

Metal Chelates of Inosine & Thermodynamic Parameters of Complexation Reactions†

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Received 27 April 1982; revised and accepted 28 May 1983

Potentiometric equilibrium measurements have been made at 25°, 35° and 45°C for the complexation of anionic species of inosine with Cu(II), Ni(II), Zn(II), Co(II), Mn(II), Mg(II) and Ca(II) in 1:1 metal-ligand ratio at $\mu = 0.1 M$ (KNO₃). The stabilities follow the order: Mn(II) < Co(II) < Ni(II) < Cu(II) > Zn(II). The stability constants of Mg(II) and Ca(II) complexes could not be computed, as their titration curves overlapped with the free ligand titration curve. The enthalpy and entropy changes for the formation of normal chelates of inosine have been calculated from temperature coefficient data. The relatively small values of ΔH_f° coupled with large positive values of ΔS_f° provide evidence for the role of entropy as the primary factor influencing the formation of normal 1:1 metal chelates.

The title investigation is in continuation of our work on the complexation reactions of nucleosides^{1,2}. Christensen *et al.*³ and Albert⁴ have reported the dissociation constant of inosine at 25°C and partial stability constants of its chelates with Cu(II), Ni(II) and Co(II) at 20°C. Tu and Friederich⁵ have also reported on the interaction between Cu(II) and inosine. The present study has been carried out to determine the stability constants of normal chelate species of inosine with Cu(II), Ni(II), Zn(II), Co(II), Mn(II), Mg(II) and Ca(II) at 25°, 35° and 45°C. The corresponding thermodynamic quantities, ΔH_f° , ΔS_f° and ΔG_f° have been calculated from temperature coefficient data.

Chromatographically pure sample of inosine was obtained from Sigma Chemical Company, USA. The ligand solution was always prepared afresh for each titration to avoid hydrolysis. All transition and alkaline earth metal salts were of AR grade and their solutions in doubly distilled water were standardised volumetrically by titration with the disodium salt of EDTA in the presence of a suitable indicator as outlined by Schwarzenbach⁶. Carbonate-free sodium hydroxide was prepared and standardised by titration with potassium hydrogen phthalate. The experimental method employed was similar to the one described in our earlier publications^{1,2}.

For this investigation as well as for a large number of similar investigations in the literature, the standard state is defined as 0.10 *M* (KNO₃) solution, so that the activity coefficient of any species becomes unity when it is highly dilute in 0.10 *M* (KNO₃).

The acid dissociation constant (*K_a*) of neutral inosine and the stability constants (*K₁*) of 1:1 complexes, formed during the titration of 1:1 ligand-metal ion solutions were calculated with the help of the procedure previously described¹.

The values of ΔH_f° , ΔG_f° and ΔS_f° were calculated in a manner similar to those in our previous work².

Determination of *pK* values of inosine

The *pK_a* values of inosine at 25°, 35° and 45°C are found to be 8.75, 8.48 and 8.35 respectively. These values are comparable to *pK_a* = 8.98 (25°) obtained potentiometrically by Christensen *et al.*³. These authors obtained *pK_{2a}* = 12.35 at 25° colorimetrically. However, we could not obtain *pK_{2a}*, since the second dissociation from inosine occurred at high buffer region (*pH* = 12). The thermodynamic parameters

Table 1—Stability Constants of 1:1 Metal-Inosine Systems and Corresponding Thermodynamic Parameters

	[$\mu = 0.1 M$ (KNO ₃)]				
	Cu(II)	Zn(II)	Ni(II)	Co(II)	Mn(II)
log <i>K</i> (25°)*	5.02	3.04	3.37	2.88	2.68
ΔH_f° (kJ mol ⁻¹)	-2.26 ± 0.17	-2.76 ± 0.29	-5.52 ± 0.29	-0.59 ± 0.13	-3.10 ± 0.17
ΔG_f° (25°) (kJ mol ⁻¹)	-28.66 ± 0.25	-19.50 ± 0.25	19.25 ± 0.25	-16.44 ± 0.25	-15.27 ± 0.25
ΔS_f° (25°) J mol ⁻¹ K ⁻¹)	+88.70 ± 0.84	+56.07 ± 1.26	+46.02 ± 1.26	+53.14 ± 0.84	+41.00 ± 0.84

*The constants are accurate to ±0.06 log *K* Unit.

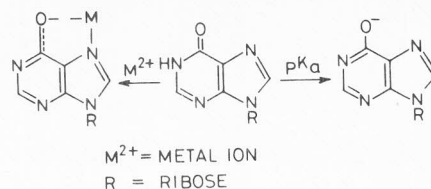
†Presented in part at the Annual Convention of Chemists, Madras, December 26-31, 1981.

ΔH_f^0 , ΔG_f^0 and ΔS_f^0 for the ionisation of inosine are 36.12, 50.11 and 46.62 respectively.

In the titrations of equimolar amounts of ligands and the metal ions against CO_3 -free NaOH , precipitates invariably appeared before the inflection points could be reached. The formation constants were, therefore, calculated from the experimental points taken over the $p\text{H}$ range far below the precipitation point employing the procedure outlined earlier¹. The formation constants, thus calculated are presented in Table 1. The formation constant values increase in the order: $\text{Mn(II)} < \text{Co(II)} < \text{Ni(II)} < \text{Cu(II)} > \text{Zn(II)}$, in accord with the Irving-Williams order. The thermodynamic parameters of metal chelate formation are also recorded in Table 1. The stability constants of Mg(II) and Ca(II) complexes would not be computed, as their titration curves overlapped with the free ligand titration curve.

The closeness of pK value of inosine (8.35) and hypoxanthine⁸ (8.40), may be due to the fact that in both the cases the proton ionization may be from the same site, $\text{N}^1\text{C}^6\text{O}$. The stability constants of normal 1:1 chelates of inosine are lower than those of inosine triphosphate⁹ and hypoxanthine⁸. This observation is in accord with the basicities of the ligands.

The enthalpy change for the dissociation of first proton of inosine and for the dissociation of second proton in xanthosine² is almost the same. This may be explained as follows: The delocalisation of uninegative charge over $\text{N}^1\text{N}^6\text{O}$ (three atoms) in inosine and two negative charges over $\text{N}^1\text{C}^6\text{OC}^2\text{ON}^3$ (six atoms) in xanthosine accounts for the same charge distribution effect per atom and thereby accounts for the same enthalpy change in the dissociation of first proton of inosine and second proton of xanthosine. However, there is difference in values of ΔS_f^0 , the entropy being 16.74 J/mol/deg more positive in uninegative inosine than in dinegative xanthosine. Thus the increased negative charge over xanthosine makes the ionization



Scheme 1

of the second proton weaker by an entropy effect. This is not so in the case of inosine.

The enthalpies for the 1:1 normal metal chelates of inosine are small and the corresponding entropy values are higher. The entropies of formation of normal 1:1 chelates of inosine with bivalent metal ions are roughly proportional to the reciprocal of the ionic radii of the metal ions, a trend that has been observed for a variety of ligands.

The relatively small values of ΔH_f^0 coupled with large positive values of ΔS_f^0 provide evidence for the role of entropy as the primary factor influencing the formation of normal metal chelate species in solution. The postulated sites of proton ionization and metal binding of inosine are shown in Scheme 1.

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