BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 980—987 (1968)

Dihydroxyquinoxaline Studies. Solubility, Ionization Constant, and Chelating Behavior*[1]

Shoshichi OGUCHI

Department of Chemistry, Faculty of Education, The Tokyo Gakugei University, Koganei, Tokyo

(Received October 12, 1967)

The solubility, ionization constant, and chelating behavior of dihydroxyquinoxaline, mainly 5,8-dihydroxyquinoxaline (5,8-DHQ) derivatives, have been measured and will be discussed. The introduction of a hydroxyl group into quinoxaline greatly lowers the solubility. The order of the decreasing solubility of 2,3-disubstituted 5,8-DHQ in water (at 20°C) is: $O(CH_2)_2OC_2H_5 < H < OH < CH_3 < C_6H_5 < OC_2H_5 < Cl < SH < SC_2H_5$. For 5,8-DHQ the introduction of electron-repelling groups into 2,3-positions raises both the pK_{NH} and pK_{OH} values, while the introduction of electron-attracting groups into the same positions lowers both pK_{NH} and pK_{OH}. 5,8-DHQ and its derivatives form colored precipitates with metal ions, but some derivatives which have pK_{NH} values lower than zero fail to show any precipitation or coloration. 6,7-DHQ forms precipitate, and the precipitation colors distinctively with Cr(III) or Fe(II). The composition and stability constant (K) of copper(II) chelates of 5,8-DHQ and its derivatives in a dioxane-water (10 : 90 v/v) solution were studied spectrometrically. The copper chelate of 5,8-DHQ had a metal: ligand ratio of 1 : 1 and a $\log K$ value of 6.28 at pH 4.0. The structures of these copper chelates will be proposed.

It has been reported that 5,8-dihydroxyquinoxaline (5,8-DHQ) produces more deeply colored inner salts with many kinds of metallic ions¹⁾ than 8-hydroxyquinoline, and that 5-hydroxyquinoxaline²⁾ and 5,8-DHQ³⁾ show a growth-inhibiting bacterial action. In this series of studies the author has attempted to find some useful knowledge about DHQ derivatives in the field of analytical chemistry and pharmaceutical science. Many derivatives of DHQ have been prepared,⁴,⁵⁾ and their solubility, ionization constants, and chelating behavior have been determined.

Experimental

Materials. All the reagents used in this work except 2,3,5,8-tetrahydroxyquinoxaline and 1,4-dimethyl-5,8-dimethoxy-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline have been described previously⁴,⁵⁾ (see Table 1). Those two were prepared as follows.

2,3,5,8-Tetrahydroxyquinoxaline. A mixture of 2,3-dihydroxy-5,8-dimethoxyquinoxaline,⁵⁾ acetic acid, and hydrobromic acid (48%) was refluxed for 6 hr; then the mixture was poured into water and neutralized with aqueous ammonia. The precipitate thus formed was filtered and washed with water. The compound was hardly soluble in the organic solvents tested, even in pyridine or dimethylformamide. The compound was purified by repeated dissolutions in alkali and by reprecipitation by acetic acid. A colorless powder which does not melt below 360°C was produced. Yield, 75%.

Found: N, 14.37%. Calcd for $C_8H_6O_4N_2$: N, 14.43%.

1,4-Dimethyl-5,8-dimethoxy-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline. 5,8-Dimethoxy-2,3-DHQ (1.5 g) was dissolved in a 2 N aqueous solution (60 m*l*) of sodium hydroxide and shaken with dimethyl sulfate (6 m*l*) for 2 hr. The reaction mixture was then cooled and extracted with chloroform. After the removal of the chloroform, the residue was repeatedly recrystallized from methanol. Yield, 1.1 g (65%). Colorless needles which melt at 180°C were produced. Found: C, 57.52; H, 5.38; N, 10.58%. Calcd for $C_{12}H_{14}O_4N_2$: C, 57.59; H, 5.64; N, 11.20%.

Apparatus and Procedure. Measurements of the absorbance in the visible and ultraviolet regions were made with a Hitachi EPU-2A spectrophotometer and an EPS-3T recording spectrophotometer, using quartz-stoppered cells with a light path of 10 mm.

pH Measurements were made with a Hitachi-Horiba Model P extension glass and calomel electrodes.

The first ionization constant of pK_{NH} quinoxaline derivatives, the so-called "*proton-gained* pK_a" value, was measured by the spectrometric method in a dioxane-water (10 : 90 v/v) solution in the usual manner.⁶,⁷⁾

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*[1] Part V, Studies of Chelating Reagents Containing *N*-Heterocycles. Part IV: see Ref. 4.

1) S. Kawai, K. Kimura and T. Furuhata, *Proc. Japan Acad.*, **29**, 344 (1953).

2) S. K. Freeman and P. E. Spoerri, *J. Org. Chem.*, **16**, 438 (1951).

3) J. Adachi, *Nippon Kagaku Zassi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **76**, 311 (1955).

4) S. Oguchi, *ibid.*, **86**, 435 (1965).

5) S. Oguchi, *ibid.*, **86**, 319 (1965).

6) A. Albert and E. P. S. Serjeant, "Ionization Constants of Acids and Bases," Methuen & Co., London (1962), p. 69.

7) M. Iwazumi and H. Azumi, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **84**, 694 (1963).

For the pH range from 1 to 9, a hydrochloric acid-formic acid buffer, acetate buffer, a phosphate buffer and a borax-potassium hydroxide buffer were used, in that order. For the compounds whose pK_a values lie below 1, hydrochloric acid or sulfuric acid was used and the pK_a values were calculated using the acidity function.[8,9] The first ionization constant of the pK_{OH} hydroxyl group, the so-called "*proton-lost* pK_a" value, was calculated from the data of the titration curve in a dioxane-water (50 : 50 v/v) mixture.[10,11] A mixed solvent was used because of the insolubility of DHQ in water.

The solubility in water was measured at 20±1°C spectroscopically and gravimetrically by the method Albert has reported.[12] A sample was dissolved in deoxidized water under a nitrogen stream at 100°C and left to stand at 20±1°C for one day under a nitrogen atmosphere before measurements.

Reactions with Metal Ions. The following metal ions were tested at pH 5.2 (A), 8.4 (B), and 12.4 (C) for precipitation and coloration: Mg(II), Ca(II), Cu(II), Cd(II), Hg(II), Al(III), Pb(II), Sn(II), Sn(IV), Th(IV), Zr(IV), Ce(IV), As(III), As(V), Cr(III), Mn(II), Fe(II), Fe(III), Co(II), Ni(II), Ag(I).

The degree of dissociation (α) and the stability constant (K) of chelate compounds were determined by the following formula, which was measured spectrophotometrically by the molar ratio method: $\alpha=(A_m-A_s)/A_m$, where A_m is the maximum extinction obtained from the horizontal portion of the curve and whose A_s is the extinction at the stoichiometric ratio. The stability constant, K, for a chelate compound, ML_n, was calculated by the following formula:[13,14] $K=(1-\alpha)/n^nC^n\alpha^{n+1}$, where C is the total concentration of the chelate in mol/l.

Results and Discussion

Solubility. The solubility of a number of quinoxaline derivatives has been determined; the results are shown in Table 1. The introduction of one hydroxyl group into quinoxaline lowers the solubility roughly 400 times. When two hydroxyl groups are introduced into quinoxaline, the solubility decreases from 1000 to 15000 times (Nos. 3—5). As Albert pointed in his study of pteridine[15] and purin series,[16,17] these decreases are probably to be attributed to unusually strong crystal lattice forces originating in the hydrogen bonding between the hydroxyl groups and the ring-nitrogen atoms of the neighbouring molecules of quinoxaline derivatives. These very hydrophilic groups in the organic molecules exert more attraction toward each other than toward water molecules. This is clearly demonstrated by the following facts. The alkoxyl derivatives or *N*-methyl derivatives of quinoxaline, which are not capable of forming hydrogen bonding, show a remarkable increase in solubility. 5-Methoxyquinoxaline is 22 times more soluble than 5-hydroxyquinoxaline (Nos. 1 and 2; see also Nos. 3 and 7, Nos. 4 and 8, and Nos. 10 and 19). *N,N'*-Dimethyl derivatives of 2,3-DHQ are 115 times more soluble than 2,3-DHQ (Nos. 5 and 31; see also Nos. 23 and 28), which exists predominantly in the diamide form in solution.[18] However, the *O*-methyl derivative (No. 9) of 2,3-DHQ (No. 5) shows an exceptionally smaller solubility than 2,3-DHQ.

Lipoid-solubilizing groups (*e. g.*, Me, Ph, Cl, OC_2H_5, and SC_2H_5) decreased the solubility of 5,8-dimethoxyquinoxaline (5,8-DMQ) and 5,8-DHQ. This phenomenon can be seen in the following compounds: Nos. 7 : 19, Nos. 3 : 10 (Me); Nos. 7 : 20, Nos. 3 : 11 (Ph); Nos. 7 : 26 Nos. 3 : 17 (Cl); Nos. 7 : 21, Nos. 3 : 12 (OC_2H_5), and Nos. 7 : 24 and Nos. 3 : 15 (SC_2H_5). The order of the decreasing solubility of 2,3-disubstituted 5,8-DHQ is: $O(CH_2)_2OC_2H_5 < H < OH < CH_3 < C_6H_5 < OC_2H_5 < Cl < SH < SC_2H_5$. Hydrophobic CH_3- and $(CH_3)_2N$- groups decrease the solubility of 5,8-DMQ, but the degree of decrease is small (Nos. 19 and 27). This phenomenon may be explained by the basicity increase of the ring nitrogen by electron-repelling groups, such as the CH_3 or $(CH_3)_2N$- group. The electron pair on the ring-nitrogen atom is able to form hydrogen bonds with water; this causes the 5, 8-DMQ to be more soluble in water than is expected from hydrophobic groups. The special insolubility of 6,7-DHQ and its derivatives may be attributed to a high crystal-lattice force between *o*-dihydroxyl groups and ring nitrogens. In harmony with this concept, 6,7-DHQ derivatives (Nos. 4, 32 and 33) do not melt below 360°C, but 6,7-DMQ and 2,3-dichloro-6, 7-DMQ (Nos. 8 and 35) melt at 151°C and 178°C respectively.

Ionization Constant. *a) pK_{NH} Value.* The results of the measurement of the pK_a values of quinoxaline and 8-hydroxyquinoline in aqueous dioxane are given in Tables 2 and 3. The pK_a values observed in a dioxane-water (10 : 90 v/v) solution are somewhat lower than those in water. This lowering effect is usually observed in mixed

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[14] Y. Kidani, *Chem. & Pharm. Bull. (Tokyo)*, **6**, 563 (1958).

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[17] A. Albert, "Heterocyclic Chemistry," Univ. of London Press. (Althlone), London (1959), p. 43.

[18] G. W. H. Cheeseman, *J. Chem. Soc.*, **1958**, 108.

TABLE 1. SOLUBILITIES AND MELTING POINTS

No.	Quinoxaline deriv.	m*l*. of H_2O, which can dissolve 1g of the compd. (20°C)	Mp °C	Source*
	Quinoxaline	1.5	29—30	A
1	5-Hydroxy-	570	101—102	B
2	5-Methoxy-	25	100	C
3	5,8-Dihydroxy-	1700	237	D
4	6,7-Dihydroxy-	22100	360	E
5	2,3-Dihydroxy-	4700	360	F
6	2,3-Dimercapto-	5400	290—295(dec.)	G
7	5,8-Dimethoxy-	530	150	D
8	6,7-Dimethoxy-	2460	151	E
9	2,3-Dimethoxy-	12500	94	F
10	5,8-Dihydroxy-2,3-dimethyl-	4010	225	H
11	-2,3-diphenyl-	5900	176	I
12	-2,3-diethoxy-	12300	148	J
13	-2,3-bis(β-ethoxyethoxy)-	1280	65	J
14	-2,3-dihydroxy-	3270	360	K
15	-2,3-bis(ethylthio)-	41200	152	J
16	-2,3-dimercapto-	16800	360	L
17	-2,3-dichloro-	14300	244	C
18	-6,7-bis(ethoxycarbonyl)-	11480	149	J
19	5,8-Dimethoxy-2,3-dimethyl-	690	170	H
20	-2,3-diphenyl-	170000	227	I
21	-2,3-diethoxy-	130200	178	J
22	-2,3-bis(β-ethoxyethoxy)-	4500	114	J
23	-2,3-dihydroxy-	2400	325—329	J
24	-2,3-bis(ethylthio)-	145000	122	J
25	-2,3-dimercapto-	77000	261 (dec.)	L
26	-2,3-dichloro-	24000	215	L
27	-2,3-bis(dimethylamino)-	970	117	J
28	-2,3-dioxo-1,4-dimethyl-1,2,3,4-tetrahydro-	1270	180	K
29	-2,3-bis(hydroxycarbonyl)-	670	186(dec.)	M
30	-2,3-bis(ethoxycarbonyl)-	1350	165	M
31	2,3-Dioxo-1,4-dimethyl-1,2,3,4-tetrahydro-	39	356—358	F
32	6,7-Dihydroxy-2,3-dichloro-	7500	360	L
33	-2,3-dimercapto-	8700	360	L

* Source—A: R. G. Jones and K. C. Mclaughin, "Organic Syntheses", **30**, 86 (195); B: 2); C: 19); D: 3); E: J. Ehrlich and M. T. Bogert, *J. Org. Chem.* **12**, 522 (1947); F: G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, **1948**, 519; G: D. C. Morrison, A. Furst, *J. Org. Chem.* **21**, 470 (1956); H: S. Kawai, S. Tanaka and K. Ichikawa, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **75**, 40 (1954); I: S. Kawai, J. Kosaka and M. Hatano, *Proc. Japan Acad.*, **30**, 774 (1954); J: 4); K: This paper; L: 5); M: S. Kawai, S. Oguchi, *et al.*, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **80**, 778 (1959); N: S. Oguchi, *ibid.* **86**, 246 (1965).

solvents.[19,20] The values of 5-[24] and 6-hydroxyquinoxaline[22] (0.9 and 1.40 respectively; quinoxaline, 0.56[21]), which were determined in an

TABLE 2. IONIZATION CONSTANTS (at 20°C)*1

Quinoxaline	(in water)	0.60*2
	(in 10 : 90 v/v dioxane-water)	0.30
8-Hydroxyquinoline		
	(in water)	5.01*3
	(in 10 : 90 v/v dioxane-water)	4.58
	(in 50 : 50 v/v dioxane-water)	4.48*4

*1 Measured spectrometrically at ionic strength 0.1.
*2 Albert reported 0.56.[21]
*3 Albert reported 5.13.[22]
*4 Irving reported 4.48.[23]

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21) A. Albert, "Physical Method in Heterocyclic Chemistry," Vol. 1, ed. by A. R. Katritzky, Academic Press, New York and London (1963), p. 76.

22) A. Albert and J. N. Phillips, *J. Chem. Soc.*, **1956**, 1294.

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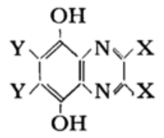
24) A. Albert and H. Hampton, *ibid.*, **1954**, 505.

TABLE 3. PHYSICAL PROPERTIES OF QUINOXALINE DERIVATIVES AND RELATED SUBSTANCES

	Ionization constants (at 20°C)				UV Absorption spectra	
Quinoxaline derivative	Proton gained pK_a (pK_{NH}) in dioxane-H_2O(10 : 90 v/v)*1	(mμ)*2	Proton lost pK_a (pK_{OH}) in dioxane-H_2O(50 : 50 v/v)*3	concn. (M)*4	Solvent	λ_{max}, mμ($\log_{10}\varepsilon$)
Quinoxaline	0.60(in H_2O)	334	—	—	EtOH	240(4.50), 325(3.80)*6
	0.30	332	—	—		
5-Hydroxy	0.9 (in H_2O)*5	—	9.29(in H_2O)*5	—	H_2O	251(4.37), 320(3.32)
5-Methoxy	—	—	—	—	H_2O	250(4.37), 324(3.39)
5,8-Dihydroxy	0.61	280	10.82	0.01	EtOH	265(4.50), 320(3.15) 402(3.09)
5,8-Dimethoxy	0.30	282	—	—	EtOH	263(4.56), 314(3.86) 399(3.42), 490(3.18)
6,7-Dihydroxy	0.89	380	—	—	H_2O	354(3.98)
5,8-Dihydroxy-2,3-dimethyl	1.65	284	11.36	0.01	EtOH	269(4.54), 377(3.09)
5,8-Dimethoxy-2,3-dimethyl	1.27	285	—	—	EtOH	265(4.57), 303(3.47) 365(3.25)
5,8-Dihydroxy-2,3-diphenyl	0.46	280	10.97	0.01	EtOH	260(4.27), 303(4.40) 360(3.51)
5,8-Dimethoxy-2,3-diphenyl	—	—	—	—	EtOH	262(4.21), 302(4.40) 345(3.62)
5,8-Dihydroxy-2,3-diethoxy	−1.88	275	10.04	0.01	Dioxane	237(3.85), 270(4.42) 315(3.56)
					EtOH	275(4.44)
5,8-Dimethoxy-2,3-diethoxy	−1.44	267	—	—	EtOH	265(4.50), 315(3.70)
2,3-Bis(β-ethoxyethoxy)-5,8-dihydroxy	−1.70	270	10.77	0.01	EtOH	275(4.51), 310(3.78)
2,3-Bis(β-ethoxyethoxy)-5,8-dimethoxy	−1.73	266	—	—	EtOH	265(4.50), 315(3.85)
2,3-Bis(ethylthio)-5,8-dihydroxy	−1.43	300	11.14	0.01	EtOH	304(4.55), 367(3.90)
2,3-Bis(ethylthio)-5,8-dimethoxy	−1.45	293	—	—	EtOH	223(4.43), 295(4.53) 414(2.80)
2,3-Bis(dimethylamino)-5,8-dimethoxy	1.93	387	—	—	Dioxane	290(4.42), 370(4.02)
2,3-Dichloro-5,8-dihydroxy	—	—	9.66	0.01	EtOH	279(4.13), 420(3.09)
2,3-Dichloro-5,8-dimethoxy	—	—	—	—	EtOH	279(4.61), 331(3.22) 397(3.20)
2,3-Bis(ethoxycarbonyl)-5,8-dimethoxy	—	—	—	—	EtOH	281(4.62), 342(3.21) 416(3.18)
2,3-Bis(ethoxycarbonyl)-6,7-dimethoxy	—	—	—	—	EtOH	227(4.43), 262(4.56) 365(4.20)
6,7-Bis(ethoxycarbonyl)-5,8-dihydroxy	0.62	280	9.28	0.01	EtOH	280(4.45), 340(3.45) 355(3.45)
2,3,5,8-Tetrahydroxy	1.66	279	—	—	EtOH	230(3.90), 238(3.66) 247(3.66), 285(4.01) 315(3.57), 440(2.24)
5,8-Dihydroxy-2,3-dimercapto	—	—	—	—	EtOH	317(3.81), 398(3.46)
2,3-Dimercapto-5,8-dimethoxy	—	—	—	—	EtOH	243(4.28), 309(4.30) 437(4.09)
6,7-dihydroxy-2,3-dimercapto	—	—	—	—	EtOH	275(4.51), 407(4.25)
6,7-Dimethoxy-2,3-dimercapto	−0.93	395	—	—	EtOH	239(4.32), 390(3.97)

*1 Measured spectrometrically. *2 Analytical wavelength *3 Measured potentiometrically at ionic strength 0.2. *4 Concentration of the substance. *5 Cited from Ref. 24.
*6 Cited from *J. Chem. Soc.*, **1956**, 123.

TABLE 4. REACTIONS WITH METAL IONS AND IONIZATION CONSTANTS OF 5,8-DIHYDROXYQUINOXALINE

Ligand	X=H Y=H	X=H Y=$COOC_2H_5$	X=CH_3 Y=H	X=OH Y=H	X=C_6H_5 Y=H	X=SC_2H_5 Y=H	X=$O(CH_2)_2OC_2H_5$ Y=H	X=OC_2H_5 Y=H	X=Cl Y=H
Metal formed precipitate in the buffer solution A, B, C*	Zn(II): C Fe(II): C Fe(III): A, B, C Ni(II): C Pb(II): C Cu(II): A, B, C	Fe(II): A Fe(III): A Cd(II): C Ni(II): B, C Mn(II): B, C Pb(II): A, B Th(IV): B, C Cu(II): A, B, C	Zn(II): C Co(II): C Fe(III): C Pb(II): C Cu(II): A	Zn(II): A, B Cd(II): C Fe(II): A Ni(II): B, C Cr(III): C Al(III): C Hg(II): A, B, C Ce(IV): C Cu(II): A, B Ag(I): B, C	Zn(II): C Cd(II): C Fe(II): C Co(II): C Pb(II): C Cu(II): A, B	Non	Non 	Non	Non
pK_{NH}(20°C)	0.61	0.62	1.65	1.66	0.46	−1.43	−1.70	−1.88	—
pK_{OH}(20°C)	10.82	9.28	11.36	—	10.97	11.14	10.77	10.04	9.66

* A, B and C indicate precipitaion under pH 5.2, 8.4, 12.4 buffer solution, respectively. Three drops of buffer solution, one drop of metal ion solution (1000γ/m*l*) and one drop of 0.025—0.005M of reagent solution in ethanol.

aqueous solution by Albert, show that the hydroxyl groups in the phenyl nucleus of quinoxaline has some electron-repelling effect; this effect also exists in 5,8-DHQ (0.61) and 6,7-DHQ (0.89) and their *O*-methyl derivatives (Table 3). From Table 3 it can also be seen that the base-strengthening effect of the methoxyl group is somewhat weaker than that of the hydroxyl group. It has been reported[18] that the pK_a values of 2-methoxyquinoxaline (0.28 in water) and 2,3- DMQ (-1.15 in water) are considerably smaller than that of quinoxaline (0.56 in water); this fact suggests that the inductive effect is more effective than the mesomeric effect at 2 and/or 3 positions of quinoxaline. Similar effects are observed in the following compounds: 2,3-diethoxy-, 2,3-bis(ethoxyethoxy)- and 2,3-bis(ethylthio)-substituents of 5,8-DHQ and 5,8-DMQ. The pK_a values of the 2, 3-DHQ derivatives can be expected to be the same as that of 2-hydroxyquinoxaline because of their same partial structures. However, their pK_a values could not be determined by the spectrometric method, because their spectra did not change with the pH of medium as in the case of 2,3-DHQ. Electron-repelling substituents, such as methyl and dimethylamino groups, in the 2,3-position raise the pK_a values of 5,8-DHQ and 5,8-DMQ. Phenyl groups in the same positions lower the pK_a value. In 2,3-dichloro-5,8-DHQ, chlorine atoms are expected to have a base-weakening effect. However, its pK_a value could not be determined by the spectrometric method. The introduction of the alkoxycarbonyl group into the 6,7-positions of 5,8-DHQ induces hardly any appreciable effect on the pK_{NH} value.

b) pK_{OH} Value. By comparing the pK_a value of the 8-hydroxyquinoline anion (in dioxane-water 50 : 50 v/v, 10.80) with 5-hydroxyquinoxaline (9.29 in dioxane-water 50 : 50 v/v,)[23] the lowering effect of the pK_a value upon the further introduction of ring nitrogen may be seen. On the contrary, the further introduction of the hydroxyl group into the 8-position of 5-hydroxyquinoxaline raises the pK_a value (by an acid-weakening effect) (Table 3). The introduction of electron repelling substituents such as the methyl group into the 2,3-positions of 5,8-DHQ raises the pK_{OH} value (11.36), while the introduction of electron-attracting substituents, such as ethoxy and chloro groups, into the same positions, or that of the ethoxycarbonyl group into the 6,7-positions, lowers the pK_{OH} value (10.04, 9.66, and 9.28 respectively).

Chelating Behavior with Metal Ions. Reactions with metal ions are shown in Table 4. 5,8-DHQ and its derivatives formed a colorful precipitate, but some 2,3-disubstituted 5,8-DHQ failed to show any precipitation or coloration with metal ions in the buffer solution tested. Table 4 also shows the metal chelates and pK_{NH} and pK_{OH} values of 5,8-DHQ and its derivatives. According to Irving,[16] a linear relationship between $\log\beta$ (β: stability constant of the metal chelate) and the pK_{OH} of ligand exists for the chelate formation of 8-hydroxyquinoline and related compounds. Form Table 4, it is found that a close relationship exists between the precipitation of the meatl chelate of 5,8-DHQ derivatives and the pK_{NH} value of the ligand, but the pK_{OH} value has not special relation with the precipitation of the chelate. The basicity of a precipitate-forming ligand is higher than that of a ligand which does not form any precipitate. The limit of the value of pK_{NH} for causing the precipitation and coloration of chelates of 5,8-DHQ derivatives seems to lie near $0 - -1$ (obtained in dioxane-water, 50 : 50 v/v).

2,3-DHQ and its 5,8- or 6,7-dimethoxy-derivatives fail to show any precipitation or coloration with metal ions. 6,7-DHQ, however, gives a distinct coloration and precipitations with Fe(II) and Cr(III) like catechol.[25,26] It is interesting to note that 2,3,5,8-tetrahydroxyquinoxaline can form precipitates with a larger number of metals (Table 4).

Kawai *et al.*[27] reported that the composition of copper chelates of 5,8-DHQ was not in accord with the molar ratio of metal : ligand = 1 : 1, whose ratio was based on the assumed structure of Fig. 1.

Though 5,8-DHQ and its derivatives give precipitates with copper salt in an aqueous solution, in aqueous dioxane the copper chelates were kept in a colloidal solution. The composition of the copper chelate of 5,8-DHQ in a dioxane-water (10 : 90 v/v) solution was measured by the following two methods:

(1) Job's Continuous Variation Method: Fig. 3. The composition of the chelate was determined to be 1 : 1 (reagent : copper) at pH 4; 400 mμ.

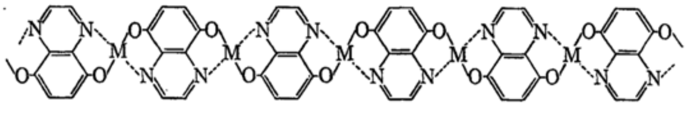


Fig. 1.

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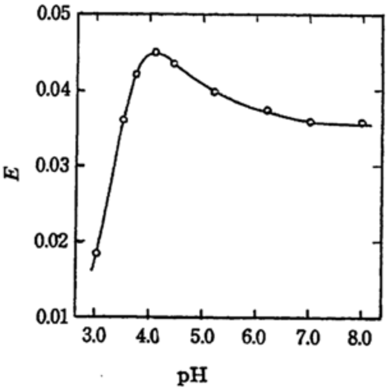

Fig. 2. Effect of pH on the absorbance of copper chelate of 5,8-DHQ. at 500mμ. Concn. of 5,8-DHQ: 2×10^{-4} M/l

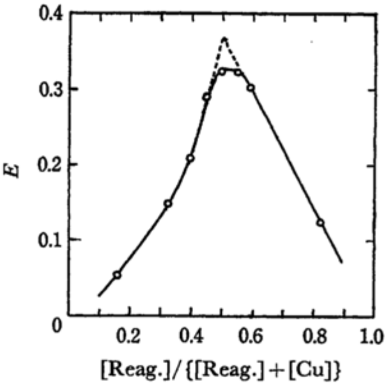

Fig. 3. Absorption curve of copper chelate of 5,8-DHQ (Continuous variation method).
Total concn.: 2.5×10^{-4} M/l, $\mu=0.1$, pH 4.0 at 500 mμ

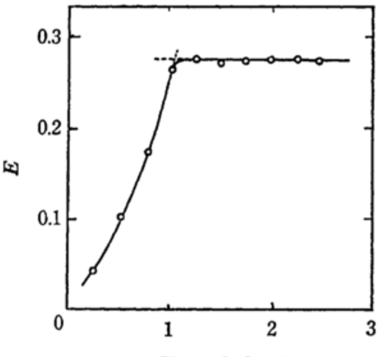

Fig. 4. Absorption curve of copper chelate of 5,8-DHQ (Molar ratio method).
Concn. of copper: 2×10^{-4} M/l, $\mu=0.1$, pH 4.0 at 500 mμ

(2) Molar Ratio Method: Fig. 4. The composition of the chelate was found to be 1 : 1 (reagent : copper) at pH 4: 400 mμ.

By the same procedures, the compositions of

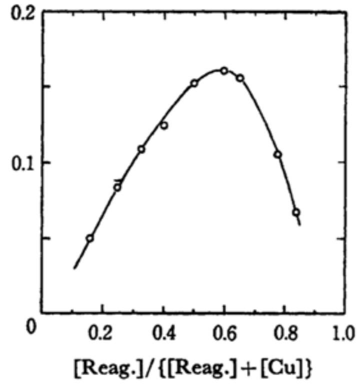

Fig. 5. Absorption curve of copper chelate of 6,7-bis(ethoxycarbonyl)-5,8-DHQ (Continuous variation method).
Total concn.: 2.5×10^{-4} M/l, $\mu=0.1$, pH 6.2 at 625 mμ

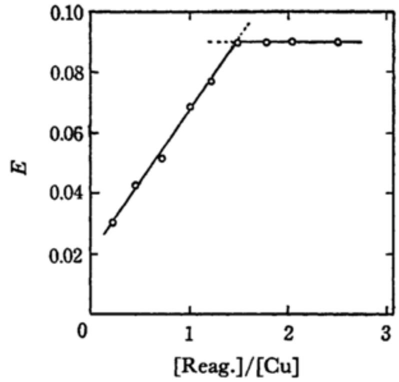

Fig. 6. Absorption curve of copper chelate of 6,7-bis(ethoxycarbonyl)-5,8-DHQ (Molar ratio method)
Concn. of copper : 1×10^{-4}M/l, $\mu=0.1$, pH 6.2 at 625 mμ

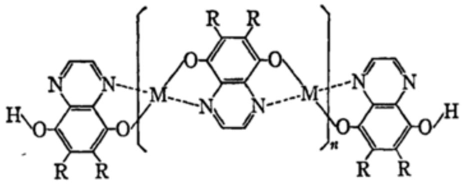

Fig. 7. R=H, 5,8-DHQ Cu chelate
R=COOC$_2$H$_5$, 2,3-Bis(ethoxycarbonyl)-5,8-DHQ Cu chelate $n=1$

TABLE 5. COMPOSITION, DEGREE OF DISSOCIATION (α) AND STABILITY CONSTANT (K) OF COPPER CHELATES OF 5,8-DHQ

Ligand	Composition Cu : Ligand	α	log K	pH
5,8-DHQ	1 : 1	0.05	6.28	4.0
6,7-Bis(ethoxy-carbonyl)-5,8-DHQ	2 : 3	0.01	10.73	6.2
2,3-Dimethyl-5,8-DHQ	could not be obtained			

the copper chelates of 5,8-DHQ derivatives were measured (Figs. 5 and 6). The compositions, the degrees of dissociation (α), and the stability constants (K) of the copper chelates calculated are shown in Table 5. The composition of the copper chelate of 2,3-dimethyl-5,8-DHQ could not be obtained by these procedures, however, because the absorbance of the mixed solution of cupric ions and the ligand varied rapidly and the precipitates separated.

From these chelate compositions (Table 5), the structures of chelates may be represented as in Fig. 7.

The author wishes to express his deep thanks to Professor Sin'iti Kawai and Professor Noboru Sugiyama for their encouragement and support. Grateful acknowledgement is also made to Professor Jisuke Seki for his helpful advice.