Metal Complexes of Uridine in Solution

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The stability constants of binary and ternary complexes of Cu^{II}, Ni^{II}, Zn^{II}, Co^{II}, Mn^{II}, Mg^{II}, and Ca^{II} with uridine as a primary ligand and glycine, histidine, histamine, and oxalic acid as secondary ligands have been determined in aqueous medium by potentiometric pH-titration techniques [I = 0.10 mol dm^{-3} (KNO_3) at 35 °C]. In the binary systems the uridine acts as a bidentate ligand involving N(3) and O(4) in metal co-ordination. However, in the ternary systems studied it behaves as a unidentate ligand, bonding only through N(3). These observations are explained on the basis of the dependence of the binding of uridine on the pH of the reaction medium.

Nucleosides are nucleic bases linked to D-ribose or D-deoxyribose sugars. The glycosyl bond occurs between either the N(1) position of the pyrimidines or the N(9) position of the purines. Studies on metal–nucleoside interactions are gaining importance[1-13] because they provide indirect evidence for the base *versus* phosphate binding as they act as a link between purine and pyrimidine bases and nucleotides. Also, they facilitate a variety of approaches in solution, because of their high degree of solubility. In our earlier publications[14,15] we have reported the interaction of various metal ions, having different sizes and charges, with cytidine, the simplest examples of metal–nucleic base interactions; previous investigations on the binary complexes of uridine have revealed no detectable interactions with Cu^{II},[16,17] Zn^{II},[18,19] Cd^{II},[20] Hg^{II},[19-21] and Pt^{II}.[22,23] However, other studies indicated that mercury binds to uridine[24-26] and the interaction of Cu^{II}[27,28] and platinum[29] with uridine has been reported.

The preparation of solid complexes of uridine with Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II}, and Cd^{II} has also been reported.[30] However, ternary complexes of uridine have been confined to the preparation of solid Pt^{II} complexes with some amino acids.[11] Since preparation of solid complexes refers to a particular pH and there is high dependence of uridine complexes on pH, we decided to carry out a detailed physicochemical study on the ternary complexes of uridine in solution covering the pH range 4—9.5.

The metal ions (M) and the various secondary ligands (H_2A) used in this study are Cu^{II}, Ni^{II}, Zn^{II}, Co^{II}, Mn^{II}, Mg^{II}, and Ca^{II} and glycine, oxalic acid, histidine, and histamine. The stability constants of the binary uridine complexes are higher than the corresponding constants of cytidine complexes. The ternary complexes of uridine and cytidine are also compared to see the influence of donor atoms on the structure and stability of metal nucleoside complexes in solution. The structures of cytidine and uridine are given in Figure 1 along with the secondary ligands histidine and histamine.

Experimental

Uridine, glycine, histidine, and histamine were obtained from Sigma (U.S.A.) and oxalic acid from Fluka (Switzerland). For every titration, fresh solid ligand was weighed out into the reaction cell to avoid possible hydrolysis. Transition and alkaline-earth metal ions were of AnalaR grade and were standardised volumetrically by titration with the disodium salt of ethylenediaminetetra-acetic acid in the presence of a suitable indicator as outlined by Schwarzenbach.[31] Carbonate-free sodium hydroxide was prepared by the method of Schwarzenbach and Biedermann.[32]

The experimental method consisted of a potentiometric titration of metal–uridine and the secondary ligands glycine, histidine, histamine, or oxalic acid in a 1:1:1 ratio at 35 ± 0.1 °C with standard NaOH solution. The experimental conditions maintained were similar to those described in our previous work.[33]

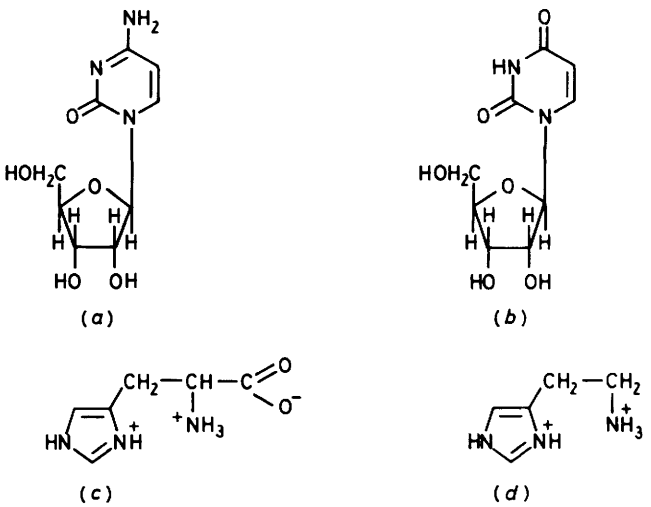

Figure 1. Structures of the primary ligands (*a*) cytidine and (*b*) uridine, and the secondary ligands (*c*) monoprotonated histidine and (*d*) diprotonated histamine

Results

Calculation of the Dissociation Constants.—The acid dissociation constants of the primary ligand uridine and the dibasic secondary ligands such as glycine, histidine, and histamine were calculated by the usual algebraic method. However, the oxalic acid dissociations were calculated by the graphical method.[34] The constants are presented in Table 1.

Calculation of the Stability Constants.—For the determination of stability constants for 1:1 metal–uridine complexes the following equations are used (charges are omitted for clarity), where k^{M}_{ML} = stability constant of 1:1 metal–uridine complex, T_M = total concentration of the metal ion species, [M] = concentration of unbound metal ion, and [L] = concentration of unbound ligand.

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Table 1. Acid dissociation constants of the ligands: 35 °C, I = 0.10 mol dm^{-3} (KNO_3)

Ligand	pK_a	pK_{2a}
Uridine	9.01 ± 0.02	
Glycine	2.50 ± 0.02	9.75 ± 0.02
Histidine	6.00 ± 0.04	9.00 ± 0.04
Histamine	5.87 ± 0.04	9.63 ± 0.04
Oxalic acid	2.18 ± 0.05	4.20 ± 0.05

$$M + HL \rightleftharpoons ML + H^+ \quad (1)$$

$$M + L \overset{K^M_{ML}}{\rightleftharpoons} ML \quad (2)$$

$$K^M_{ML} = \frac{T_M - [M]}{[M][L]} \quad (3)$$

To calculate the stability constants of the ternary complexes of Ni^{II}, Zn^{II}, Co^{II}, Mn^{II}, Mg^{II}, and Ca^{II} with uridine and the secondary ligand glycine in a 1:1:1 ratio equations (4)—(9) were employed (charges are omitted for clarity) in the buffer region between m = 0 and m = 1 (m = moles of base added per mole of metal ion). In the buffer region between m = 1 and m = 3, equations (7)—(9) are used. For equations (4)—(9), HL = uridine, H_2A = glycine, T_M = total concentration of metal ion species, M(HA) = 1:1 metal–glycinate(1−) complex.

$$M + H_2A \rightleftharpoons M(HA) + H^+ \quad (4)$$

$$M + HA \overset{K^M_{M(HA)}}{\rightleftharpoons} M(HA) \quad (5)$$

$$K^M_{M(HA)} = \frac{T_M - [M]}{[M][HA]} \quad (6)$$

$$M(HA) + HL \rightleftharpoons MLA + 2H^+ \quad (7)$$

$$M + L + A \overset{K^{M(HA)}_{MLA}}{\rightleftharpoons} MLA \quad (8)$$

$$K^{M(HA)}_{MLA} = \frac{T_M - [M]}{[M][L][A]} \quad (9)$$

Equations (4)—(9) were also employed to calculate the stability constants of the ternary complexes of Mn^{II}, Mg^{II}, and Ca^{II} with uridine and histidine and the ternary complexes of Mn^{II}, Mg^{II}, and Ca^{II} with uridine and histamine in a 1:1:1 ratio.

In the case of the ternary complex of Cu^{II} with uridine and glycine in a 1:1:1 ratio, equations (10)—(13) were employed, where MA = Cu^{II}–glycinate(2−) 1:1 complex and HL = uridine.

$$M + H_2A \rightleftharpoons MA + 2H^+ \quad (10)$$

$$MA + HL \overset{K^{MA}_{MLA}}{\rightleftharpoons} MLA + H^+ \quad (11)$$

$$MA + L \overset{K^{MA}_{MLA}}{\rightleftharpoons} MLA \quad (12)$$

$$K^{MA}_{MLA} = \frac{T_M - [M]}{[MA][L]} \quad (13)$$

It is assumed that in the buffer region between m = 0 and m = 2 a simple 1:1 Cu^{II}–glycine complex is formed and in the buffer region between m = 2 and m = 3 the ternary complex is formed.

Equations (10)—(13) were also employed to calculate the stability constants of the ternary complexes of Cu^{II}, Ni^{II}, Zn^{II}, and Co^{II} with uridine and histidine and the ternary complexes of Cu^{II} and Ni^{II} with uridine and histamine, and also the ternary complexes of Cu^{II}, Ni^{II}, Zn^{II}, Co^{II}, Mn^{II}, Mg^{II}, and Ca^{II} with uridine and oxalic acid in 1:1:1 ratio.

All the calculations were done by Casio PB 100 personal computer with suitable programs. The proton dissociation constants of the ligands uridine, glycine, histidine, histamine, and oxalic acid are presented in Table 1.

Table 2. Stability constants* of the binary and ternary complexes of uridine (HL) with glycine (H_2A) and oxalic acid (H_2A): 35 °C, I = 0.10 mol dm^{-3} (KNO_3)

Metal ion (M)	Metal–uridine (1:1) K^M_{ML}	Metal–uridine–glycine (1:1:1) K^M_{MLA}	$K^M_{M(HA)}$	$K^{M(HA)}_{MLA}$	Metal–uridine–oxalic acid (1:1:1) K^{MA}_{MLA}
Cu^{II}	5.90	5.10			5.21
Ni^{II}	3.57		2.59	11.47	3.38
Zn^{II}	4.75		3.04	11.05	4.28
Co^{II}	3.43		2.26	9.76	3.22
Mn^{II}	3.20		3.41	9.00	2.95
Mg^{II}	2.71		2.67	8.13	2.57
Ca^{II}	2.62		2.39	8.30	2.48

* Standard deviations (between ± 0.02 and ± 0.04 log K units) are omitted for clarity.

The Metal–Uridine (1:1) *System.*—Except for Ca^{II} and Mg^{II}, for all the metal ions (Cu^{II}, Ni^{II}, Zn^{II}, Co^{II}, and Mn^{II}) precipitation appeared before m = 1. The formation of the 1:1 complex was assumed for all the metal ions studied and the corresponding formation constants K^M_{ML} were calculated using equation (3) by taking the experimental points before precipitation; the values are presented in Table 2.

The Metal–Uridine–Glycine (1:1:1) *System.*—The mixed-ligand titration curve of Cu^{II}–uridine–glycine given in Figure 2 shows an inflection at m = 2 indicating formation of a 1:1 Cu^{II}–glycine complex; this was confirmed by comparing the data with the Cu^{II}–glycine (1:1) system. The constant K^{MA}_{MLA} was calculated in the buffer region between m = 2 and m = 3 using equation (13) (m = moles of base added per mole of metal ion). The titration curve for all other metal ions resulted in an inflection at m = 1, indicating the formation of a metal–glycinate(1−) complex between the buffer region m = 0 and m = 1; the constant $K^M_{M(HA)}$ was calculated using equation (6). The constant $K^{M(HA)}_{MLA}$ was, however, calculated in the buffer region between m = 1 and m = 3 using equation (9). All the constants calculated in this way are presented in Table 2.

The Metal–Uridine–Histidine (1:1:1) *System.*—The mixed-ligand titration curve of Cu^{II} with uridine and histidine (1:1:1) shows an inflection at m = 2 (Figure 2) indicating the formation of a 1:1 Cu^{II}–histidine complex and this was confirmed by comparing data in this region with the 1:1 Cu^{II}-histidine system; the constant K^{MA}_{MLA} was calculated in the buffer region between m = 2 and m = 3 using equation (13). Similar trends were observed for Ni^{II}, Zn^{II}, and Co^{II}. The constants are presented in Table 3.

In the case of other metal ions (Mn^{II}, Mg^{II}, and Ca^{II}) an inflection was obtained at m = 1 indicating the formation of a metal–histidinate(1−) complex between m = 0 and m = 1. The constant $K^M_{M(HA)}$ was calculated using equation (6). The constant $K^{M(HA)}_{MLA}$ was calculated between m = 1 and m = 3 using equation (9). All the constants thus calculated are listed in Table 3.

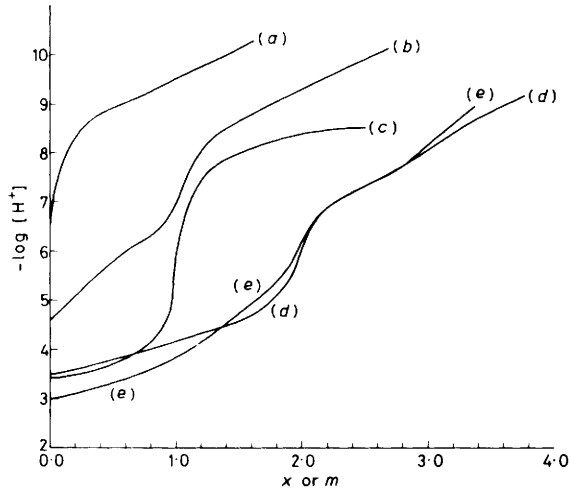

Figure 2. Potentiometric titrations curves for the Cu^{II}–uridine–glycine and Cu^{II} uridine histidine (1:1:1) systems at 35 °C, I = 0.10 mol dm^{-3} (KNO_3): (*a*) free uridine, (*b*) free histidine, (*c*) free glycine, (*d*) Cu^{II}–uridine–histidine, (*e*) Cu^{II}–uridine–glycine; m = moles of base added per mole of metal ion [curves (*d*) and (*e*)]; x moles of base added per mole of ligand [curves (*a*)—(*c*)]

The Metal–Uridine–Histamine (1:1:1) *System.*—This system is similar to the metal–uridine–histidine system, except for the Zn^{II} and Ni^{II} complexes with uridine and histamine where, after m = 2, precipitation occurs. The constants thus calculated are presented in Table 3.

The Metal–Uridine–Oxalic Acid (1:1:1) *System.*—In the oxalic acid system all the metal ions studied showed similar trends. The inflections in these cases were obtained at m = 2, indicating the formation of a simple 1:1 metal–oxalic acid complex. This was confirmed by the mathematical treatment of the data in this region (between m = 0 and m = 2) and comparing it with a 1:1 metal-oxalic acid system. However, after m = 2 the formation of a MLA complex was assumed and the constants were calculated using equation (13) and are presented in Table 2.

Discussion

The stability constants pertaining to the interaction of uridine with Cu^{II}, Ni^{II}, Zn^{II}, Co^{II}, Mn^{II}, Mg^{II}, and Ca^{II} in a (1:1) ratio are presented in Table 2. These constants decrease in the order $Zn^{II} < Cu^{II} > Ni^{II} > Co^{II} > Mn^{II} > Mg^{II} > Ca^{II}$ which is the Irving–Williams order of stability. Uridine is unique among the nucleosides in the sense that its metal-binding capacity depends on the pH of the reacting media. In acidic medium it co-ordinates with the metals through O(4)[35] and in slightly basic medium through N(3).[36] The metal–uridine complexes are more stable than the metal–cytidine complexes.[10] The higher stability of uridine may be due to the presence of an additional donor group, O(4), which may be involved in metal co-ordination in addition to N(3). Here it is worth mentioning the results obtained in the case of uracil. It was shown that uracil acts as a bidentate ligand, co-ordinating through N(3) and O(2).[37] However, in uridine, due to the presence of a large sugar residue on N(1), the probability of O(2) co-ordination can be ruled out based on steric reasons; this leaves O(4) as an obvious choice for the metal. Atom O(4) acting as a prime co-ordination site in uridine was also shown by spectroscopic studies.[30] The experimental pH range of the systems under investigation also supports this conclusion [uridine acting as a bidentate ligand involving N(3) and O(4) in metal bonding].

Table 3. Stability constants* of the binary and ternary complexes of uridine (HL) with histidine (H_2A) and histamine (H_2A): 35 °C, I = 0.10 mol dm^{-3} (KNO_3)

Metal ion (M)	Metal–uridine–histidine (1:1:1) K^{MA}_{MLA}	$K^{MA}_{M(HA)}$	$K^{M(HA)}_{MLA}$	Metal–uridine–histamine (1:1:1) K^{MA}_{MLA}	$K^{M}_{M(HA)}$	$K^{M(HA)}_{MLA}$
Cu^{II}	5.15			5.07		
Ni^{II}	3.52			3.17		
Zn^{II}	4.00					
Co^{II}	3.09					
Mn^{II}		2.68	8.80		2.60	8.35
Mg^{II}		2.63	8.05		2.58	8.25
Ca^{II}		2.86	7.95		2.47	8.08

* Standard deviations (between ± 0.02 and ± 0.04 log K units), are omitted for clarity.

Table 4. Values of Δ log K for various metal–ligand systems in aqueous solution: 35 °C, I = 0.10 mol dm^{-3} (KNO_3)

Metal ion (M)	Metal–uridine–glycine (1:1:1)	Metal–uridine–histidine (1:1:1)	Metal–uridine–histamine (1:1:1)	Metal–uridine–oxalic acid (1:1:1)
Cu^{II}	−0.80	−0.75	−0.83	−0.69
Ni^{II}		−0.05	−0.40	−0.19
Zn^{II}		−0.75		−0.47
Co^{II}		−0.34		−0.21
Mn^{II}				−0.25
Mg^{II}				−0.14
Ca^{II}				−0.14

Data for the ternary complexes of uridine with glycine and oxalic acid and with histidine and histamine are compiled in Tables 2 and 3 respectively. In the ternary system there exists two types of complex: (*i*) complexes in which interligand interaction occurs and (*ii*) complexes in which there is no such interaction. These interligand interactions have been found to be most effective in enhancing the stability of the ternary complexes in solution along with other factors like solvent effects, nature of the metal ion, and geometry of the metal complex as a whole, for example. These interligand interactions become more important when the ligands participate in stacking interactions. However, it should be noted here that even this stacking interaction is neither automatic nor universal, but varies from ligand to ligand and from metal ion to metal ion.

The Δ log K values (the difference between overall 1:1:1 and 1:1 constants) are listed in Table 4. As can be seen from Table 4 the Δ log K values for the metal–glycine systems could not be computed as the required data are not available for both ternary and binary systems. The Δ log K values reported for the other systems show negative values. This trend is quite different from that observed for the corresponding complexes of cytidine, where Δ log K values are positive. This shows that the ternary complexes of uridine are less stabilised than the cytidine complexes. However, the magnitude of the stabilisation in the cytidine complexes is much higher.

The negative Δ log K values of uridine complexes suggest that the mode of bonding is different in the binary and ternary complexes. In the ternary complexes probably the uridine acts as a unidentate ligand, involving only N(3) in metal co-ordination. Similar observations were also made previously for 1:1:1[11] and 1:2[38] (using Pd) systems of uridine in the solid

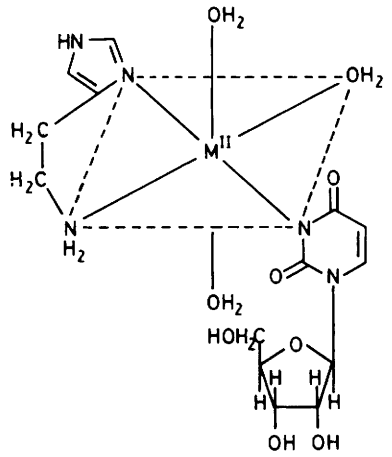

Figure 3. Tentative structure of the 1:1:1 metal–uridine–histamine system

state. Thus the negative values of Δ log K for the ternary complexes of uridine compared to cytidine may be due to the higher stability of its binary complexes and the reduced number of co-ordination sites. Based on this we propose the structure for the 1:1:1 metal–uridine–histamine complex shown in Figure 3.

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