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Studies on the Metal Complexes of Quinoxaline Derivatives. III.1) Metal Chelates of 2-Quinoxalinecarboxylic Acid and Its *N*-Oxides

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Spectrophotometric measurements were carried out for the stability constants of the divalent metal chelates of 2-quinoxalinecarboxylic acid and copper, nickel, cobalt and zinc in a 5% aqueous ethanol solution. Successive stability constants, log K_1, of the copper, nickel, cobalt and zinc chelates were 3.30, 2.87, 2.83 and 2.80, respectively. The metal complexes were difficult to dissolve in water. Copper and cadmium afforded both 1 : 1 and 2 : 1 complexes, while other divalent metals such as nickel, cobalt, manganese, zinc and lead resulted in the 2 : 1 complex formation. From the results of IR and Far-IR spectral analyses it was found that the carboxyl group and the ring nitrogen group appear simultaneously in the chelate formation. Copper complexes of 2-quinoxalinecarboxylic acid 1- and 4-oxides, as well as its 1,4-dioxide were also studied.

Dutt *et al.*2) attempted the use of 2-quinoxalinecarboxylic acid (2-QxCOOH) as a coprecipitant, since it forms water insoluble metal complexes with various divalent metals, as in the case of quinaldic acid. We reported3) on the polarographic behavior of quinoxaline derivatives including 2-QxCOOH, and gave hypothesis that among the quinoxaline derivatives studied, the 2-QxCOOH is merged to form structural metal chelate compounds. Syntheses of copper, nickel, cobalt and zinc chelates with 2-QxCOOH were attempted and the stability constants of the metal chelates were determined in a 5% aqueous ethanol solution spectrophotometrically. In order to find the binding site of the metals, cadmium, manganese and lead chelates were also synthesized. Copper complexes of 2-QxCOOH 1- and 4-oxides, and 1,4-dioxide were prepared and examined by IR and Far-IR spectral analyses.

Experimental

Apparatus. Measurements were carried out with a Hitachi EPS-3T spectrophotometer, a Hitachi Model 139 spectrophotometer, a Nihon Bunko IRA-2 infrared spectrophotometer, a Nihon Bunko DS-701G infrared spectrophotometer, a Shimadzu IR 450 infrared spectrophotometer and a Hitachi-Horiba M-5 pH meter.

Reagents. 2-Quinoxalinecarboxylic acid was synthesized according to the method of Maurer and Boettger4) and its *N*-oxides were prepared by Elina's method.5) The ligand were recrystallized from EtOH and identified by melting point and elemental analyses. The other reagents used were of reagent grade.

Syntheses of Metal Complexes. Two parts of 0.1 M 2-QxCOOH EtOH solution and one part of a 0.1 M metal acetate aqueous solution were mixed in a 2 : 1 ratio and then heated on a water bath. On being cooled, precipitates were separated and removed and washed first in water and then in hot EtOH. The complexes obtained were dried at 90 °C under reduced pressure, chelates in the ratio 2 : 1 being prepared.

Aqueous solution of metal chloride and 2-QxCOOH EtOH solution were mixed in a 10 : 1 molar ratio, the precipitates deposited were washed with water and dried at 70 °C under reduced pressure. The 1 : 1 chelates of Cu and Cd were thus prepared.

Similarly, a EtOH solution of copper chloride was added to the EtOH solution each of 2-QxCOOH 1-oxide, 4-oxide and 1,4-dioxide in a 2 : 1 molar ratio and then heated. The mixture on being cooled, gave Cu complexes with the ratio 2 : 1. Elemental analyses of the complexes are shown in Table 1.

Measurements of Stability Constants. One ml of the 2.0×10^{-3} M 2-QxCOOH EtOH solution, and 5 ml of aqueous $(2.4-8.0)\times10^{-2}$ M metal chloride solution of Cu, Ni, Co and Zn were mixed together. To this mixture was added a

Table 1. Elemental analyses of metal complexes

Formula	Analyses (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
(2-QxCOO)$_2$Cu·H$_2$O	50.53	2.82	13.09	50.72	2.54	12.94
2-QxCOO·CuCl·2H$_2$O	36.39	2.40	9.63	36.12	2.67	9.36
(2-QxCOO)$_2$Ni·2H$_2$O	49.02	3.19	12.70	48.93	3.35	12.76
(2-QxCOO)$_2$Co·2H$_2$O	48.99	3.19	12.70	48.77	3.06	12.79
(2-QxCOO)$_2$Zn·2H$_2$O	48.29	3.14	12.51	48.06	2.97	12.41
(2-QxCOO)$_2$Cd·2H$_2$O	43.70	2.93	11.28	43.70	2.85	11.32
2-QxCOO·CdCl·H$_2$O	31.50	2.04	8.07	31.34	2.22	8.01
(2-QxCOO)$_2$Mn·2H$_2$O	49.44	3.22	12.81	49.16	3.14	12.60
(2-QxCOO)$_2$Pb·H$_2$O	37.72	1.93	9.80	37.83	2.11	9.93
(2-QxCOO 1-oxide)$_2$Cu·2H$_2$O	45.05	3.36	11.68	45.23	3.39	11.79
(2-QxCOO 4-oxide)$_2$Cu	56.84	3.18	14.73	56.73	3.16	14.88
(2-QxCOO 1,4-dioxide)$_2$Cu·2H$_2$O	42.23	3.15	10.95	42.37	3.21	11.06

2 M KCl–HCl buffer of pH 1.40 to make the volume of the sample 20 ml. The absorptions were measured at each wavelength, and the ionic strength of the sample was kept at 0.1 with KCl. The measurements were carried out at 25 °C.

Results and Discussion

Stability Constants of Metal Chelates. A 5% aqueous ethanol solution of 2-QxCOOH shows a maximum absorption at 250 and 319.5 nm. However, the metal chelates have a maximum absorption at about 325 nm. The acid dissociation constant of the carboxylic acid group as measured by potentiometric method reported by Gum and Joullie[6] is 2.875. A spectrophotometric determination of the stability constants of the metal chelates was made according to the method of McConnell and Davidson.[7] When the divalent metal, M^{2+}, reacted with the ligand LH to give complex $L_nM_m^{2m-n}$, the stability constant $K_{m.n}$ is given as follows;

$$m\mathrm{M}^{2+} + n\mathrm{LH} \rightleftharpoons \mathrm{L}_n\mathrm{M}_m^{2m-n} + n\mathrm{H}^+$$

$$K_{m,n} = \frac{[\mathrm{L}_n\mathrm{M}_m^{2m-n}][\mathrm{H}^+]^n}{[\mathrm{M}^{2+}]^m[\mathrm{LH}]^n}$$

If the pH is maintained constant, the conditional stability constant, $K'_{m,n}$ is given by

$$K'_{m,n} = \frac{[\mathrm{L}_n\mathrm{M}_m^{2m-n}]}{[\mathrm{M}^{2+}]^m[\mathrm{LH}]^n}$$

When the total ligand concentration b remains constant and a total metal concentration a is added in very large excess of b, only one species, namely, the metal complex of $n=1$, can be taken into account, the linear relation falls between $b/(A-A_L)$ and $1/a^m$, where A and A_L are the total and ligand absorbances, respectively.

As an example, a 1 : 1 complex at pH 1.48 shows a straight line when $m=1$, and a curve when $m=2$. (Fig. 1).

Under these conditions, a 1 : 1 complex is usually the dominant form. The conditional stability constant, K', was calculated from the intercept and slope of the straight line, $b/(A-A_L)$ and $1/a$. From the $[H^+]$ and the dissociation constant, the successive stability constants log K_1 were obtained.

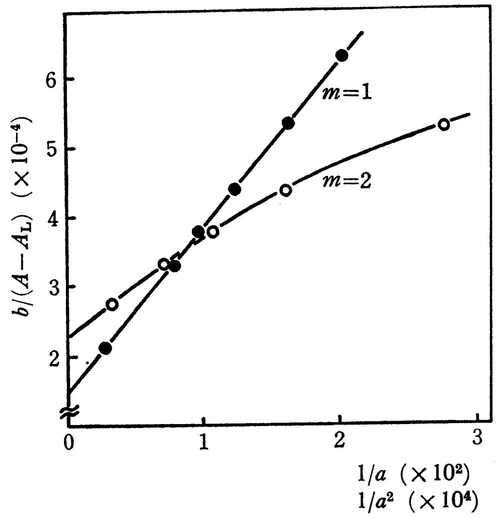

Fig. 1. Relationship between $b/(A-A_L)$ and $1/a^m$ of 2-QxCOOH-Cu complex at pH 1.48 in 5% aqueous EtOH.

The copper complex shows λ_{max} around 750 nm. Stability constants were determined using the method of Suzuki *et al.*[8] Table 2 gives a summary of the results obtained. In the case of the copper complex, the values measured in the ultraviolet region were recorded satisfactorily.

TABLE 2. STABILITY CONSTANTS OF 2-QxCOOH–METAL CHELATES

Metal	λ_{max}(nm)	Analytical wavelength (nm)	pH	log K_1
Cu	326	341	1.48	3.29
Cu		748	1.48	3.31
Ni	325.5	342	1.45	2.87
Co	325	342	1.48	2.83
Zn	325	340	1.41	2.80

The values found for the stability constants of nickel, cobalt and zinc were about the same, but the stability constant log K_2 could not be measured, since precipitation takes place when a ligand is added in excess.

IR Spectral Analyses. Measurements of IR spectra (4000—600 cm^{-1}) were made by means of the KBr disk method. The 2-QxCOOH shows two broad bands, one at 2423 and the other at 1875 cm^{-1}. These bands are also observed in a heterocyclic carboxylic acid, such as picolinic acid and pyrazinecarboxylic acid at the same reading. Yoshida and Asai[9] explain that the bands result from the hydrogen bond formation between the ring nitrogen and the carboxyl groups. The two bands of 2-QxCOOH could be explained in the same way, since 2-QxCOOH potassium salt is not found in these hydrogen bonds.

On the other hand, the absorption bands due to the stretching of the carbonyl group appearing at 1740 and 1705 cm^{-1} in dioxane solution shift to 1750 and 1721 cm^{-1}, respectively. The band at a higher frequency is considered to be due to monomeric form without any hydrogen bond, while the other can be attributed to the intramolecular hydrogen bond formation.

Potassium salt of 2-QxCOOH shows asymmetric and symmetric stretching frequencies at 1618 and 1387 cm^{-1}, respectively.

IR Spectra of Metal Complexes. By a detailed examination of IR spectra of metal chelates of the various amino acids Condrate and Nakamoto[10] concluded that the increment of coordination character between the carboxyl group and metals shifts the asymmetric stretching vibration of the carboxyl group toward higher and the symmetric stretching vibration toward lower frequencies, resulting in a wider separation between the two absorption bands. By a similar argument of the metal chelates of picolinic and nicotinic acids, the following order was given among the metals for the increment of coordination charac-

TABLE 3. ASYMMETRIC AND SYMMETRIC ν_{COO} AND ΔE OF 2-QxCOOH METAL COMPLEXES (cm^{-1})

Compounds	ν_{asym}COO	ν_{sym}COO	ΔE
2-QxCOOK	1618	1387	231
$(2\text{-QxCOO})_2Cu \cdot 2H_2O$	1632	1360	272
$(2\text{-QxCOO})_2Ni \cdot 2H_2O$	1630	1363	267
$(2\text{-QxCOO})_2Co \cdot 2H_2O$	1630	1361	269
$(2\text{-QxCOO})_2Zn \cdot 2H_2O$	1626	1364	262
$(2\text{-QxCOO})_2Cd \cdot 2H_2O$	1628	1362	266
$(2\text{-QxCOO})_2Mn \cdot 2H_2O$	1610	1376	234
$(2\text{-QxCOO})_2Pb \cdot H_2O$	1593	1376	217
$2\text{-QxCOO} \cdot CuCl \cdot 2H_2O$	1677	1360	317
$2\text{-QxCOO} \cdot CdCl \cdot H_2O$	1655	1365	290

ters.[11]

$$Cu > Co > Ni > Zn$$

Table 3 shows the asymmetric and symmetric stretching frequencies of the carboxyl group together with the degree of separation (ΔE) between the two bands for the metal complexes of 2-QxCOOH.

As in the case of metal chelates of picolinic acid, ΔE obtained shows the same tendency of coordination character among the metals examined. The copper complex has a stronger coordination bond.

For the sake of comparison, the separation between the asymmetric and symmetric frequencies of the carboxyl group for sodium or potassium salts and copper complexes of acetic,[12] benzoic[13] and picolinic acids[14] is shown together with the dissociation constants of the carboxylic acid and stability constants ($\log K_1$) of the copper chelates in Table 4.

The amount of separation found for copper complexes of picolinic acid and 2-QxCOOH is much greater than that of copper acetate and benzoate, the same tendency being observed for the potassium carboxylates.

The ΔE values obtained increase in the order picolinic, 2-quinoxalinecarboxylic, acetic and benzoic acids, corresponding to the stability constants of these carboxylates. From these ΔE values, we see that copper complex of 2-QxCOOH is more stabilized by the additional bond formation between the ring nitrogen and copper than copper benzoate and acetate, where bond formation is expected only between the carboxyl group and copper.

In spite of the fact that the dissociation constant of 2-QxCOOH is smaller than that of benzoic acid, the stability constants of the former with copper is larger, showing the chelate formation compensate for the gap in the dissociation constants.

The fact that asymmetric stretching of manganese and lead complexes of 2-QxCOOH appears in a lower frequency than that of the corresponding potassium salt leads to the conclusion that in these metal complexes the bond between the metal and carboxyl groups is ionic and the interaction between the metal and ring nitrogen is negligible.

Figure 2 illustrates the spectra of 1 : 1 and 2 : 1 copper complexes.

With regard to the two bands located at 1380 cm^{-1}, the 2 : 1 chelate shows a band of stronger intensity in the higher frequency region, while the 1 : 1 complex shows the reverse tendency. A similar phenomenon was observed for the cadmium chelate.

Far-IR of Metal Chelates. Measurements of Far-IR spectra (600—200 cm^{-1}) were made by means of the nujol mulls method. The metal complexes expected to form a chelate ring cause shortening of the bond

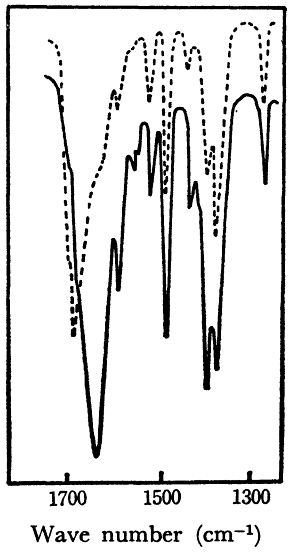

Fig. 2. IR spectra of 2-QxCOOH-Cu complexes.
----: $2\text{-QxCOO} \cdot CuCl \cdot 2H_2O$,
——: $(2\text{-QxCOO})_2Cu \cdot H_2O$

TABLE 4. CARBOXYLATE ASYMMETRIC AND SYMMETRIC STRETCHING FREQUENCIES, DIFFERENCES, pK_a AND COPPER COMPLEX STABILITY CONSTANTS ($\log K_1$)

Compounds	ν_{asym}COO	ν_{sym}COO	ΔE	Ref.	pK_a	$\log K_1$
Acetic acid-Na	1580	1422	158	12)		
-Cu	1590	1418	172	12)	4.55[a]	1.89[a]
Benzoic acid-Na	1555	1416	139	13)		
-Cu	1564	1408	156	13)	4.01[b]	1.6[b]
Picolinic acid-K	1608	1395	213	14)		
-Cu	1639	1350	289	14)	5.44[c]	8.6[c]
2-QxCOOH-K	1618	1387	231			
-Cu	1632	1360	272		2.875	3.30

a, b, c) These pK_a and $\log K_1$ values were quoted from Refs. 15, 16 and 8, respectively.

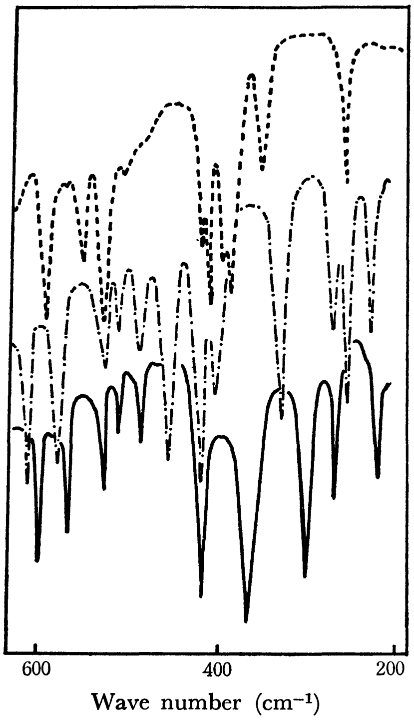

Fig. 3. Far-IR spectra of 2-QxCOOH and its metal complexes.
----: 2-QxCOOH, —·—: (2-QxCOO)$_2$Cu·H$_2$O,
——: (2-QxCOO)$_2$Ni·2H$_2$O.

distance between metal–oxygen and metal–nitrogen to shift the stretching vibration of M–O and M–N toward higher frequencies.

The main peaks of 2-QxCOOH metal chelates are listed in Table 5. Absorption spectra of copper and nickel chelates of 2-QxCOOH are shown in Fig. 3.

According to the work of Taylor *et al.*[17] on lanthanide benzoate, out of and in plane rocking frequencies of carboxylate appear at 516—560 cm^{-1} and 390—425 cm^{-1}, respectively.

2-QxCOOH shows two bands at 546 and 392 cm^{-1} which, on chelation with metals, shift to around 550—580 cm^{-1} and 347—453 cm^{-1}, respectively, which is attributable to the stretching frequencies of metal-oxygen with combination of carboxyl rocking modes. These M–O stretchings take place at higher frequencies in the order Cu>Co>Ni>Zn. This correspond to the coordination character of the carboxyl group, namely, M–O bond in the copper chelate has stronger coordination character than the other metals examined. Billing *et al.*[18] investigated the copper metals of substituted quinoxaline derivatives and concluded that the band at 208—246 cm^{-1} is assigned to the stretching frequencies of M—N. From these values the bands around 326—257 cm^{-1} and 228—200 cm^{-1} are assigned to the M—N stretching. The first bands in particular show marked metal dependence on both absorbance and their shifts.

The 1 : 1 chelate shows a similar pattern of bands to that of the 2 : 1 chelate, indicating that the 1 : 1 chelate can assume a dimeric form including chlorine bridge.

Metal Chelates of 2-QxCOOH N-*Oxides*. The IR and Far-IR data of 2-QxCOOH *N*-oxides and their metal chelates are summarized in Table 6.

2-QxCOOH 4-oxide shows two broad bands around 2400 and 1900 cm^{-1} indicating hydrogen bond formation between the ring nitrogen and the carboxyl group, while in 2-QxCOOH 1-oxide and its 1,4-dioxide no such bands are observed. The stretching vibration of the carbonyl group shifts to higher frequencies in the order 2-QxCOOH 4-oxide, 1-oxide and 1,4-dioxide (Table 6). The band at 1702 cm^{-1} of 2-QxCOOH 4-oxide splits into two bands at 1722 and 1753 cm^{-1} in dioxane solutions, indicating non-existence of the hydrogen bond formation in 1-oxide and 1,4-dioxide.

The absorption bands of the *N*-oxide groups appeared at 1348—1378 cm^{-1} and those of the 2-QxCOOH 1,4-dioxide appeared in the higher frequency region, as in the case $\nu_{C=O}$.

The copper chelates of these ligands show $\nu_{asym COO}$ at 1646—1667 cm^{-1}, $\nu_{sym COO}$ at 1368—1388 cm^{-1}

TABLE 5. CHARACTERISTIC FREQUENCIES OF 2-QxCOOH-METAL COMPLEXES (cm^{-1})

2 : 1 Complexes							1 : 1 Complexes		Assignments
Cu	Ni	Co	Zn	Cd	Mn	Pb	Cu	Cd	
580	564	567	558	559	558	550	575	560	ν_{M-O}
453	366	382	357	355	359	347	432	351	
326	298	286	264	261	265	257	315	267	ν_{M-N}
228	221	214	205	207	202	205	211	200	

TABLE 6. CHARACTERISTIC FREQUENCIES OF 2-QxCOOH *N*-OXIDES AND ITS COPPER COMPLEXES (cm^{-1})

2-QxCOOH 1-oxide		2-QxCOOH 4-oxide		2-QxCOOH 1,4-dioxide		Assignments
Ligand	Complex	Ligand	Complex	Ligand	Complex	
1710	1654	1702	1667	1721	1646	$\nu_{asym COO}$
	1383		1388		1368	$\nu_{sym COO}$
1372	1357	1348	1364	1378	1353	ν_{N-O}
	531		567		542	ν_{Cu-O}
	405		417		403	
	395				350	ν_{Cu-O}
			240			ν_{Cu-N}

and ν_{N-O} at 1353—1364 cm^{-1}. The lower frequency shift of $\nu_{asymCOO}$ apparently indicates the bond formation between the carboxyl group and the copper atom. On the other hand, ν_{N-O} of 2-QxCOOH 4-oxide–copper complex shifts to higher frequency and those of 1-oxide and 1,4-dioxide–copper complexes shift to lower frequency.

We previously reported¹⁾ that in Qx 1-oxide–cupric chloride complex the bond formation between copper and the ring nitrogen caused a ν_{N-O} higher frequency shift, and in Qx 1,4-dioxide–cupric chloride complex coordination of copper to the oxygen atom of *N*-oxide group a ν_{N-O} lower frequency shift. The coordination of copper to the ring nitrogen of 2-QxCOOH 4-oxide increases the double bond character of N–O bond to shift ν_{N-O} to a higher frequency. The other copper *N*-oxide complexes, namely, 1-oxide and 1,4-dioxide–copper coordination site of the ligands is the oxygen atom of *N*-oxide group, which causes lower frequency shifts of ν_{N-O}.

The fact that Qx 1,4-dioxide–cupric chloride complex dissociates into its components in aqueous solution¹⁾ but not the 2-QxCOOH *N*-oxide-copper complexes can be explained by the increase in stabilization energy caused by the chelate ring formation in the latter.

Studies on the Far-IR spectra of these complexes were also made. The absorption peaks observed at 531—542 cm^{-1} and 403—407 cm^{-1} are assigned to the ν_{Cu-O} from the behavior of 2-QxCOOH–copper complex. The absorption peaks at 395 and 350 cm^{-1} of 2-QxCOOH 1-oxide and 1,4-dioxide are close to that of Qx 1,4-dioxide–cupric chloride complex at 397 cm^{-1},¹⁾ and assigned to the Cu–O band between copper and the oxygen atom of the *N*-oxide group. The band due to Cu–O with the carboxyl oxygen of 2-QxCOOH 4-oxide copper complex is observed at a higher frequency than that of 1-oxide and 1,4-dioxide copper complexes.

This can be explained to be due to the fact that formation of the five-membered ring nitrogen, carboxyl oxygen and copper is more stable than that of the six-membered ring including oxygen atom of the *N*-oxide group. The same conclusion was also reported by Gupta *et al.*¹⁹⁾ concerning oxine and its *N*-oxide metal complexes.

2-QxCOOH 4-oxide–copper complex gives an absorption peak at 240 cm^{-1}, which is attributed to ν_{Cu-N} from the data of 2-QxCOOH–copper complex. IR and Far-IR analytical data indicate that 2-QxCOOH *N*-oxide–copper complexes forms the chelate ring as in the case of 2-QxCOOH complexes.

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