Protonation and Complex Formation of 5-Substituted Uracils with Cu(II) & Ni(II)

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Protonation constants of uracil, 5-methyluracil, 5-bromouracil and 5-nitrouracil and stability constants of their metal complexes in different aqueous media are reported here.

5- Halogenated uracils act as chemical mutagens and inhibit synthesis of protein and nucleic acids; consequently they are cancerostatic and anti-viral agents [1]. The protonation and complex formation equilibria of uracil and some 5-substituted uracils with some metal ions has been reported in aqueous solution only [2-4]; no such information is available in literature in mixed aqueous-organic solvents. The present study reports the protonation constant of uracil, 5-methyluracil, 5-bromouracil and 5-nitrouracil and stability constants of their metal complexes in aqueous, methanol-water, ethanol-water, isopropanol-water and dioxan-water mixtures.

EXPERIMENTAL

Uracil, 5-methyluracil, 5-bromouracil and 5-nitrouracil (Sigma) were used for this study. All other chemicals were of analytical grade. Glass distilled water was used for preparing solutions. The pH titration technique [5] was used to determine protonation constant of the ligands and stability constants of metal-ligand complexes. An ECIL digital pH meter (of accuracy ±0.01 pH units) with combined glass and calomel electrode assembly was used for titrations. The pH values in aqueous-organic solvents were corrected using the method of Van Uitert and Haas [6]. The following solutions

(A) 1×10^{-2} M HCl (acid solution)

(B) A + 10^{-3}M ligand (Ligand solution) and

(C) B + 2×10^{-3}M metal ion (Metal complex solution)

(20 ml each) were prepared in water, methanol-water (42.5:57.5), ethanol-water (51.8:48.2), isopropanol-water (58.6:41.4) and dioxan-water (61.2:38.8, %v/v) mixtures - ionic strength being maintained at 0.15 M with NaCl.

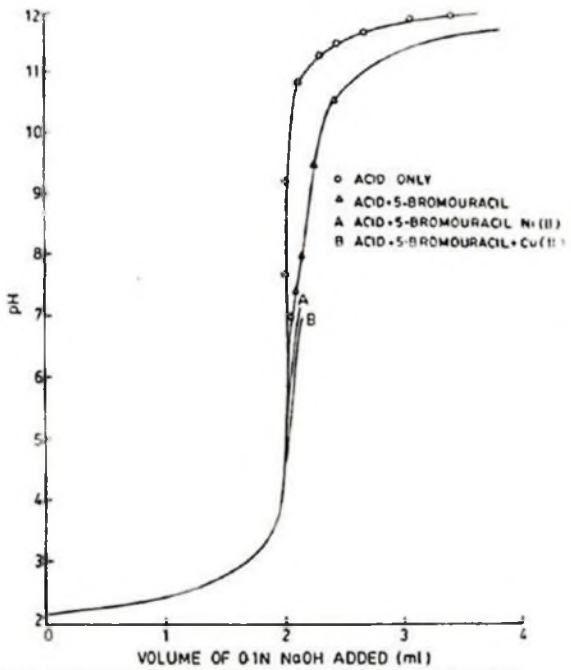


FIG 1 TITRATION CURVES FOR 5-BROMOURACIL, Cu(II)-5-BROMOURACIL, AND Ni(II) 5 BROMOURACIL IN WATER-METHANOL MEDIUM

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Each of these mixtures was separately titrated potentiometrically against 0.1N NaOH solution. The titration curves were drawn in each case. A typical plot for 5-bromouracil in methanol-water is shown in Fig.1. The values of $\bar{n}_A$, $\bar{n}$ and pL were calculated from the equations reported earlier [5]. The protonation constant (log K_1^H) has been determined from first two titrations using the relationship

$$\log K_1^H = pH + \log \frac{\bar{n}_A}{1 - \bar{n}_A}$$

Values of metal-ligand stability constants (log K_1 and log K_2) were obtained from plots of $\bar{n}$ vs pL, using the following equation reported earlier [5]:

$$\frac{\bar{n}}{(\bar{n} - 1)\,L} = \frac{(2 - \bar{n})\,L}{(\bar{n} - 1)} K_1K_2 - K_2$$

Table 1

Protonation Constants of Uracils and Metal Ligand Stability Constants of their Complexes in aqueous organic solvents

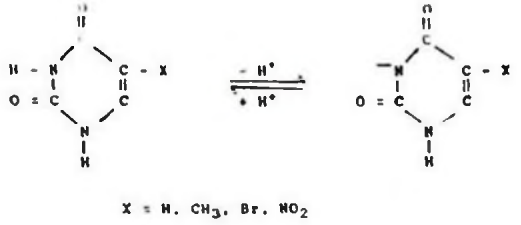
Mole fraction of Organic Solvent = 0.24 ; Ionic Strength 0.15 M NaCl; Temp. 17°C

Solvent (%v/v organic solvent)	H+ log K_1^H	Log values of Cu(II) K_1	K_2	ß	Log values of Ni(II) K_1	K_2	ß
Ligand: Unsubstituted Uracil							
Aqueous (Nil)	9.00	6.08	5.0	11.08	5.58	4.85	10.43
Aq. Methanol (42.5)	9.15	5.89	4.92	10.81	5.50	4.97	10.47
Aq. Ethanol (51.9)	9.15	6.48	5.57	12.05	5.96	5.76	11.72
Aq. i-Propanol (58.2)	10.00	7.20	6.64	13.84	6.60	6.23	12.83
Aq.Dioxan (61.2)	10.34	7.60	7.16	14.76	7.32	7.10	14.42
Ligand: 5-methyl Uracil							
Aqueous (Nil)	9.60	6.62	5.31	11.93	6.29	5.11	11.40
Aq. Methanol (42.5)	9.50	6.21	5.64	11.85	5.98	5.38	11.36
Aq. Ethanol (51.9)	9.51	6.30	5.14	11.44	6.01	4.95	10.96
Aq. i-Propanol (58.2)	9.54	6.80	6.15	12.95	6.07	5.57	11.64
Aq.Dioxan (61.2)	9.95	6.87	6.18	13.05	6.50	5.74	12.24
Ligand: 5-Bromo Uracil							
Aqueous (Nil)	7.47	5.38	4.68	10.06	5.17	4.61	9.78
Aq. Methanol (42.5)	7.78	4.54	4.46	9.00	5.07	4.54	9.61
Aq. Ethanol (51.9)	7.82	4.96	4.54	9.50	4.55	4.38	8.93
Aq. i-Propanol (58.2)	7.85	5.48	4.51	9.99	5.05	4.72	9.77
Aq.Dioxan (61.2)	8.47	5.62	4.82	10.44	5.14	4.52	9.66
Ligand: 5-nitro Uracil							
Aqueous (Nil)	6.07	4.43	3.85	8.28	4.14	3.63	7.77
Aq. Methanol (42.5)	6.15	4.40	3.95	8.35	4.13	3.61	7.74
Aq. Ethanol (51.9)	6.20	4.58	4.02	8.60	4.25	3.53	7.78
Aq. i-Propanol (58.2)	6.34	4.92	4.23	9.15	4.43	3.73	8.16
Aq.Dioxan (61.2)	6.54	5.12	4.35	9.47	4.54	3.33	7.87

RESULTS AND DISCUSSION

Acid dissociation

The values of n_A lie between 0 and 1 for each ligand in the pH range 5.5 - 12.0 which indicates only one ionizable proton as shown in the following equilibria.



X = H, CH_3, Br, NO_2

The log K_1^H value for various ligands in aqueous solution are presented in Table 1. The values are in close agreement with literature values [4]. The order is: 5-methyluracil > uracil > 5-bromouracil > 5-nitrouracil.

In general, log K_1^H is found to be larger with decrease in dielectric constant of the medium. As predicted by Born equation [7], the creation of charge in low dielectric constant media is an unfavourable process and hence the greater log K_1^H values.

Complex Formation

The values of formation function (n) lie between 0 and 2 in each metal-ligand system in all media. This indicates that all ligands formed complexes of stoichiometry 1:1 and 1:2 (metal:ligand) with both metal ions. Based on log β_2 (Table 1), the stability order Cu(II) > Ni(II) in aqueous and aqueous-organic mixtures was observed to be in accordance with Irving-William stability order [8]. The log β_2 values of complexes with different ligands in aqueous and methanol-water medium follow the sequence: 5 methyluracil > uracil > 5-bromouracil > 5-nitrouracil. This sequence is parallel to the increasing basicity of the ligand. However, in other aqueous-organic mixtures, the position of uracil and methyl uracil is reversed. The larger value of log K_1 and log K_2 in mixed solvents suggest that ion-ion interaction between the metal ion and the ligand intensifies to a greater extent than ion-depole interaction between metal ion and solvent.

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