

**BINARY METAL COMPLEXES AND THERMODYNAMIC PARAMETERS
ASSOCIATED WITH THE INTERACTION OF THYMIDINE WITH BIVALENT
METAL ION**

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ABSTRACT

The stability constant of the binary 1:1 and 1:2 metal thymidine complexes have been determined from potentiometric titrations at 15°, 25°, 35° and 45°C and 0.1 M (KNO₃) ionic strength. The metal ions studied are Cu(II), Ni(II), Co(II), Zn(II), Mg(II) and Ca(II). The stability constants of 1:2 metal thymidine are lower than the corresponding 1:1 metal thymidine system. The $\Delta \log K$ for 1:2 metal thymidine are negative, as expected from statistical considerations. The enthalpy changes for 1:2 complex formation are less negative *i.e.* less exothermic than the corresponding 1:1 systems. The entropies are however more positive for 1:2 system. This is the normal trend for neutral ligands where the enthalpy is more favorable for 1:1 complexes (exothermic) as compared to 1:2 complexes.

INTRODUCTION

In some of the earlier papers we reported¹⁻³ the stability constants of the complexes of bivalent metal ions with purine and pyrimidine bases. Recent year much attention was given for the nucleoside complexes, because of the fact that metal ions participate in many biological processes. Attempts were made to understand the mode of interaction of metal ions with important molecules like DNA and RNA. In our laboratory much work was carried out on the interaction of nucleosides^{4,5,6} with metal ions in solution. Recently we reported the interaction of metal ions with Adenosine⁷.

In the present paper we report the formation constants of binary complexes of thymidine with bivalent metal ions at different temperatures. The small positive values of enthalpy compared to entropy are the contributing factors favouring the formation of 1:1 complexes in solution.

EXPERIMENTAL

The experimental method consisted of the potentiometric titration of ligand with standard sodium hydroxide in the absence and in the presence of metal ion being investigated. Titrations were carried out at 15°, 25°, 35° and 45°C and at a constant ionic strength of 0.01 M (KNO₃). Relatively low concentrations of ligand and metal ion were used. Presaturated CO₂ - free nitrogen was passed through the experimental solution, throughout each titration. A Digisun model DI-707 pH meter, with a Toshniwal combination glass electrode was used to determine hydrogen ion concentration. The electrode system was calibrated by direct titration with acetic acid and the pH meter reading observed was compared with the actual hydrogen ion concentration as calculated for the data tabulated by Harned and Owen. The pH regions below 3.5 and above 10.5 were calibrated by measurements in HCl and

NaOH solutions respectively.

Reagents :

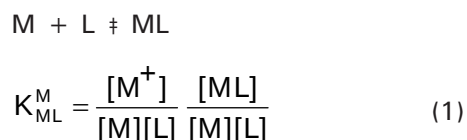
Chromatographically pure sample of thymidine was obtained from sigma chemical company, USA. The metal salt solutions were standardized by titration with the disodium salt of EDTA as described by schwarzenbach Carbonate free sodium hydroxide was prepared by the method of Schwarzenbach and Biedermann¹⁰ and was standardized by titration with pure potassium hydrogenphthalate. Fresh solid ligand was weighed for each titration to exclude the loss by hydrolysis or photochemical decomposition.

Calculations:

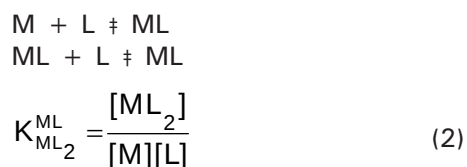
The acid dissociation constant for neutral thymidine is described by the equilibrium $HL \rightleftharpoons L^- + H^+$ by the equation.

$$K_a = [H^+] [(aT_L + [H^+] - [OH^-])] / [T_L - (aT_L + [H^+] - [OH^-])]$$

Stability constant of 1:1 and 1:2 metal ligand systems were calculated using the equation described in earlier papers^{12,13}. The equation involved in the formation of 1:1 metal-thymidine complex may be represented by



The equation involved in the formation of 1:2 metal thymidine may be represented by the following equations.



The values of ΔH_f° , ΔG_f° and ΔS_f° were

calculated by using the usual relationships as described in an earlier paper¹⁴.

RESULTS

Dissociation constant of thymidine. The potentiometric titration curve of thymidine did not show any inflection and the dissociation constants were calculated using eq (1) and are given in table (1) and the corresponding thermodynamic constants for the constant of thymidine are also given in table (1).

The potentiometric titration curves of free thymidine 1:1 Cu(II) thymidine, and 1:2 Co(II) thymidine at 15° are shown in figure (1) similar titration curves were obtained for all the other metal ions studied, at different temperatures. The stability constants of 1:1 and 1:2 metal thymidine and the corresponding thermodynamic parameters are given in table 2 and 3 respectively.

DISCUSSION

In neutral medium thymidine and thymine predominantly exists in diketo form. Thymidine is a weaker base as compared to thymine¹⁵, due to presence of diketo group and absence of N₁H. Taqui Khan *et al.*^{16,17} reported the proton ionisation is from N₃H position of thymine. In thymidine N₁H position is blocked by ribose moiety, so the proton ionisation site is N₃H position only.

The enthalpy change for the dissociation Pka of thymidine is exothermic by about 4.33 KCal/mole than thymine. The entropy is however more negative by about 14 eu than thymine. The exothermic enthalpy change this seems to be important to make thymidine less basic than thymine.

The stabilities of 1:1 metal thymidine decrease with decreasing temperature. The weak basicity of uridine is reflected in the lower stability of its metal complexes than that of the thymine. The stabilities of 1:1 metal thymidine decreases in the order Cu(II) > Zn(II) > Ni(II) > Co(II) > Mg(II) > Ca(II)

Table 1. Thermodynamic constants for ionisation reaction of ligands $\mu=0.1$ M (KNO₃)

Ligand	Reaction	ΔH° KCal/mole	ΔG° (25) KCal/mole	ΔS° (25) KCal/mole
Adenosine	$H_2L = HL + H^+$	+ 3.8	+ 5.1	- 4.0
Thymidine	$HL = L + H^+$	+ 8.9	+ 13.1	- 15.0
Uridine	$HL = L + H^+$	+ 5.9	+ 12.5	- 22.0

ΔH° values are accurate upto ± 0.2 KCal/mole

ΔS values are accurate upto ± 1 eu

Table 2. Stability constants for 1:1 and 1:2 metal-thymidine system,
 $\mu = 0.1$ M (KNO₃)

Metal ion	1:1 Metal-thymidine				1:2 Metal-thymidine			
	15°	25°	35°	45°	15°	25°	35°	45°
Cu(II)	6.09	6.18	6.28	6.36	5.90	6.01	6.12	6.19
Ni(II)	3.84	3.69	3.93	3.98	3.54	3.59	3.67	3.72
Co(II)	3.74	3.80	3.87	3.93	3.44	3.54	3.63	3.70
Zn(II)	5.19	5.28	5.39	5.50	4.75	4.85	4.93	5.02
Mg(II)	2.36	2.34	2.30	2.27	3.33	3.44	3.55	3.66
Co(II)	2.68	2.63	2.58	2.53	3.31	3.37	3.44	3.49

Values are accurate upto ± 0.05 log K units

Table 3. Thermodynamic parameters associated with the interaction of metal ion with thymidine in 1:1 and 1:2 metal thymidine ratio, $\mu = 0.10$ M (KNO₃)

Metal ion	1:1 Metal-thymidine			1:2 Metal-thymidine		
	ΔH° (KCal/mole)	ΔG° 25 (KCal/mole)	ΔS° 25 (eu)	ΔH° (KCal/mole)	ΔG° (25) (KCal/mole)	ΔS° (25) 25 (eu)
Cu(II)	+3.7	-8.44	+41	+4.1	-8.2	+41
Ni(II)	+2.0	-5.3	+24	+2.5	-4.9	+25
Co(II)	+2.6	-5.18	+26	+3.6	-4.83	+28
Zn(II)	+4.3	-7.19	+39	+4.1	-6.62	+36
Mg(II)	+4.4	-3.32	+26	+4.6	-4.68	+31
Co(II)	+2.1	-3.73	+20	+2.5	-4.58	+24

Table 4. $\Delta\Delta H$, $\Delta\Delta S$ values for Metal-thymidine system, $\mu = 0.1$ M (KNO_3)

Metal ion	$\Delta\Delta H$ (KCal/mole)	$\Delta\Delta S$ eu
Cu(II)	+0.3	–
Ni(II)	+0.6	+0.5
Co(II)	+1.0	+4.3
Zn(II)	+0.02	–1.91
Mg(II)	+0.70	+15.1
Co(II)	+0.4	+18.9

Table 5. $\Delta \log K$ values for 1:2 Metal-thymidine $\mu = 0.10$ M (KNO_3)

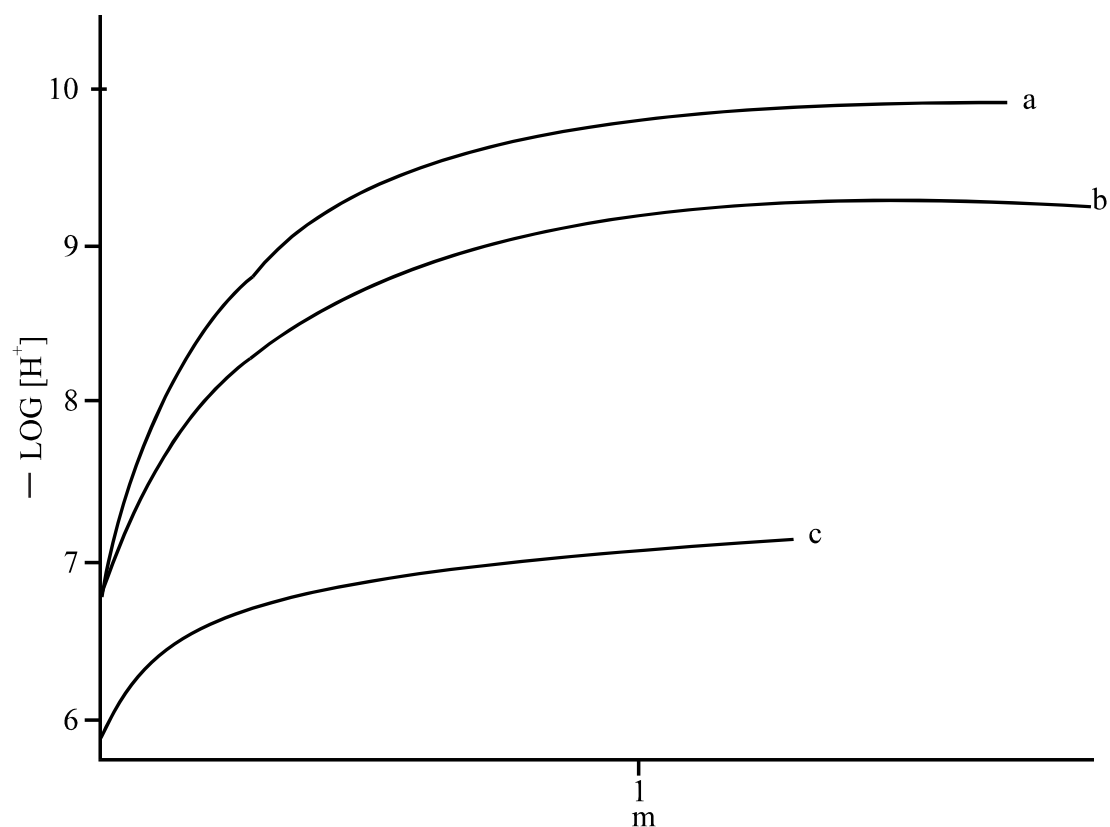
Metal ion	15°	25°	35°	45°
Cu(II)	-0.19	-0.17	-0.16	-0.17
Ni(II)	-0.30	-0.30	-0.26	-0.26
Co(II)	-0.30	-0.26	-0.24	-0.23
Zn(II)	-0.44	-0.43	-0.46	-0.46
Mg(II)	+0.77	+1.0	+1.01	+0.99
Co(II)	+0.63	+0.64	+0.66	+0.66

in according with Irving Williams order. The enthalpy changes for the 1:1 metal thymidine complexes are endothermic and the entropy changes value are positive. The enthalpy and entropy values are more positive than the corresponding metal-thymine systems similar trend was also observed in 1:1 metal uridine systems. In metal thymidine or uridine systems, the relatively small positive values of enthalpy compared with entropy, are contributing factors for the formation of 1:1 complexes in solution.

The stability constants for 1:2 metal thymidine are lower than the 1:1 metal thymidine systems. The $\Delta \log K$ is negative (Table 2) similar trend was also observed in metal uridine systems. The enthalpy change for 1:2 system are less negative than the

corresponding 1:1 system (Table 2). The entropies values are positive. The lower enthalpy coupled with positive entropy is responsible for the formation of 1 : 2 complexes. This is the normal trend in neutral ligands where the enthalpy is more favourable for 1:1 metal complexes as compared to 1:2 complexes.

The $\Delta \log K$ values vary with temperature however the quantities of fundamental importance are $\Delta\Delta H$, and $\Delta\Delta S$ ($\Delta\Delta H = H_2 - \Delta H_1$ where ΔH_2 and ΔH_1 , are the ΔH_f° of values 1:2 and 1:1 complexes respectively). The $\Delta\Delta H$ values for 1:2 complexes of thymidine are endothermic, given in Table 4. This indicates that there is lack of extra stabilization due to steric hinderance in the 1:2 metal thymidine systems. The $\Delta\Delta S$ values are



Potentiometric Titration Curves of Thymidine at 15°C, $\mu = 0.1$ M (KHO_3)
 in = moles of base added per mole of metal ion
 a) Thymide Free Ligand b) 1:2 Co(II)-Thymidine c) 1:1 Cu(II)-Thymidine

positive and negative indicating that there are solvation differences in the 1:2 and 1:1 metal thymidine systems and a similar trend was also

observed for thymine, uracil and uridine systems.

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