Proton-ligand stability constants of cefadroxil and stability constants of its metal complexes in aqueous-organic mixtures

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Abstract : Proton-ligand stability constants of cefadroxil and its metal-ligand stability constants with Cu^{2+}, Cd^{2+} and Co^{2+} ions were determined pH-metrically at 30 °C and ionic strength of 0.15 M KCl in aqueous, water-alcohol (75 : 25% v/v) and water-dioxane (75 : 25% v/v) mixtures. Cefadroxil formed 1 : 1 (ML) complexes with Cd^{2+} and Co^{2+} whereas 1 : 2 (ML_2) with Cu^{2+} in aqueous, water-alcohol (75 : 25% v/v) and water-dioxane (75 : 25% v/v) mixtures.

Keywords : Stability constants, cefadroxil, metal complex.

Cefadroxil is an essential pharmaceutical drug used in the treatment of many diseases and is active against many bacteria, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* (the cause of strep throat), *Moraxella catarrhalis*, *E. coli*, *Klebsiella* and *Proteus mirabilis*. The synthesis, characterization and electronic spectra of cefadroxil complexes of *d*-block elements have been reported[1]. Very little information is available on the determination of ionization constants of this drug. The pK_a values of cefadroxil have been determined by capillary electrophoresis and chromatographic techniques[2]. Due to its popular use in many pharmaceutical forms, the proton-ligand stability constants of cefadroxil as well as metal-ligand formation constants of its complexes with Cu^{2+}, Cd^{2+} and Co^{2+} ions in different aqueous-organic mixtures have been determined by pH-metric titration technique[3].

Results and discussion

Proton-ligand stability constants : Protonated cefadroxil (1) has three potentially ionizable protons. pK_{a1} (log K_3^H) corresponds to release of proton from carboxyl group, pK_{a2} (log K_2^H) corresponds to release of proton from NH_3^+ group, pK_{a3} (log K_1^H) corresponds to release of proton from hydroxyl group in each aqueous-organic mixture. The calculated $\bar{n}_H$ values are in the range of 0 to 3 for cefadroxil, thereby, indicating ionization of three protons. The pK_a values were calculated by various computational methods[3].

The values for the proton-ligand stability constants (log K_1^H, log K_2^H and log K_3^H) with error limits ±0.02
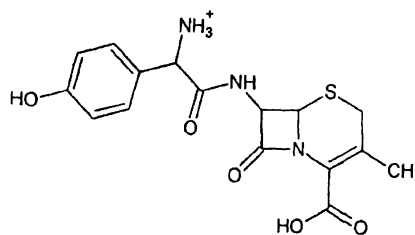
(1)

are given in Table 1. The dielectric constants (ε) of the three solvent systems used decrease in the order : water > water-alcohol > water-dioxane while the pK_a values in these three solvent systems follow the order : water-dioxane > water-alcohol > water. This suggests that the ionization is less favorable in aqueous-organic mixtures as compared to water only as expected. It should be noted that, as predicted by Born equation, the creation of charge in media of low dielectric constants is an unfavorable process and hence resulting in lesser dissociation that is, greater pK_a's values. Furthermore, for the same (v/v) composition, log K^H values in different solvent-water mixtures follows the sequence : water-dioxane > water-alcohol which may be explained on the basis of dielectric constant (ε) of the aqueous-organic mixture (water-dioxane ε = 66.07 and water-alcohol ε = 60.57).

Metal-cefadroxil stability constants :

The $\bar{n}_A$ values were found within the range 0-2 for Cu^{2+} in pH range 4.0-6.4 while within 0-1 for Cd^{2+} and Co^{2+} in pH range 4.0-5.6 and 4.5-5.0 respectively

Table 1. Proton-ligand constants (pK_a's) of cefadroxil and metal-ligand stability constants log K_1 (log K_2) of its complexes at 30 °C and ionic strength of 0.15 M KCl in aqueous-organic mixtures. The values in parentheses are log K_2 values

Medium Constants	Aqueous	Water-alcohol 75 : 25 (% v/v)	Water-dioxane 75 :: 25 (% v/v)
pK_{a3}	10.70	10.90	11.21
pK_{a2}	8.55	8.63	9.17
pK_{a1}	3.86	4.18	4.85
log K_1 (log K_2)			
Cu^{2+}	12.80 (10.68)	15.04 (12.65)	13.74 (10.05)
Cd^{2+}	11.96	14.43	16.48
Co^{2+}	11.78	13.86	15.88

in aqueous medium. In case of water-alcohol (75 : 25% v/v) medium, $\bar{n}_A$ values were found within 0–1 for Cd^{2+} and Co^{2+} in pH range 3.5–4.0 and 3.3–3.7 respectively and within 0–2 for Cu^{2+} in pH range 3.2–4.7. In case of water-dioxane (75 : 25% v/v) medium, $\bar{n}_A$ values were within 0–1 for Cd^{2+} and Co^{2+} in pH range 3.3–4.0 and 3.6–6.7 respectively while within 0–2 for Cu^{2+} in pH range 3.9–6.7. Based on log K_1 values the stability trend for various metal ions was found to be : $Cu^{2+} > Cd^{2+} > Co^{2+}$ in aqueous and water-alcohol medium and $Cd^{2+} > Co^{2+} > Cu^{2+}$ in water-dioxane mixture. The order of stability constants is largely determined by electrostatic effects but there are also the effects of the crystal field stabilization energy. Deviations from Irving-Williams stability order in water-dioxane mixtures may arise due to dipolar aprotic nature of dioxane and less electrostatic effects i.e. more covalent character of metal-ligand interactions[4].

The greater stability of metal-cefadroxil complexes (log K_1 values) in water-alcohol and water-dioxane medium as compared to aqueous medium suggests that coordinate bond formed between metal and cefadroxil has more covalent character in aqueous-organic mixtures. Cefadroxil and cephalexin differ only by a phenolic hydroxyl on the acyl chain of the former. Studies on related ligand cephalexin showed that metal ions interact with the amido group, side chain amino and carbonyl groups and as a monoanionic tridentate ligand[5]. Regarding mode of coordination of cefadroxil, infrared spectra proved the presence of M---N and M---O bonds[1]. However, these studies correspond to complexes in solid phase and mode of coordination of ligand may not be similar in solution studies.

Experimental

Cefadroxil ($C_{16}H_{17}F_2N_3O_3$.HCl, M.W. 387.8) was procured from M/s Sigma-Aldrich Chemical Co., St. Louis, MO, USA. All other reagents used were of AnalaR grade. A Digital pH meter Model 5652 A (Electronic Corporation of India Limited) with glass and calomel electrodes assembly, reading up to 0.01 units was used for measuring the pH of solutions prepared. Before starting the experiment, the pH meter was standardized with the help of buffer solutions of pH 4.0, 7.0 and 9.2. Calvin-Bjerrum pH titration technique as modified by Irving and Rossotti[3] was used for potentiometric determination of proton-ligand and metal-ligand stability constants. The experimental procedure involves three sets of solutions :

(i) 5×10^{-2} M HCl, (ii) [(i) + 5×10^{-3} M ligand] and (iii) [(ii) + 1×10^{-3} M metal ion solution] against standard carbonate free 0.095 N KOH in aqueous, 75 : 25 water-alcohol, 75 : 25 water-dioxane (% v/v) media.

All these titrations were performed at 30 °C and $I = 0.15$ M KCl. The pH meter readings in aqueous-organic mixtures were corrected[6]. From the shift in pH titration curves, values of $\bar{n}_H$, $\bar{n}_A$ and pL were obtained using the method of Irving and Rossotti and proton-ligand stability constants (log K_1^H, log K_2^H and log K_3^H) and metal-ligand stability constants (log K_1, log K_2) were obtained by various computational methods[3].

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