Thermodynamic Studies of Complexation of Some Bivalent Transition Metal Ions with Piperidine-2-carboxylic Acid & 6-Methylpiperidine-2-carboxylic Acid in Aqueous Medium†

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The stability constants of chelates of piperidine-2-carboxylic acid and 6-methylpiperidine-2-carboxylic acid with Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) have been determined pH-metrically in aqueous medium at different temperatures and ionic strengths. Thermodynamic functions ΔG^+, ΔH^+ and ΔS^+ have been evaluated and separated into temperature-dependent (electrostatic) and temperature-independent (cratic or non-electrostatic) components and discussed in relation to the nature of bonding in these complexes. The effect of varying dielectric constant of the medium on stabilities has been investigated in the case of Cu(II) chelates.

Piperidine-2-carboxylic acids find wide applications in medicine and agriculture[1-3], and their activity is assumed to be due to the formation of chelated rings with metal ions. We report herein the stabilities and the thermodynamic parameters associated with the chelation of piperidine-2-carboxylic acid and 6-methyl piperidine-2-carboxylic acid with transition elements like Mn(II), Co(II), Ni(II) Cu(II) and Zn(II). The effects of variation of ionic strength and dielectric constant of the medium on the complex-formation equilibria have also been investigated.

Materials and Methods

Piperidine-2-carboxylic acid (Aldrich Chemicals, UK) was used as such. 6-Methylpiperidine-2-carboxylic acid was synthesized by the known procedure[4], and was used as the hydrochloride salt[5], which was repeatedly recrystallized from ethanol and its purity checked on the basis of IR spectrum, m.p. and neutralization equivalent. All the chemicals used were of A R/GR grade. The experimental procedure was the same as reported elsewhere[6].

The acid-dissociation constants of the ligands and metal-ligand formation constants were computed by the method of Irving-Rossotti[7]. Refined values of formation constants were obtained by the method of least squares.

Results and Discussion

The ligands, piperidine-2-carboxylic acid (P-2-CA) and 6-methylpiperidine-2-carboxylic acid (6-Me-P-2-

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CA) do not undergo hydrolysis under the present experimental conditions[6], as indicated by the rapid attainment of equilibrium during the titrations and by the absence of any significant drift in the pH even after 2 hr. The acid dissociation constant of piperidine-2-carboxylic acid determined presently is in good agreement with that reported by Von Peter Hermann and Karin Lemke[8]. There is a regular decrease in the acid dissociation constants of both P-2-CA and 6-Me-P-2-CA with rise in temperature. As expected from steric consideration the acid dissociation constant of 6-Me-P-2-CA is lower than that of P-2-CA.

The metal to ligand ratio was maintained at 1 : 5. At 30°C, Mn(II) formed only 1:1 complex with both the ligands whereas Co(II), Ni(II), Cu(II) and Zn(II) formed both 1:1 and 1:2 chelates with P-2-CA. The maximum value of $\bar{n}$ at each ionic strength for Co(II) and Ni(II) chelates of 6-Me-P-2-CA was around 0.7 and 0.9 respectively, before the pH of precipitation. This shows that only 1:1 complex is formed before the commencement of hydrolysis. However, Cu(II) and Zn(II) formed both mono- and bis-complexes.

The stabilities of the metal chelates (Table 1) with both the ligands studied are in the decreasing order: Cu(II) > Zn(II) > Ni(II) > Co(II) > Mn(II) which is in accordance with the Irving-Williams order. The decrease in stabilities of 6-Me-P-2-CA chelates as compared to those of P-2-CA chelates is due to steric hindrance by the methyl group in proximity with the donor nitrogen in 6-Me-P-2-CA. This is in general agreement with the results reported in literature[9,10].

The stabilities of picolinic acid and picolinic acid N-oxide have been reported by us elsewhere[11]. The thermodynamic formation constants of metal-ligand complexes of piperidine-2-carboxylic acid are higher

than those of picolinic acid. This is due to the fact that the lone pair of electrons on the pyridine nitrogen atom, due to conjugation, is accommodated in an orbital that has more s-character. The electrons are thus drawn closer to the nitrogen nucleus and held more tightly by it, thereby becoming less available for forming bonds. On the other hand in the case of P-2-CA the unshared pair of electrons on the nitrogen, with a sp^3-character, becomes more readily available for forming a bond with proton or a metal ion.

Effect of ionic strength

The proton-ligand and metal-ligand formation equilibria were studied at 30°C and at $\mu = 0.05$, 0.10, 0.15 and 0.20 M. The thermodynamic formation constants were obtained by extrapolation of the linear plots of $\log K$ versus $\sqrt{\mu}$ to $\mu = 0$. It was observed that the increase in ionic strength decreases the values of $\log K_1$ and $\log K_2$. On plotting $\log K_1$ and $\log K_2$ against $\sqrt{\mu}$, the slope values observed in all cases were less than the values expected on the basis of the Brønsted equation. This indicates that the reacting species are oppositely charged[12]. Also, the shapes of the formation curves were unaltered at different ionic strengths[13]. Both these observations suggest that the ligands interact in the dissociated as well as the undissociated forms and that the various species co-exist in solution.

Effect of temperature

Potentiometric titrations were carried out at 30°, 40° and 50°C at a constant ionic strength of 0.10 M. The values of the overall changes in free energy ($\Delta G^{\neq}$), enthalpy ($\Delta H^{\neq}$) and entropy ($\Delta S^{\neq}$) for the complexation reaction of Co(II), Ni(II), Cu(II) and Zn(II), given in Table 1, were calculated using the temperature coefficient and Gibbs-Helmholtz equations. Mn(II) complexes could not be studied at 40° and 50°C as precipitation occurred.

It is evident from the data that the stepwise and overall stability constants decrease with rise in temperature, indicating that the formation equilibria are exothermic in nature This is also borne out by the fact that $\Delta H^{\neq}$ and $\Delta G^{\neq}$ are both negative. The $\Delta S^{\neq}$ values are positive and relatively larger in magnitude as compared to $\Delta H^{\neq}$ values. Hence, the large entropy contribution is the major driving force for the metal-ligand coordination equilibria in aqueous solution. Williams[14] has pointed out that usually a high entropy value is associated with the combination of positive and negative ions. Combination of a metal ion with a negatively charged ligand always involves displacement of water molecules which then become part of the solvent. Since the water molecules bound to the metal ion are highly distorted and oriented, their entropy is

Table 1—Stability Constants of 1:1 Chelates of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) in Aqueous Medium and Thermodynamic Parameters of Corresponding Complexation Reactions*

[$\mu = 0.1 M$; temp. $= 30°C$]

Metal ion	Stability constant (± 0.05)	$-\Delta G^{\neq}$ kJ mol^{-1} (± 2.0)	$-\Delta H^{\neq}$ kJ mol^{-1} (± 8.0)	$\Delta S^{\neq}$ kJ mol^{-1}
Piperidine-2-carboxylic acid				
H$^+$	10.47	—	—	—
Mn(II)	4.03	23.4	—	—
Co(II)	4.8	27.8	64.4	117.4
	(4.0)	(23.2)	—	—
Ni(II)	5.47	31.7	152.0	397.5
	(4.57)	(26.5)	(71.8)	(149.5)
Cu(II)	7.49	43.5	69.3	85.6
	(6.1)	(35.4)	(160.6)	(413.3)
Zn(II)	5.86	33.9	71.0	122.2
	(5.58)	(32.3)	(33.8)	(4.7)
6-Methylpiperidine-2-carboxylic acid				
H$^+$	10.40	—	—	—
Mn(II)	3.90	22.6	—	—
Co(II)	4.65	26.9	28.5	5.1
Ni(II)	5.33	30.8	120.1	294.5
Cu(II)	6.76	39.2	88.3	162.1
	(5.75)	(33.4)	(177.5)	(475.8)
Zn(II)	5.79	33.6	60.8	89.8
	(5.54)	(32.1)	(33.3)	(3.8)

*Figures in the parentheses indicate the values of $\log K_2$ and the thermodynamic parameters for 1:2 complexes.

low. Thus, any process which releases water molecules from this type of strain results in increase in entropy. The very high values of entropy change for Ni(II) and Cu(II) chelate-forming reactions probably indicate that complete chelation extensively alters the solvation of the various species.

Degischer and Nancollas[15] have pointed out that for systems involving nitrogen and carboxylate oxygen, the $\Delta H^{\neq}$ values reflect the changes in the number and strengths of bonds made and broken during the reactions, and have correlated the values of $\Delta H^{\neq}$ to the type of bonding between the metal ion and the ligand molecules and to the structural features of the complex. Accordingly, we have separated $\Delta G^{\neq}$ and $\Delta H^{\neq}$ values into their electrostatic ($\Delta G_{el}^{\neq}$ and $\Delta H_{el}^{\neq}$) and non-electrostatic or cratic ($\Delta G_c^{\neq}$ and $\Delta H_c^{\neq}$) components, in order to get an insight into the nature of bonding in these complexes. The results are presented in Table 2. The $\Delta H_c^{\neq}$ values are significantly more negative than the corresponding $\Delta H_{el}^{\neq}$ values, suggesting that the nature of interaction between the metal ions and the ligands is largely covalent both in the mono- and bis-complexes[16]. The $\Delta H_c^{\neq}$ values vary in the order. Co(II) < Ni(II) > Cu(II) > Zn(II). This

Table 2—Electrostatic and Cratic Components of Thermodynamic Parameters of 1:1 and 1:2 Metal Chelates

[Values in $kJ\,mol^{-1}$; uncertainty $= \pm 2.0\,kJ\,mol^{-1}$]

Metal ion	1:1 Complex				1:2 Complex			
	$-\Delta G_e^{\ddagger}$	$\Delta H_e^{\ddagger}$	$\Delta G_c^{\ddagger}$	$-\Delta H_c^{\ddagger}$	$-\Delta G_e^{\ddagger}$	$\Delta H_e^{\ddagger}$	$\Delta G_c^{\ddagger}$	$-\Delta H_c^{\ddagger}$
	Piperidine-2-carboxylic Acid							
Co(II)	33.0	12.6	−4.9	76.0	—	—	—	—
Ni(II)	94.3	36.2	52.5	188.4	40.0	15.5	3.4	87.2
Cu(II)	26.1	9.9	−27.5	79.3	97.8	37.5	52.3	198.2
Zn(II)	34.1	13.1	−10.0	74.1	8.4	3.2	−34.1	37.0
	6-Methylpiperidine-2-carboxylic Acid							
Co(II)	8.4	3.2	−28.6	31.7	—	—	—	—
Ni(II)	71.8	27.5	30.8	157.7	—	—	—	—
Cu(II)	42.8	16.4	−6.5	104.7	111.5	42.8	68.0	220.3
Zn(II)	26.9	10.4	−16.7	71.2	8.1	3.1	−34.1	36.4

Table 3—Stability Constants of Cu(II) in Ethanol-Water Mixtures of Different Compositions

[$\mu = 0.1\,M$; temp. $= 30°C$]

Ethanol % (v/v)	Mol. fr	I/E	P-2-CA				6-Me-P-2-CA			
			pK	$\log K_1$	$\log K_2$	$\log \beta_2$	pK	$\log K_1$	$\log K_2$	$\log \beta_2$
30	0.116	0.016	10.532	8.470	7.090	15.560	10.652	6.810	5.700	12.510
40	0.169	0.0175	10.603	8.62	7.24	15.860	10.659	7.02	5.88	12.90
50	0.231	0.0194	10.687	8.78	7.44	16.22	10.692	7.28	6.10	13.38
60	0.318	0.0219	10.732	9.02	7.72	16.74	10.702	7.66	6.37	14.03
70	0.355	0.0263	10.762	9.37	8.13	17.50	10.742	8.28	6.88	15.16

probably indicates that the extent of ionic character of bonding in these metal chelates decreases along the series Co(II) > Ni(II) > Cu(II) < Zn(II).

Dependance of formation equilibria on solvent characteristics

The pK values of the ligands and the stability constants of Cu(II) chelates with P-2-CA and 6-Me-P-2-CA were determined in 30%, 40%, 50%, 60% and 70% (v/v) ethanol-water mixtures at 30°C and $\mu = 0.10\,M$ and the results are presented in Table 3. The data in Table 3 show that the proton-dissociation constants and the metal-ligand formation constants increase with increase in the percentage of organic solvent in the medium. The plots of $\log K_1$ and $\log K_2$ against the reciprocal of dielectric constant are linear upto 60% (v/v) ethanol in ethanol-water mixtures for both the ligands. Linear dependance of $\log K_1$ and $\log K_2$ is also seen with mol fraction of the solvent.

The change of $\log K$ with solvent composition may be explained with reference to the electrostatic and non-electrostatic effects. It is reported[17] that the non-electrostatic phenomenon becomes increasingly important in solvents containing greater than 50%

methanol. Addition of alcohol to solutions rich in water promotes *inter alia* breakdown of water-structure. The basic oxygen centres of the water molecules thus become increasingly available for participation in protolytic reactions with the solutes present[18]. This is consistent with the solvent effect of ethanol on the proton-ligand dissociation constant and Cu(II)-ligand formation constants as reported here.

Acknowledgement

References

1 Takahama K, Miyata T, Okano Y, Katoka M, Hitoshi T & Kase Y, *Euro J Pharmacol*, 81 (1982) 327.

2 Wilson Michael F & Bell Arthur E, *Phytochemistry*, 17 (1978) 403.

3 Adams C M & Bernays E A, *Entomol Exp Appl*, 23 (1978) 101.

4 Rubstov M V, Nikitskaya E S & Usovskaya U S, *J gen Chem*, 26 (1956) 129.

5 Donald Caddy E & James Utley H P, *J chem Soc, Perkin II*, (1973) 1258-62.

6 Kashiram & Ram Reddy M G, *Indian J Chem*, **20A** (1981) 1042.

7 Irving H & Rossotti H S, *J chem Soc*, (1953) 3397.

8 Von Peter Hermann & Karin Lemke, *Hoppe-Seyler's Z Physiol Chem Bd*, **349** (1968) 390.

9 Irving H & Rossotti H S, *J chem Soc*, (1954) 2910.

10 Holmes F & Crimmin W R C, *J chem Soc*, (1955) 1180.

11 Sudhaker Reddy M & Ram Reddy M G, *Indian J Chem*, **21A** (1982) 853.

12 Palaskar N G, Jahagirdar D V & Khanolkar D D, *J Indian chem Soc*, **52** (1975) 135.

13 Verma J K & Patel R B, *J Indian chem Soc*, **59** (1982) 44.

14 Williams R J P, *J phys Chem*, **58** (1954) 121.

15 Degischer C & Nancollas G H, *J chem Soc*, (A) (1970) 1125.

16 Narcollas G H, *Quart Rev*, **14** (1960) 402.

17 Braude E A & Stern E S, *J chem Soc*, (1948) 1976.

18 Paabo M, Bates R G & Robinson R A, *J phys Chem*, **70** (1966) 247.