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Interaction of thorium(IV) and dioxouranium(VI) with histidine, cysteine and guanosine-binary and ternary complexes in solution

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Interaction of thorium(IV) and dioxouranium(VI) with guanosine and aminoacids, viz., histidine and cysteine in a 1 : 1 and 1 : 1 : 1 ratios has been investigated at 35°C. Stabilities of various systems are evaluated by computer program. The *p*H profile of various species have also been generated in order to identify the stable species at biological *p*H. The results suggest involvement of N(7) in guanosine, ring nitrogen and thio group in histidine and cysteine respectively along with carboxylate group in metal coordination.

Metal ion interaction with nucleic acid constituents especially with guanosine derivatives has gained considerable importance during the last few years[1], because the best selling antitumor drug cis-platin has a special preference for guanine-N(7) over adenine N(7) and N(1). This has been attributed not only to intrinsic stronger basicity, but also hydrogen bonding. However, most of these interactions have been confined to transition metal ions and very little is known about the nature of other metal complexes. Studies on uranyl complexes with respect to glycine[2], amino acids[3] and EDTA[4] have been reported earlier. Complexes of thorium(IV) and dioxouranium(VI) with nucleic bases were reported previously[5]. In the present note the interaction of Th(IV) and dioxouranium(VI) with histidine, cysteine and guanosine has been investigated at 308°K in 1 : 1 and 1 : 1 : 1 ratios with an objective of identifying stable species both in binary and ternary systems in particular at biological *p*H.

Experimental

Histidine, cysteine and guanosine were obtained from Sigma Chemical Company, USA. For every titration, fresh solid ligand was weighed out into the reaction cell to avoid possible concentration effects. Stock solutions of analytically pure Th(IV) and UO_2(II) nitrates (BDH) were prepared and their concentrations determined by usual volumetric and gravimetric methods[6]. Carbonate free sodium hydroxide was prepared and standardized by titration with potassium acid phthalate. The experimental method consisted of potentiometric titration of the free ligands and solutions containing metal ion, guanosine and amino acids (histidine and cysteine) in 1 : 1 and 1 : 1 :1 ratios at 35°C. The ionic strength was maintained constant at 0.1 *M* using KNO_3 as the supporting electrolyte and relatively low concentrations of the reactants (1×10^{-3} *M*). Other experimental details can be found elsewhere[7].

Calculations

Calculations pertaining to various dissociation and association equilibria were performed by setting up appropriate material balanced equations as dictated by the experimental evidence.

For binary systems, the experimental evidences suggest involvement of only pK_a in the case of guanosine and both pK_a and pK_{2a} in the case of histidine and cysteine systems. Accordingly, the following material balanced equations were used to determine the binary constants (omitting charges).

Guanosine system :

$$M + H_2A \rightleftharpoons MHA + H^+ \quad \ldots (1)$$

$$M + HA \overset{K^M_{MHA}}{\rightleftharpoons} MHA \quad \ldots (2)$$

Histidine and cysteine system :

$$M + H_3L \rightleftharpoons MHL + 2H^+ \quad \ldots (3)$$

$$M + HL \overset{K^M_{MHL}}{\rightleftharpoons} NHL \quad \ldots (4)$$

In the case of ternary (five proton) systems, a solid phase appeared before an inflection point could be reached. Therefore, all possible species were assumed to generate the ternary constants. However, only a diprotonated species involving a proton from guanosine and two protons from histidine or cysteine gave constant values. Accordingly, the following equilibria (omitting charge were used.

$$M + H_2A + H_3L \rightleftharpoons M(HA)(HL) + 3H^+ \quad \ldots (5)$$

$$M + HA + HL \overset{K^M_{MH_2HL}}{\rightleftharpoons} MH_2AL \quad \ldots (6)$$

where M, H_2A and H_3L represent Th(IV) or UO_2(II), guanosine and histidine or cysteine respectively.

The ionization constants of various ligands were calculated using the computer program PKAS[8]. All the formation constants were subjected to refinement considering all possible species using computer program BEST[9].The constants are given in Table 1.

Results and discussion

The dissociation constants of various ligands are in good agreement with the literature values[4,10]. In binary systems, a precipitate invariably appeared before the inflection point could be reached ($a=2$). However, the calculations were performed taking experimental points well ahead of the precipitation points. The involvement of pK_a and pK_{2a} of amino acids in metal coordination is justified as there was no inflection at $a=1$, which is indicative of exclusive carboxylate coordination[3]. In the case of ternary systems, the titration curves corresponding to the dissociation of one proton from guanosine were calculated by Eq. (6). The constants for both binary and ternary systems are presented in Table 1.

It can be seen from the Table that thorium forms more stable complexes than uranium for the systems studied. Within the complexes of thorium, the cysteine system is more stable. Similar trends were observed in uranyl systems also. This is in accordance with the basicities of the ligands under investigation. This is further reflected in the $\Delta\log K$ values (Table 1) of the systems, the values being the difference between the stabilities of binary and ternary systems. The positive values of $\Delta\log K$ indicate that ternary complexes are more stable than the binary complexes, whereas negative values indicate that binary complexes are more stable than ternary complexes. However, the negative values do not preclude the formation of ternary complexes in solution. The $\Delta\log K$ values for both Th(IV) and dioxouranium(VI) systems suggest that the ternary complexes are more stable than their respective binary complexes. In fact, the *p*H profile of various species as generated by the computer programme[9], reveals that the ternary complexes are formed to the extent of ~ 80% (Fig. 1). This extra stabilization found in these systems is due to the cooperative effect of the ligands and the expanded coordination number of metal ions. The more stability of thorium complexes than that of the uranyl may be due to the charge differences of the central metal ions and also to the presence of oxygen atoms in latter

Table I—Formation constants* of thorium and uranium ions with various ligands in binary and ternary systems along with $\Delta\log K$ values
[Temp. = 35°C, $\mu = 0.1\ M(KNO_3)$]

Ligand		Binary systems (1 : 1) (Protonated constants)	
		Th(IV) log K	UO_2(II) log K
Guanosine	$pK_a = 2.47$ $pK_{2a} = 9.08$	3.40	3.10
Histidine	$pK_a = 2.43$ $pK_{2a} = 5.94$ $pK_{3a} = 8.83$	6.46	4.56
Cysteine	$pK_a = 2.38$ $pK_{2a} = 8.07$ $pK_{3a} = 9.94$	8.40	6.53

System	Ternary systems (1 : 1 :1) (Protonated constants) log K(1 : 1 :1)	$\Delta\log K$
Th(IV) : Gua : His	11.41	+1.55
Th(IV) : Gua : Cys	13.40	+1.60
UO_2(II) : Gua : His	10.31	+2.65
UO_2(II) : Gua : Cys	12.44	+2.81

*The constants are accurate upto ±0.04 units.

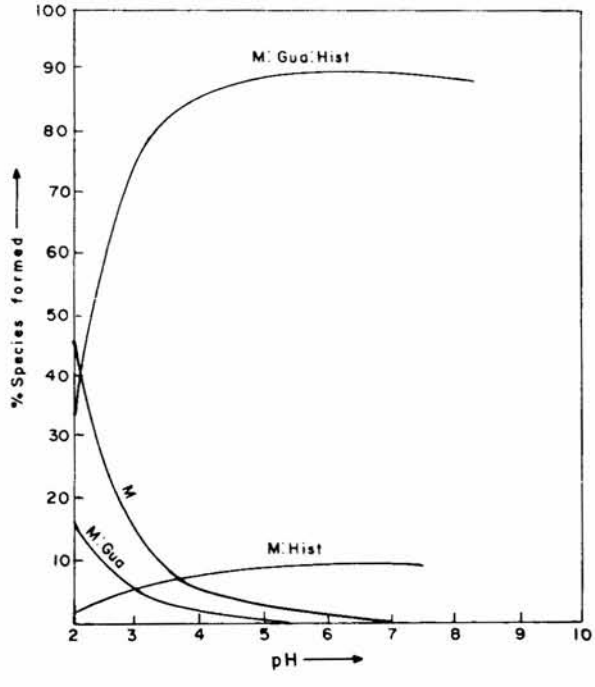

Fig. 1—Species distribution curve for Th(IV)-guanosine-histidine system

which may exert a steric influence on the participating ligands.

The data suggest the involvement of N(7) in guanosine, ring nitrogen and thio group in histidine and cysteine respectively along with carboxylate groups in metal coordination. These conclusions are justified as there was no evidence of deprotonation of amino protons from histidine and cysteine and N(I) proton of guanosine. Preliminary spectroscopic (UV) studies indicate a shift of ~7-10 nm in the λ_{max} in the ternary systems compared to free ligands. This confirms the involvement of N(7) in guanosine and ring nitrogen in histidine in metal coordination. The binding modes in the ternary systems where competitive biomolecules are involved may lead to a more comprehensive understanding of the reactions that occur in biological systems.

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