Inorganica Chimica Acta, *135* (1987) 211–214

Stabilities of Bivalent Metal Complexes with Biologically Active 2-Hydroxy-1,4-naphthoquinone Monosemicarbazone (HNQS) in Dioxan–Water Mixtures

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(Received June 30, 1986; revised September 18, 1986)

Abstract

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

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

The other thermodynamic parameters and ligand field stabilitzation energies have been calculated from the stability constants.

Introduction

The semicarbazones and thiosemicarbazones of certain ketones and aldehydes have significant antimicrobial activities [2–6]. Domagk *et al.* [7] reported for the first time the antitubercular activities of metal semicarbazones and thiosemicarbazones. Since then a number of papers have appeared on the pharmacology of these compounds. The activity of semicarbazones is thought to be due to their power of chelation with traces of metal ions present in biological systems.

As part of an intensive study undertaken in our laboratory on the chelation behaviour of metal complexes of biologically active *o*-hydroxynaphthoquinone and its derivatives, we describe here potentiometric studies on the chelation behaviour of bivalent metal complexes of 2-hydroxy-1,4-naphthoquinone monosemicarbazone.

Experimental

Reagents

2-Hydroxy-1,4-naphthoquinone monosemicarbazone (HNQS) was prepared by dissolving the requisite amount of 2-hydroxy-1,4-naphthoquinone in a minimum amount of alcohol and adding to it an aqueous solution containing semicarbazide hydrochloride and an equal amount of anhydrous sodium acetate. The mixture was refluxed for one hour and the HNQS was precipitated by adding dilute hydrochloric acid. The HNQS thus obtained was recrystallised from ethanol. HNQS solution was prepared in freshly distilled 75% (*v*/*v*) dioxan. The solutions of bivalent metal ions were standardised by conventional methods. Me_4NOH(TMAH) (E. Merck, A. G., Darmstadt) in 75% dioxan (aqueous) was used as titrant. Its solution was standardised with oxalic acid. $HClO_4$ was standardised with standard 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 A.R. (B.D.H.) was purified by the method given by Vogel [8].

Apparatus

A digital pH meter (ECIL, model pH 5651) in conjunction with a glass electrode was used for pH measurements. The pH meter was standardised with potassium hydrogen phthalate and phosphate buffers before performing the titration. All measurements were made at a definite temperature maintained constant by using an MLW (F.R.G.) (NBE type) thermostat. An IBM 360 computer was used for most of the calculations.

Titration Technique

Investigations were carried out at different 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 TMAH. The titrations were carried out in a covered double-walled glass cell in an atmosphere of N_2, which was presaturated with the solvent (dioxan in H_2O), before being passed into the reaction solution.

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0020-1693/87/$3.50

Results and Discussion

Order of Stability Constants

The order of the stability constants of the metal complexes with HNQS is as follows:

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

The order is in good agreement with that found by Mellor and Maley [9] and Irving and Williams [10, 11]. In all the systems, the values of log $K_1 >$ log K_2. The log K_1, log K_2, log β_2 and S_{min} values at different ionic strengths and solvent compositions are given in Tables I–VI.

The results show that the stability of the metal chelates increases regularly from Mn to Cu and falls again at Zn. Furthermore, the stability order is independent of the ligand. Minor deviations can be predicted on theoretical grounds. The regularity of this stability sequence can be correlated with a monotonic decrease in the ionic radii, and a monotonic increase in the second ionisation potential which, in passing from Mn to Cu, may be taken to indicate that either coordination has not altered the electronic ground state of the metal ions or that any modifications are of secondary importance. $\bar{n}$ values greater than 2.0 have not been obtained for these chelates. We therefore conclude that not more than two chelates, *i.e.* 1:1 and 1:2 (M:L), are formed in each system.

TABLE I. Stability Constants of Bivalent Metal Complexes with HNQS in 75% (v/v) Dioxan–Water Media at μ = 0.2 M $NaClO_4$ and Temperature = 20 ± 0.5 °C

Metal ion	Weighted least-squares method			S_{min}
	log K_1	log K_2	log β_2	
H^+	7.00			
Cu(II)	4.80	4.63	9.43	0.0326
Pb(II)	4.74	4.21	8.95	0.0307
Zn(II)	4.25	3.17	7.42	0.0028
Ni(II)	4.07	2.66	6.73	0.0002
Co(II)	3.92	2.46	6.38	0.0001
Cd(II)	3.77	2.37	6.14	0.0002
Mn(II)	3.21	2.41	5.62	0.0000
Mg(II)	2.73	1.45	4.18	0.0000

TABLE II. Stability Constants of Bivalent Metal Complexes with HNQS in 75% (v/v) Dioxan–Water Media at μ = 0.1 M $NaClO_4$ and Temperature = 20 ± 0.5 °C

Metal ion	Weighted least-squares method			S_{min}
	log K_1	log K_2	log β_2	
H^+	7.56			
Cu(II)	5.68	5.00	10.68	0.0030
Pb(II)	5.27	4.67	9.94	0.0186
Zn(II)	4.82	3.75	8.57	0.0394
Ni(II)	4.55	3.74	8.29	0.0108
Co(II)	4.25	3.56	7.81	0.0080
Cd(II)	4.20	3.47	7.67	0.0315
Mn(II)	3.63	2.85	6.48	0.0000
Mg(II)	3.41	2.98	6.39	0.0137

TABLE III. Stability Constants of Bivalent Metal Complexes with HNQS in 75% (v/v) Dioxan–Water Media at μ = 0.05 M $NaClO_4$ and Temperature = 20 ± 0.5 °C

Metal ion	Weighted least-squares method			S_{min}
	log K_1	log K_2	log β_2	
H^+	8.00			
Cu(II)	6.17	6.08	12.25	0.0049
Pb(II)	5.98	5.50	11.48	0.0162
Zn(II)	5.62	5.36	10.98	0.0813
Ni(II)	4.93	4.68	9.61	0.0108
Co(II)	4.83	4.47	9.30	0.0213
Cd(II)	4.61	4.38	8.99	0.0252
Mn(II)	4.23	3.40	7.63	0.0117
Mg(II)	4.04	2.74	6.78	0.0081

TABLE IV. Stability Constants of Bivalent Metal Complexes with HNQS in 75% (v/v) Dioxan–Water Media at μ = 0.01 M $NaClO_4$ and Temperature = 20 ± 0.5 °C

Metal ion	Weighted least-squares method			S_{min}
	log K_1	log K_2	log β_2	
H^+	8.50			
Cu(II)	7.32	6.13	13.45	0.0036
Pb(II)	6.39	5.40	11.79	0.0820
Zn(II)	6.28	5.45	11.73	0.0102
Ni(II)	5.45	5.13	10.58	0.0232
Co(II)	5.36	4.95	10.31	0.0472
Cd(II)	5.24	4.78	10.02	0.0771
Mn(II)	4.97	4.27	9.24	0.0195
Mg(II)	4.79	3.78	8.57	0.0288

TABLE V. Stability Constants of Bivalent Metal Complexes with HNQS in 60% (v/v) Dioxan–Water Media at μ = 0.1 M $NaClO_4$ and Temperature = 30 ± 0.5 °C

Metal ion	Weighted least-squares method			S_{min}
	log K_1	log K_2	log β_2	
H^+	6.68			
Cu(II)	5.32	4.69	10.01	0.0014
Pb(II)	5.04	4.15	9.19	0.0013
Zn(II)	4.62	3.68	8.30	0.0055
Ni(II)	4.35	3.47	7.82	0.0022
Co(II)	3.92	3.41	7.33	0.0021
Cd(II)	3.76	3.26	7.02	0.0026
Mn(II)	3.51	2.96	6.47	0.0002
Mg(II)	3.12	1.84	4.96	0.0015

TABLE VI. Stability Constants of Bivalent Metal Complexes with HNQS in 50% (v/v) Dioxan–Water Media at $\mu = 0.1$ M $NaClO_4$ and Temperature = 30 ± 0.5 °C

Metal ion	Weighted least-squares method			S_{min}
	$\log K_1$	$\log K_2$	$\log \beta_2$	
H^+	6.40			
Cu(II)	5.13	4.23	9.36	0.0064
Pb(II)	4.16	3.57	7.73	0.0008
Zn(II)	3.52	2.93	6.45	0.0027
Ni(II)	3.37	2.68	6.05	0.0001
Co(II)	3.18	2.69	5.87	0.0002
Cd(II)	2.90	2.69	5.59	0.0001
Mn(II)	2.46	2.12	4.58	0.0000
Mg(II)	2.37	1.72	4.09	0.0000

Effect of Ionic Strength

In the present studies it has been observed that the value of the dissociation constant of the ligand (pK_a) and the stability constants decrease with increasing ionic strength of the medium (μ), which is in agreement with the Debye-Huckel equation [12]. Thermodynamic stability constants were obtained by extrapolating the straight line plot of $\log K_1$ *vs.* $\sqrt{\mu}$ to zero ionic strength.

Thermodynamic Parameters

Orders of enthalpies, free energies and ligand field stabilization energies (Table VII) have been found to be: Mn < Co < Ni < Cu > Zn; Mn < Co < Ni < Cu > Zn and Co < Ni > Cu, respectively.

TABLE VII. E_r(Mn–Zn) and δH Values for Complexes of HNQS

Parameters[a]	Metal ions				
	Mn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
$\log K_1{}^0$	5.40	5.70	5.80	8.00	6.75
ΔF	7.24	7.64	7.77	10.72	9.05
ΔF_r		0.40	0.53	3.48	1.81
ΔH_H		43.00	62.00	63.00	47.00
ΔH_L		43.40	62.53	66.48	48.81
$[(n-5)/5]E_r$		19.52	29.29	39.05	
δH		23.88	33.24	27.43	

[a] ΔF = free energy change = $2.303RT \log K_1{}^0$, where R, T and $K_1{}^0$ have the usual significance and the temperature = 293 K; ΔF_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 referring to the metal ion in the gaseous state and the ligand in solution; 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 used in the above calculations have been obtained by extrapolating the $\log K_1$ *vs.* $\sqrt{\mu}$ plot (straight line) to zero ionic strength.

Solvent Effects on the Stability Constants

The dissociation constant 'pK_a' and the stability constants of the metal complexes in various concentrations of an organic solvent (dioxan) are given in Tables II, V, VI. The dielectric constant of the medium was changed by varying the percentage of the organic component of the medium. It can be seen from Tables II, V, and VI that the pK_a value increases with an increase in the percentage of organic solvent in the medium. The values of $\log \beta_1$ and $\log \beta_2$ have also become similar. The same has been observed by Shin-ichi Ishiguro *et al.* [13]. They observed that values of the formation constants of the nickel(II)--ethylene diamine complexes increased with the dioxan content in the solvents. Gergely and Kiss [14] made similar observations while studying 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 [15–17], due to the decrease in the dielectric constant of the bulk solvents. 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 the ion–dipole interaction between the proton (or metal ion) and the solvent molecules. The observed increase in stabilities may be due to the O metal link being strongly affected.

Acknowledgement

One of the authors, R.K.S., thanks C.S.I.R., New Delhi, for the award of a Senior Research Fellowship.

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