideoxy-D–glycero-D–galactononulosic acid (NANA), commonly called N-acetyl neuraminic acid, formed with biological metal ions such as Co(II) and Cu(II) and toxic metal ions such as Cd (II) and Pb (II) were investigated in aqueous solution by means of potentiometry, UV and NMR spectroscopy [11].

The presence of toxic metals in natural environments presents a potential health hazard for humans. Metal contaminants in these environments are usually tightly bound to colloidal particles and organic matter. This represents a major constraint to their removal using currently available in situ remediation technologies. Successful application of rhamnolipid in metal removal requires knowledge of the rhamnolipid-metal complexation reaction [12]. The pK_avalues of ligands and stability constants of the complexes with some hydroxamic acids : a comparative study of three different potentiometric methods was reported by Senthilnithy [13]. The data obtained by pH-metric method were analyzed by three standard methods namely, Bjerrum's method, Irving and Rossotti method, and Sarkar and Kruck method. Aectohydroxamic acid, $CH_3CONHOH$, forms highly stable complexes with vanadium (V) and vanadium (IV) in 1 : 1, 1 : 2 and 1 : 3 mole ratios [14]. The stability of these complexes can be determined in terms of thermodynamic parameters; ΔG, ΔH and ΔS . The preliminary data, obtained through pH titration at various temperatures, was processed and analyzed by the computer program. Another study on the stability constant of the transition metal complexes with some medicinally important compounds was reported by Chudhari [15]. The formation of bioligand complexes of some medicinal drugs with Co (II), Ni (II) and Cu (II) ions were investigated. The formation const. of Ranitidine Hydrochloride and 6-methoxy naphthaldehyde has been carried out pH metrically in aq. soln. at 30°C, at 0.1 M fixed ionic strength [15]. The stability consts. were deted. by using Calvin Bjerrum pH titrn. techniques as modified by lrving Rossotti.

Various biological aspects related to the absorption, transport, activity, biological transformations, toxicity and excretion of different biometals is extensively studied during the recent years [16-19]. Since some of the metal ions such as Lead and Copper are responsible for the epilepsy and neuropathic pain; these metal ions can also be metabolized with some drugs by forming complexes with them.

MATERIAL AND METHODS

The potentiometric titrations were carried out in a jacketed cell. Chemicals and ligand used were of analytical grade. Ligand solutions were prepared in twice distilled deionized, carbon dioxide free water. Metal salt solutions were prepared by dissolving the corresponding metal salt in twice distilled deionized water 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 pH meter was ± 0.01. 50% v/v ethanol-water medium is 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 (total volume 50 mL in each case) were prepared as follows : (*a*) 5.0 mL of 0.005 mol L^{-1} HNO_3 (*b*) 5.0 mL of 0.005 mol L^{-1} HNO_3 + 5.0 mL of 0.0025 mol L^{-1} ligand (*c*) 5.0 mL of 0.005 mol L^{-1} HNO_3 + 5.0 mL of 0.0025 mol L^{-1} Ligand + 5.0 mL of 0.005 mol L^{-1} metal ion solution.

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}). 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 (*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. In the present work, we investigate the stability constants of Aspirin and Paracetamol complexes with Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Sn^{2+} and Pb^{2+} potentiometrically using pH metric technique in 50% v/v ethanol-water medium 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 method of Calvin and Bjerrum [20,21] as adopted by Irving and Rossotti [22] has been employed to determine log *K* values.

CALCULATION OF $\overline{n_A}$, $\bar{n}$ AND *pL*

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

$$\overline{n_A} = Y + \frac{(V' - V'')(N + E^\circ)}{(V^\circ + V')T_{Lo}} \quad ...(1)$$

Where Y = number of replaceable hydrogen ion, V^o = total volume 50 ml, V' = volume of alkali used by acid V'' = Volume of alkali used by acid and ligand, N = concentration of alkali, E^o = total strength of acid, T_L^o = total concentration of ligand.

The proton ligand formation curves were obtained by plotting the degree of formation $\overline{n_A}$ of the proton complex against pH values, 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 and are summarized in Table 1.

The values of $\bar{n}$ (average number of ligand molecules attached per metal ion) were calculated using equation (2)

$$\bar{n} = \frac{(V''' - V'')(N + E^o)}{(V^o + V')\overline{n_A}\, T_{M^o}} \quad ...(2)$$

Where V''' = volume of alkali used for acid + ligand + metal ion, T_M^o = total concentration of the metal ion, rest of

term symbols are as given in equation (1). The free ligand exponent, pL was calculated using equation (3) as given below :

$$pL = \log_{10}\left[\frac{\sum \beta^{H_n}(1/\text{anti}\log\beta)^n}{T_L{}^o - \bar{n}T_M o}\cdot\frac{V^o + V'''}{V^o}\right] \quad ...(3)$$

The thermodynamic stability of a species is the measure of extent of its formation under a particular set of conditions. In the language of thermodynamics, the equilibrium constant of a reaction is the measure of the heat expelled from the reaction system and entropy change during the reaction. The entropy of a system is the measure of the amount of disorder. The greater the amount of disorder in the products of a reaction relative to the reactants, the greater will be the increase in entropy during the reaction and higher is the stability of products.

RESULT AND DISCUSSION

(*a*) Effect of pH : The titration curves indicate that the ligand curve is slightly shifted to the left of the acid titration curve at lower pH value. The shift is due to the interaction of proton with the ligand and then with the metal ion.

(*b*) Effect of Temperature : The perusal of data in Table 1 shows that the values of stability constants decreases with an increase in temperature. So the degree of dissociation of ligand increases with rise in temperature but there is decrease in the stability constants of the complexes of these metal ions with ligand with temperature. The degree of ionization also increases for a ligand with temperature. Paracetamol complexes have higher stability constants in comparison to Aspirin complexes with various metal ions.

(*c*) Order of stability : The order of metal-ligand stability constants (log *K*) has been found to be : $Cu^{2+} > Cd^{2+} > Co^{2+} \approx Ni^{2+} > Pb^{2+} > Zn^{2+} > Hg^{2+} \approx Sn^{2+}$. This order is in accordance with Irving-Williams order of stability.

(*d*) Thermodynamic functions : The values of free energies of formation of the complexes becomes more negative with increase in temperature. This shows that the complex formation is a spontaneous process and spontaneity increases with temperature. The ΔH values indicate the endothermic nature of complexation reaction and explains the effect of temperature on the values of formation constants.

Table 1 : Metal-ligand stability constants of complexes of Aspirin and Paracetamol at three different temperatures

Cation	Stability Constant	Temperatures			$-\Delta G$ (KJ mol^{-1}) = 2.303 R T log k			ΔH (KJmol^{-1})	ΔS (Jmol^{-1} deg^{-1})
		25° C	35° C	45° C	25° C	35° C	45° C	(At 35° C)	(At 35° C)
Co^{2+}	*D_1	2.55	2.51	2.47	14.543	14.795	15.032	– 7.02	25.2
	*D_2	2.97	2.95	2.91	16.938	17.388	17.709	– 3.52	45.0
Ni^{2+}	D_1	2.55	2.50	2.45	14.543	14.736	14.910	– 8.78	19.3
	D_2	2.94	2.91	2.9	16.767	17.152	17.649	– 5.27	38.5
Cu^{2+}	D_1	2.56	2.51	2.46	14.600	14.795	14.971	– 8.78	19.5
	D_2	3.06	3.03	3.01	17.451	17.860	18.318	– 5.27	40.8
Zn^{2+}	D_1	2.52	2.48	2.44	14.372	14.618	14.850	– 7.02	24.6
	D_2	2.86	2.81	2.8	16.310	16.563	17.040	– 8.78	25.2
Cd^{2+}	D_1	2.49	2.47	2.45	14.201	14.441	14.910	– 3.51	35.5
	D_2	2.86	2.81	2.8	16.310	16.563	17.040	– 8.78	25.2
Sn^{2+}	D_1	2.69	2.68	2.61	15.341	15.797	15.884	– 1.76	45.5
	D_2	2.75	2.7	2.65	15.683	15.915	16.127	– 8.78	23.1
Hg^{2+}	D_1	2.66	2.61	2.51	15.170	15.384	15.275	– 8.78	21.4
	D_2	2.76	2.7	2.7	15.740	15.915	16.431	– 10.54	17.4
Pb^{2+}	D_1	2.58	2.52	2.46	14.714	14.854	14.971	– 10.53	14.0
	D_2	2.85	2.8	2.76	16.253	16.504	16.797	– 8.78	25.0

D_1 = Aspirin; D_2 = Paracetamol

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