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A STUDY OF THE CHELATION BEHAVIOUR OF BIVALENT METAL COMPLEXES OF BIOLOGICALLY ACTIVE 2-HYDROXY-1,4-NAPHTHOQUINONE MONOXIME (HNQM) IN DIOXAN–WATER MIXTURES

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ABSTRACT

Equilibria between 2-hydroxy-1,4-naphthoquinone monoxime and proton or bivalent metal ions have been investigated potentiometrically at various ionic strengths and solvent compositions (dioxan : water). The method of Bjerrum and Calvin, as modified by Irving and Rossotti, was used to determine the values of $\bar{n}$ and pL. The stability constants were calculated using an IBM 360 computer, by the weighted least-squares method. The values of $S_{\min} = \chi^2$ were also calculated. The stability constants were found to decrease in the order.

Cu > Ni > Co > Zn > Pb > Cd > Mn > Mg

Other thermodynamic parameters and ligand field stabilization energies were calculated from the stability constants.

INTRODUCTION

Recently it has been found that metal chelates of *o*-hydroxy-naphthoquinone and its derivatives have increased therapeutic properties [1,2]. It has been suggested that the remarkable activity [2–4] of *o*-hydroxy-naphthoquinone and its derivatives might be due to a chelate compound formed as an intermediate. In consideration of the biological and analytical applications of 2-hydroxy-1,4-naphthoquinone monoxime and its metal chelates, the present study was undertaken to assess the stability and other thermodynamic properties of some bivalent metal chelates which could prove to have biological applications in the improved form.

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MATERIALS AND METHODS

Reagents

2-Hydroxy-1,4-naphthoquinone monoxime (HNQM) was prepared by the method of Goldstein and Grandjean [5]. A solution of HNQM was prepared using freshly distilled dioxan.

The solutions of bivalent metal ions were standardized by conventional methods.

Me_4NOH (TMAH) (E. Merck, A.G. Darmstadt) in 75% dioxan (aqueous) was used as titrant. The solution was standardized using oxalic acid. $HClO_4$ was standardized using prestandardized Na_2CO_3, and diluted to the required molarity (0.05 M) with double distilled water. $NaClO_4$ (Riedel) was used to maintain the ionic strength.

Dioxan, AnalaR, B.D.H., was purified by the method given by Vogel [6].

Apparatus

The pH measurements were taken using a digital pH-meter (ECIL, model PH 5651) in conjunction with a glass electrode. The pH-meter was standardized using potassium hydrogen phthalate and phosphate buffers before the titration was performed. All measurements were taken at a constant temperature maintained using an NBE-type (MLW, West Germany) thermostat. An IBM 360 computer was used for most of the calculations.

Titration technique

Investigations were carried out at various ionic strengths (0.2, 0.1, 0.05 and 0.01 M) and solvent compositions (75, 60 and 50%). For each set of experiments, the final volume was made up to 20 cm^3. Each set was titrated against 0.05 M TMAH. pH and volume correction factors were applied for each set of titrations.

The titrations were carried out in a covered double-walled glass cell in an atmosphere of nitrogen which had been presaturated with the solvent (dioxan in water) before being passed into the reaction solution.

RESULTS AND DISCUSSION

Order of stability constants

The stability constants of the metal complexes with HNQM were found to decrease in the order

$Cu > Ni > Co > Zn > Pb > Cd > Mn > Mg$

This order is in good agreement with that reported by Mellor and Maley [7] and Irving and Williams [8,9]. In all the systems, the values of log K_1 were greater than those of log K_2. The values of log K_1, log K_2, log β_2 and $S_{\min}$ obtained for the various ionic strengths and solvent compositions are given in Tables 1–6.

The regularity of this stability sequence can be correlated with a monotonic decrease in the ionic radii and a monotonic increase in the second ionization potential, which, in passing from Mn to Cu, can be taken to indicate either that coordination does not alter the electronic ground state of the metal ions, or that any modifications are of secondary importance. Values of $\bar{n}$ greater than 2.0 were not obtained for these chelates. We therefore conclude that not more than two chelates (1 : 1 and 1 : 2 (M : L)) are formed in each system.

Effect of ionic strength

In the present study, it was observed that the values of the dissociation constant of the ligand pK_a and the stability constant decrease with increasing ionic strength of the medium, which is in agreement with the Debye–Hückel equation [10]. Thermodynamic stability constants were obtained by extrapolating the straight line plot of log K_1 vs. $\sqrt{\mu}$ to zero ionic strength.

Thermodynamic parameters

Values of enthalpies, free energies and ligand field stabilization energies, respectively, were found to be ordered (Table 7)

Mn < Co < Ni < Cu > Zn
Mn < Co < Ni < Cu > Zn
Co < Ni < Cu

Solvent effects on the stability constants

The dissociation constant pK_a and the stability constants of the metal complexes in various concentrations of organic solvent (dioxan) are given in Tables 2, 5 and 6. The dielectric constant of the medium was changed by varying the percentage of the organic component of the medium. From Tables 2, 5 and 6 it can be seen that pK_a increases with increasing percentage of organic solvent of the medium. Further, the orders of the values of log β_1 and log β_2 become almost identical. Similar findings have been reported by Shin-ichi Ishiguro et al. [11], who have observed that the formation constants of nickel(II)–ethylene diamine complexes increase with increasing dioxan content in the solvents. Gergely and Kiss [12] have noted

TABLE 1

Stability constants of bivalent metal complexes with HNQM in 75% (v/v) dioxan–water media at $\mu = 0.2$ M $NaClO_4$ and $T = 20 \pm 0.5\,^{\circ}C$

Metal ion	Weighted least-squares method			S_{min}
	$\log K_1$	$\log K_2$	$\log \beta_2$	
H^+	5.00	–	–	–
Cu(II)	4.52	4.29	8.81	0.0225
Ni(II)	4.19	4.00	8.19	0.0249
Co(II)	3.99	3.86	7.85	0.0194
Zn(II)	3.24	2.45	5.69	0.0004
Pb(II)	3.17	2.43	5.60	0.0003
Cd(II)	2.86	2.11	4.97	0.0000
Mn(II)	2.54	2.04	4.58	0.0000
Mg(II)	2.48	1.65	4.13	0.0000

TABLE 2

Stability constants of bivalent metal complexes with HNQM in 75% (v/v) dioxan–water media at $\mu = 0.1$ M $NaClO_4$ and $T = 20 \pm 0.5\,^{\circ}C$

Metal ion	Weighted least-squares method			S_{min}
	$\log K_1$	$\log K_2$	$\log \beta_2$	
H^+	5.58	–	–	–
Cu(II)	4.71	4.48	9.19	0.0431
Ni(II)	4.36	4.31	8.67	0.0287
Co(II)	4.23	4.02	8.25	0.0060
Zn(II)	3.54	3.22	6.76	0.0069
Pb(II)	3.35	3.24	6.59	0.0028
Cd(II)	3.30	3.20	6.50	0.0026
Mn(II)	3.22	3.01	6.23	0.0016
Mg(II)	3.06	2.62	5.68	0.0005

TABLE 3

Stability constants of bivalent metal complexes with HNQM in 75% (v/v) dioxan–water media at $\mu = 0.05$ M $NaClO_4$ and $T = 20 \pm 0.5\,^{\circ}C$

Metal ion	Weighted least-squares method			S_{min}
	$\log K_1$	$\log K_2$	$\log \beta_2$	
H^+	5.80	–	–	–
Cu(II)	5.31	5.01	10.32	0.0217
Ni(II)	5.11	4.78	9.89	0.0083
Co(II)	4.93	4.53	9.46	0.0110
Zn(II)	3.83	3.77	7.60	0.0126
Pb(II)	3.67	3.48	7.15	0.0112
Cd(II)	3.48	3.41	6.89	0.0045
Mn(II)	3.41	2.91	6.32	0.0002
Mg(II)	3.26	2.95	6.21	0.0012

TABLE 4

Stability constants of bivalent metal complexes with HNQM in 75% (v/v) dioxan–water media at $\mu = 0.01$ M $NaClO_4$ and $T = 20 \pm 0.5\,^\circ C$

Metal ion	Weighted least-squares method			S_{min}
	log K_1	log K_2	log β_2	
H^+	6.22	–	–	–
Cu(II)	5.59	5.24	10.83	0.0051
Ni(II)	5.38	4.83	10.21	0.0048
Co(II)	5.08	4.90	9.98	0.0049
Zn(II)	4.32	3.54	7.86	0.0223
Pb(II)	4.06	3.51	7.57	0.0184
Cd(II)	3.79	3.65	7.44	0.0010
Mn(II)	3.60	3.41	7.01	0.0032
Mg(II)	3.48	3.12	6.60	0.0031

TABLE 5

Stability constants of bivalent metal complexes with HNQM in 60% (v/v) dioxan–water media at $\mu = 0.1$ M $NaClO_4$ and $T = 30 \pm 0.5\,^\circ C$

Metal ion	Weighted least-squares method			S_{min}
	log K_1	log K_2	log β_2	
H^+	5.00	–	–	–
Cu(II)	3.99	3.59	7.58	0.0136
Ni(II)	3.84	3.27	7.11	0.0071
Co(II)	3.68	3.03	6.71	0.0017
Zn(II)	2.91	2.53	5.44	0.0007
Pb(II)	2.85	2.38	5.23	0.0003
Cd(II)	2.81	2.21	5.02	0.0001
Mn(II)	2.66	2.29	4.95	0.0001
Mg(II)	2.40	2.14	4.54	0.0000

TABLE 6

Stability constants of bivalent metal complexes with HNQM in 50% (v/v) dioxan–media at $\mu = 0.1$ M $NaClO_4$ and $T = 30 \pm 0.5\,^\circ C$

Metal ion	Weighted least-squares method			S_{min}
	log K_1	log K_2	log β_2	
H^+	4.82	–	–	–
Cu(II)	3.79	3.22	7.01	0.0036
Ni(II)	3.54	3.33	6.87	0.0096
Co(II)	3.31	3.14	6.45	0.0037
Zn(II)	2.54	2.47	5.01	0.0001
Pb(II)	2.47	2.33	4.80	0.0001
Cd(II)	2.47	2.23	4.70	0.0002
Mn(II)	2.39	2.06	4.45	0.0000
Mg(II)	2.14	1.77	3.91	0.0000

TABLE 7

E_r(Mn–Zn) and δH values for complexes of HNQM

Parameters [a]	Metal ions (kJ)				
	Mn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
$\log K_1^0$	3.75	5.40	5.65	5.85	4.55
ΔG (kJ)	20.96	30.16	31.54	32.67	25.39
ΔG_r (kJ)	–	9.20	10.58	11.71	4.43
ΔH_H (kJ)	–	179.91	259.40	263.59	196.64
ΔH_L (kJ)	–	189.11	269.99	275.30	201.08
$[(n-5)/5]E_r$	–	80.41	120.66	160.87	–
δH (kJ)	–	108.70	149.32	114.43	–

[a] ΔG: free energy change ($=2.303\ RT\ \log K_1^0$, where R, T and K_1^0 have the usual significance, and $T = 293$ K).

ΔG_r: change in heat content for the formation of the complex in solution.

ΔH_H: heat of hydration of the metal ion.

ΔH_L: heat of complexation referred to the metal ion in the gaseous and the ligand in the solution state.

n: number of electrons in the 3d orbital.

$[(n-5)/5]E_r$: lattice energy difference for Zn^{2+} and Mn^{2+} complexes.

δH: thermodynamic stabilization energy.

$\log K_1^0$: values employed for the above calculations were obtained by extrapolating the log K_1 vs. $\sqrt{\mu}$ straight line to zero ionic strength.

the same phenomenon in a study of the stability constants of copper and nickel complexes of alanine in dioxan–water and methanol–water media. The stability of complexes containing either an O–H or an O–M link increases with increasing organic content of the solvent [13–15], owing to the decrease in the dielectric constant of the bulk solvent. As the dielectric constant decreases, the ion–ion interaction involving the proton (or metal ion) and the anionic oxygen donor of the ligand increases to a greater extent than does the ion–dipole interaction between the proton (or metal ion) and the anionic oxygen donor of the ligand, which increases to a greater extent than does the ion–dipole interaction between the proton (or metal ion) and the solvent molecules. The observed increase in the stabilities may be due to the O–metal linkage being strongly affected.

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