BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 39 1910—1915 (1966)

The Synthesis of 2-Alkyl-8-hydroxyquinolines and Their Chelating Behavior with Metal Ions[1,2]

By Hisamitsu KANEKO and Keihei UENO

Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka

(Received December 27, 1965)

2-Ethyl-, 2-*n*-propyl- and 2-*n*-butyl-8-hydroxyquinolines have been synthesized by the reactions of 8-hydroxyquinoline with alkyl-lithium. The dissociation constants and the chelate stability constants of these ligands with copper(II), zinc(II), nickel(II) and cadmium(II) have been measured in 50% v/v aqueous dioxane at 25.0±0.1°C with no additional electrolyte. Factors affecting the acid dissociation constants and the chelate stability constants will be discussed in this paper.

As a part of our investigations into the relationship between the chemical structure of a chelating agent and the metal chelate stability, a number of 8-hydroxyquinoline derivatives have been brought under investigation. 2-Methyl and 2-phenyl derivatives have been reported in the literature, and the selectivities of their metal chelate formation for certain metal ions have been discussed from theoretical and analytical standpoints.[3]

In this connection, our interest has been focused on the derivatives of 8-hydroxyquinoline with an alkyl group at the C-2 position. For this purpose, a general method for introducing an alkyl group to the C-2 position of 8-hydroxyquinoline has been developed. After investigating several reactions which seem to give the desired products,[4,5] we have finally chosen a method which is similar to the method used for the preparation of 2-phenyl-8-hydroxyquinoline; it consists of the reaction of 8-hydroxyquinoline with alkyl lithium in ether, followed by hydrolysis.[6,7] 2-Alkyl-8-hydroxyquinolines were isolated as hydrochloride because the free bases were difficult to purify because of their low melting points. The results of the syntheses are summarized in Table I. The attempted syntheses of isopropyl and *t*-butyl derivatives were not successful, as the reaction did not give enough yield for our purposes.

It is known that 2-methyl-8-hydroxyquinoline can not form a stable chelate with aluminum, and the selectivity of this reagent is understood to be caused by the steric hindrance of the 2-methyl group of this ligand around the aluminum ion, which has a relatively small ionic radius. Similarly, it may be expected that the introduction of a higher alkyl group to the C-2 position of 8-hydroxyquinoline would result in a different selectivity for metal ions. Thus, the chelate stability constants of 2-alkyl-8-hydroxyquinoline with copper(II), zinc(II), nickel(II) and cadmium(II) have been measured. As these ligands, as well as the metal chelate compounds, were not soluble in water, the acid dissociation constants and the chelate stability constants were measured in 50% v/v aqueous dioxane by the pH titration method.

Experimental

The Synthesis of Ligands.—As an example, the synthesis of 2-*n*-butyl-8-hydroxyquinoline will be described.

All the procedures until the hydrolysis step were conducted under dry nitrogen protected from atmospheric moisture. A solution of 13.6 g. (0.099 mol.) of *n*-butyl-bromide in 30 ml. of ether was dropped into a reaction flask containing 1.7 g. (0.245 mol.) of lithium covered with 50 ml. of ether. The bromide was then added over a 40 min. period, while the temperature was kept below −10°C. After this mixture had been stirred another 1.5 hr., a solution of 2.7 g. (0.019 mol.) of 8-hydroxyquinoline in 100 ml. of ether was dropped into the reaction flask over a 20 min. period. After the stirring had been continued for an additional 2 hr. at −10°C, the reaction product was hydrolyzed by pouring it onto ice chips. The ether layer was separated, and the ether was evaporated to obtain a yellow oil. The oil was taken into hydrochloric acid, and the resulting crystalline mass was repeatedly recrystallized from ethanol. Pale yellow crystals melting at 165.8—167.3°C were thus obtained. Yield: 2.0 g. (45%).

A similar procedure was followed for the synthesis

---

[1] Contribution No. 69 from the Department of Organic Synthesis, Kyushu University.

[2] This paper is taken, in part, from the Master of Engineering thesis of Hisamitsu Kaneko (1964), Kyushu University.

[3] A. E. Martell and M. Calvin, "The Chemistry of Metal Chelate Compounds," Prentice-Hall, New York, N. Y. (1952).

[4] I. G. Farbenindustrie, German Pat. 613066 (1935).

[5] O. Döbner, *Ann.*, **242**, 265 (1887); ibid., **281**, 1 (1894).

[6] H. Irving, E. J. Butler and M. F. Ring, *J. Chem. Soc.*, **1949**, 1489.

[7] J. P. Phillips, R. L. Elbinger and L. L. Merritt, *J. Am. Chem. Soc.*, **71**, 3984 (1949).

TABLE I. SYNTHESES OF 2-ALKYL-8-HYDROXYQUINOLINE

Alkyl	Yield[a) %]	M. p.[b) °C]	Analytical data[c)]					
			C%		H%		N%	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
Ethyl	24	194.5—196.5	63.01	62.25	5.77	5.86	6.68	6.59
n-Propyl	26	161.5—163.0	64.43	63.96	6.31	6.72	6.26	6.11
n-Butyl	45	165.8—167.3	65.68	65.59	6.78	6.69	5.89	5.82

a) Based on 8-hydroxyquinoline.
b) The melting point and analytical data are those of hydrochlorides.
c) The Elementary analyses were carried out at the Elementary Analyses Center of Kyushu University.

of 2-ethyl and 2-*n*-propyl derivatives using the corresponding alkyl bromide. The yields, melting points and analytical data for the products are summarized in Table I.

Although tetrahydrofurane was used as a solvent in place of ether in the hope of improving the yield, the reaction did not proceed; only the starting material was recovered.

Chelate Stability Measurements.—*Materials.*—All the ligands were used as hydrochloride. Dioxane, of an analytical grade, was purified by refluxing it with 20% sulfuric acid, followed by repeated distillations. An 0.1 N sodium hydroxide solution and 0.01 M metal ion solutions (nitrates) were prepared using 50% v/v aqueous dioxane as a solvent. The concentrations of metal ion solutions were determined by EDTA titration.

Apparatus and Procedure.—Potentiometric titration was carried out in a jacketed beaker equipped with a burett for the delivery of a sodium hydroxide solution, a glass electrode and a calomel electrode for pH measurement, and nitrogen inlet and outlet tubes. The pH was measured with a Horiba-Hitachi Model P pH meter which had been standardized against the pK_a value[8,9)] of acetic acid by titrating acetic acid in 50% v/v aqueous dioxane.

The titration was carried out on a solution with a ligand-to-metal ratio of 1 : 1 or 2 : 1, at 25.0±0.1°C and with no additional electrolyte. The titration curves for 2-*n*-butyl-8-hydroxyquinoline are shown in Figs. 1 and 2. The curves for the other ligands were found to be similar to those shown in Fig. 1.

Calculations

The Calculation of the Acid Dissociation Constants.—The acid dissociation constants were calculated from the titration curves of the ligands. The equilibrium constants may be expressed as follows:

$$\mathrm{H_2A^+} \rightleftarrows \mathrm{HA} + \mathrm{H^+} \quad K_{\mathrm{NH}} = \frac{[\mathrm{H^+}][\mathrm{HA}]}{[\mathrm{H_2A^+}]} \qquad (1)$$

$$\mathrm{HA} \rightleftarrows \mathrm{H^+} + \mathrm{A^-} \quad K_{\mathrm{OH}} = \frac{[\mathrm{H^+}][\mathrm{A^-}]}{[\mathrm{HA}]} \qquad (2)$$

where $\mathrm{H_2A^+}$ represents the protonated ligand (hydrochlolide).

As is shown in Fig. 1, the two buffer regions are so clearly separated that each dissociation stage can be treated independently. Thus, K_{NH} and K_{OH} can be expressed as follows, according to the standard treatment:

$$K_{\mathrm{NH}} = \frac{[\mathrm{H^+}](aT_{\mathrm{A}} + [\mathrm{H^+}])}{T_{\mathrm{A}} - (aT_{\mathrm{A}} + [\mathrm{H^+}])} \qquad (3)$$

$$K_{\mathrm{OH}} = \frac{[\mathrm{H^+}]\{(a-1)T_{\mathrm{A}} - K_{\mathrm{W}}/[\mathrm{H^+}]\}}{T_{\mathrm{A}} - \{(a-1)T_{\mathrm{A}} - K_{\mathrm{W}}/[\mathrm{H^+}]\}} \qquad (4)$$

where T_{A} and a represent, respectively, the total concentration of the ligand and the number of moles of the base added per mole of ligand, and where $K_{\mathrm{W}}=[\mathrm{H^+}]\cdot[\mathrm{OH^-}]$.

Calculation of Chelate Stability Constants.—The step-by-step chelate formation constants of the reactions, may be expressed as:

$$\mathrm{M^{2+}} + \mathrm{A^-} \leftrightarrows \mathrm{MA^+} \quad K_{\mathrm{MA}} = \frac{[\mathrm{MA^+}]}{[\mathrm{M^{2+}}][\mathrm{A^-}]} \qquad (5)$$

$$\mathrm{MA^+} + \mathrm{A^-} \rightleftarrows \mathrm{MA_2} \quad K_{\mathrm{MA_2}} = \frac{[\mathrm{MA_2}]}{[\mathrm{MA^+}][\mathrm{A^-}]} \qquad (6)$$

The stability constants were calculated by the least-squares method, using the data from 1 : 2 titrations.[10,11)] The equation employed for this method was as follows:

$$\frac{\bar{n}}{(\bar{n}-1)[\mathrm{A^-}]} = \frac{(2-\bar{n})[\mathrm{A^-}]}{(\bar{n}-1)} K_{\mathrm{MA}}\cdot K_{\mathrm{MA_2}} - K_{\mathrm{MA}} \qquad (7)$$

where $\bar{n}$ is the average number of ligands bound per metal ion.

If, by replacing each term, one simplifies the above equation as:

$$Y = \frac{\bar{n}}{(\bar{n}-1)[\mathrm{A^-}]} \qquad (8)$$

$$X = \frac{(2-\bar{n})[\mathrm{A^-}]}{(\bar{n}-1)} \qquad (9)$$

$$a = -K_{\mathrm{MA}} \qquad (10)$$

---

8) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd. ed., Reinhold Publ. Corp., New York (1958), pp. 717, 756.

9) H. J. Harries, *J. Inorg. Nucl. Chem.*, **25**, 519 (1963).

10) H. Irving and H. S. Rossotti, *J. Chem. Soc.*, **1953**, 3397.

11) A. Albert and E. P. Serjeant, "Ionization Constants of Acid and Bases," 1st Ed. Methuen & Co., London, (1962), p. 158.

TABLE II. ACID DISSOCIATION CONSTANTS AND STABILITY CONSTANTS OF 2-ALKYL-8-HYDROXYQUINOLINE AT 25.0±0.1°C, $\mu \simeq 0$, $-\log K_W = 16.1$[9]

Ligand 2-R-8-HQ	Acid dissociation constant	Stability constant				
			Ni(II)	Cu(II)	Zn(II)	Cd(II)
R=H	pK_{NH} (3.97)[a]	log K_{MA}	(11.44)	(13.49)	(9.96)	(9.43)
	pK_{OH} (11.54)	log K_{MA_2}	(9.94)	(12.73)	(8.90)	(7.68)
$R=CH_3$	pK_{NH} 4.63	log K_{MA}	9.3_5	12.4_3	9.8_9	9.1_8
	pK_{OH} 11.83	log K_{MA_2}	8.9_1	11.4_6	9.2_2	8.2_1
$R=C_2H_5$	pK_{NH} 4.47	log K_{MA}	8.6_9	12.0_5	9.6_6	8.6_6
	pK_{OH} 11.86	lcg K_{MA_2}	9.0_5	11.2_8	9.3_0	8.3_1
$R=n\text{-}C_3H_7$	pK_{NH} 4.44	log K_{MA}	9.0_1	12.0_6	8.9_6	8.8_4
	pK_{OH} 11.95	log K_{MA_2}	9.4_6	11.8_1	10.4_9	8.7_0
$R=n\text{-}C_4H_9$	pK_{NH} 4.41	log K_{MA}	9.1_8	12.0_5	9.7_5	9.2_8
	pK_{OH} 12.07	log K_{MA_2}	9.8_9	12.2_3	10.2_4	8.9_8

a) The values in parentheses have been taken from Ref. 13.

$$b = K_{MA} \cdot K_{MA_2} = \beta_2 \qquad (11)$$

then the equations for the least-squares method can be written as follows:

$$\sum Y = na + b\sum X \qquad (12)$$

$$\sum XY = a\sum X + b\sum X^2 \qquad (13)$$

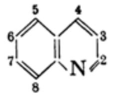
where n represents the number of observed points employed for each set of calculations. The experimental data corresponding to the $\bar{n}$ values of 0.95—1.05 were omitted in the calculations, because these values are very critical to the results. The results of the calculations[12] are summarized in Table II.

Results and Discussion

The Structural Proof for the Ligand.—In order to confirm the proposed structure for 2-alkyl-8-hydroxyquinoline, the NMR spectra were observed on the hydrochlorides in a deuterium oxide solution.

The spectra were measured at 60 Mc./sec., using tetramethylsilane as an internal standard. The results are summarized in Table III, along with their assignments. The table also includes the data for quinoline hydrochloride, 8-hydroxyquinoline hydrochloride and 2-methyl-8-hydroxyquinoline hydrochloride. The peaks at 1.43 τ of 8-hydroxyquinoline hydrochloride are assigned to the protons on C-2 and C-4; the decrease in the intensities of the corresponding peaks in the $1.4-1.6\ \tau$ region for the 2-alkyl derivatives indicates the elimination of a proton on either C-2 or C-4 by alkyl substitution. However, the spin-spin coupling constant of these peaks (8.5 c. p. s.) is closer to a J_{34} coupling constant of 7.3 c. p. s. than to the J_{23} coupling constant of quinoline[14]

TABLE III. ASSIGNMENTS OF NMR SPECTRA OF 2-ALKYL-HYDROXYQUINOLINE



Compound	Peaks (τ)*	Intensity	Assignments of proton
Quinoline HCl	0.90	2	C-2, C-4
	1.95	5	C-3, C-5, C-6 C-7, C-8
8-Hydroxy-, HCl	1.43	2	C-2, C-4
	2.03	1	C-5
	2.93	2	C-6, C-7
	3.25	1	C-7
2-Methyl-8-hydroxy-, HCl	1.63	1	C-4
	2.50	1	C-3
	2.80	2	C-6, C-7
	3.07	1	C-3
	7.23	3	$-CH_3$
2-Ethyl-8-hydroxy-, HCl	1.63	1	C-4
	2.37	1	C-5
	2.88	2	C-6, C-7
	3.10	1	C-3
	6.97	2	$-CH_2-$
	8.65	3	$-CH_3$
2-n-Propyl-8-hydroxy-, HCl	1.50	1	C-4
	2.40	1	C-5
	2.73	2	C-6, C-7
	2.93	1	C-3
	6.95	2	$-CH_2-$ (α)
	8.27	2	$-CH_2-$ (β)
	9.00	3	$-CH_3$
2-n-Butyl-8-hydroxy-, HCl	1.47	1	C-4
	2.35	1	C-5
	2.68	2	C-6, C-7
	2.88	1	C-3
	6.93	2	$-CH_2-$ (α)
	8.50	4	$-CH_2-CH_2-$(β,γ)
	9.07	3	$-CH_3$

* The values listed in the table show the center of multiplet peaks.

---

12) Such calculations were carried out at the Computing Center of Kyushu University.

13) W. D. Johnston and H. Freiser, *J. Am. Chem. Soc.*, **74**, 5239 (1952).

14) J. A. Pople, W. G. Schneider and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill, New York (1959), p. 269.

of 5.0 c. p. s., which was chosen as a model compound. Therefore, it is quite likely that the proton on C-2 is eliminated by the alkyl substitution, while the proton on C-4 remains unaltered.

Titration Curves.—The corrected potentiometric titration curves for 2-*n*-butyl-8-hydroxyquinoline, with or without an equivalent amount of metal ions, are given in Fig. 1.

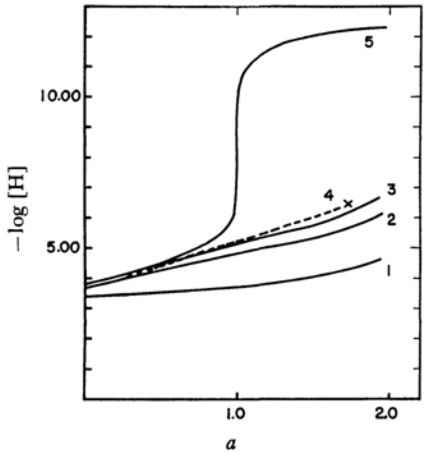


Fig. 1. Titration curves for 1 : 1 solution. Concn. of ligand and metal ions: 1×10^{-3} M
1: Cu(II), 2: Zn(II), 3: Ni(II), 4: Cd(II), 5: ligand

The titration curves for the solutions with a 1 : 2 metal ligand ratio are illustrated in Fig. 2. It was noticed that some chelates began to precipitate at the point indicated by "X".

The curves of the other ligands are very similar to those of 2-*n*-butyl-8-hydroxyquinoline. The pK_{NH} and pK_{OH} values were calculated from the data of the titration curves of the ligands, in the ranges of $a=0.3$—0.7 and $a=1.3$—1.7 respectively.

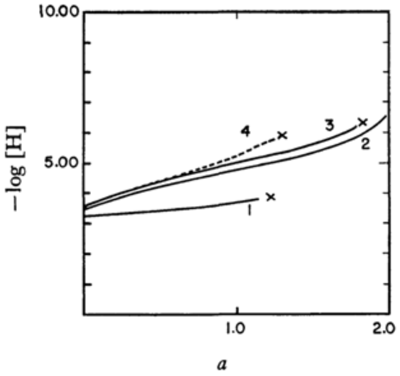


Fig. 2. Titration curves for 1 : 2 solution. Concn. of ligand: 2×10^{-3} M
1: Cu(II), 2: Zn(II), 3: Ni(II), 4: Cd(II)

Formation Functions and Equilibrium Constants.—The acid dissociation constants for 2-alkyl-8-hydroxyquinoline are shown in Table II. The pK_{NH} and pK_{OH} values stand for the dissociation of protons from the quinoline nitrogen and the phenolic oxygen respectively.

The chelate stability constants of these ligands with various metal ions are also shown in Table II. The reported values for 8-hydroxyquinoline, as well as those for 2-methyl-8-hydroxyquinoline,[13] are also included in the table for the sake of comparison. The chelate stability constants were computed by the least-squares method on the basis of the data on 1 : 2 titration described above. A typical example of calculations, those on the copper(II)-2-*n*-butyl-8-hydroxyquinoline system, is shown in Table IV. It may be seen from the table that fairly consistent stability constants are obtained over a wide range of $\bar{n}$ values, and that one could use the values of three significant figures in a meaningful discussion. These results are satisfactory if one considers the experimental conditions under which the titration was conducted in a non-aqueous solvent without an added electrolyte,

TABLE IV. CALCULATIONS OF CHELATES STABILITY CONSTANTS ON THE SYSTEM COPPER(II)-2-*n*-BUTYL-8-HYDROXYQUINOLINE (1 : 2 TITRATION)

	[A]	$\bar{n}$	$X=\frac{(2-\bar{n})[A]}{(\bar{n}-1)}$	$Y=\frac{\bar{n}}{(\bar{n}-1)[A]}$	$\log K_{MA}$	$\log \beta_2$
1	0.19874×10^{-12}	0.2949	-0.48061×10^{-12}	-0.21045×10^{13}	12.07	24.31
2	0.24700×10^{-12}	0.3668	-0.63706×10^{-12}	-0.23451×10^{13}	12.05	24.28
3	0.29789×10^{-12}	0.4446	-0.83422×10^{-12}	-0.26870×10^{13}	12.04	24.27
4	0.34875×10^{-12}	0.5272	-0.10863×10^{-11}	-0.31967×10^{13}	12.05	24.28
5	0.40366×10^{-12}	0.6127	-0.14460×10^{-11}	-0.39195×10^{13}	12.07	24.29
6	0.46969×10^{-12}	0.6998	-0.20345×10^{-11}	-0.49639×10^{13}	12.04	24.28
7	0.52703×10^{-12}	0.7919	-0.30600×10^{-11}	-0.72217×10^{13}	12.14	24.30
8	0.61205×10^{-12}	0.8827	-0.58285×10^{-11}	-0.12291×10^{14}	12.07	24.28

$\sum X=-0.15407\times10^{-10}$ $\sum Y=-0.38729\times10^{14}$ $\log K_{MA}=12.05$

$\sum X^2=0.52078\times10^{-22}$ $\sum XY=0.11772\times10^{3}$ $\log \beta_2=24.28$

$\log K_{MA}=12.09\pm0.05$
$\log K_{MA_2}=12.20\pm0.07$
$\log \beta_2=24.29\pm0.02$

and the early onset of precipitation. Therefore, the following discussion is based mainly on those values of three significant figures.

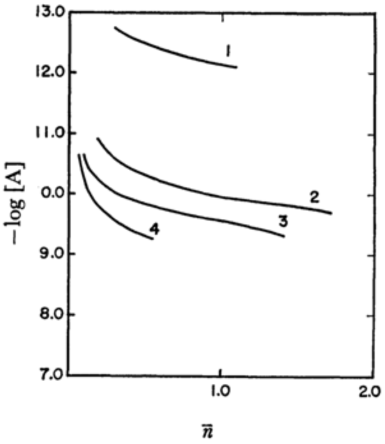


Fig. 3. Formation functions of some divalent metal chelates of 2-*n*-butyl-8-hydroxyquinoline.
Concn. of ligand: 2×10^{-3} M
Metal ions: 1×10^{-3} M
1: Cu(II), 2: Zn(II), 3: Ni(II), 4: Cd(II)

The Bjerrum's formation functions for the metal chelates of 2-*n*-butyl-8-hydroxyquinoline are shown in Fig. 3. Because of the early appearance of the precipitation, the formation curves only extended to $\bar{n}\approx 0.6$ for cadmium(II) and $\bar{n}\approx 1.0$ for copper(II). Only in the case of zinc(II) was a curve extending over almost the entire range found. Although the formation curve for a 1 : 1 or 1 : 2 chelate ratio has been shown to be symmetrical about $\bar{n}=1$, it does not seem likely in this case. The deviation from symmetry may be due to the easy precipitation.

The Effect of the Alkyl Group on the Chelate Stability.—As is shown in Table II, the pK_{NH} value is almost constant, regardless of the kind of alkyl groups, with the exception of the 2-methyl derivative, which shows a slightly higher pK_{NH} value than the rest of the ligands. On the other hand, the pK_{OH} value increases slightly with the increasing carbon number of the alkyl group.

Irving and Rossotti investigated the effect of alkyl substitution on the acid dissociation constant of 8-hydroxyquinoline; they found that pK_{OH} value increased and the pK_{NH} value decreased when the position of the methyl substitution moved from the C-2 to the C-7 position of the quinoline ring.[15] This effect is understood to be due to the *I*-effect of the methyl group. Similarly, one can expect an *I*-effect of the 2-alkyl group for the 2-alkyl-8-hydroxyquinolines, which have higher pK_{NH} values than 8-hydroxyquinoline, as is shown in Table II. However, the contribution of the *I*-effect of the 2-alkyl group to the pK_{NH} value may be partly cancelled by the steric effect of higher alkyl groups, which will interfere with the access of protonium ions to the quinoline nitrogen. Thus, the pK_{NH} value is highest for the 2-methyl derivative, while 2-ethyl, 2-*n*-propyl and 2-*n*-butyl derivatives have lower pK_{NH} values than the 2-methyl derivative. Regarding the pK_{OH} values, the access of protonium ions to the phenolate oxygen will not be interfered with by a 2-alkyl group. Therefore, pK_{OH} may be influenced only by the *I*-effect of the 2-alkyl group, although this influence may be fairly weak. The increase in the pK_{OH} value with the increase in the carbon number of the alkyl group supports this theory.

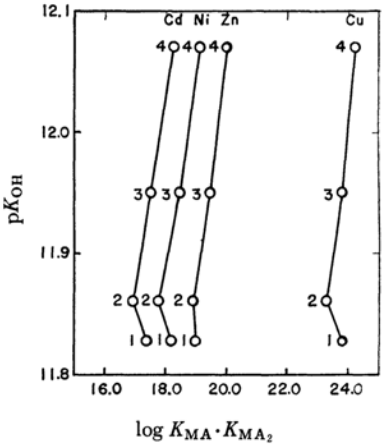


Fig. 4. Correlation between pK_{OH} and $\log K_{MA}\cdot K_{MA_2}$.
1: Me, 2: Et, 3: *n*-Pr, 4: *n*-Bu

As to the chelate stability constants, the values change rather slightly with the variation in alkyl group, as is shown in Table II. However, their differences seem to be large enough to allow us to make a meaningful interpretation of the results.

The order for the decreasing stability constants of 8-hydroxyquinoline was found to obey the Mellor-Maley order. However, the order of nickel and zinc was inverted in the case of 2-alkyl derivatives; thus:

8-hydroxyquinoline: Cu>Ni>Zn>Cd
2-alkyl derivative: Cu>Zn>Ni>Cd

The relationship between the overall stability constants and the acidity of the ligands is shown in Fig. 4. The $\log K_{MA}\cdot K_{MA_2}$ values are plotted against the pK_{OH} values, since the pK_{NH} values are almost contant for all the ligands except the 2-methyl derivatives. As expected, the overall stability constants increase linearly with the increase in the pK_{OH} values. However, in the case of the 2-methyl derivative, the relatively higher pK_{NH} value contributes to the overall stability constants, so that the values for the 2-methyl derivative deviate from linearity.

---

[15] H. Irving and H. S. Rossotti, *J. Chem. Soc.*, **1954**, 2910.

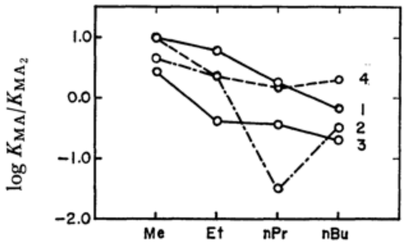


Fig. 5. Correlation for substituents.
1: Cu(II), 2: Zn(II), 3: Ni(II), 4: Cd(II)

The plots of log K_{MA}/K_{MA_2} against the carbon number of the alkyl group are shown in Fig. 5. It may be seen from this figure that the relative stability of 1 : 1 chelate to 1 : 2 chelate decreases with an increase in the carbon number of the alkyl group, with the exceptions of zinc and cadmium chelates of the 2-butyl derivative. This result is quite surprising, because it indicates that the formation of 1 : 2 chelate becomes more favorable when the higher alkyl group is introduced at the C-2 position of 8-hydroxyquinoline. The irregular behavior of zinc and cadmium may be partly explained in terms of the steric hindrance to the tetrahedral coordination structure; however, more experimental data will be needed before we can make a clear-cut explanation of the results obtained in this investigation.

The authors are greatful to the Ministry of Education, Japanese Government, for a grant in support of this work. They also thank to Dr. Kenji Motojima of Japan Atomic Energy Institute for his advice of the initiation of this work.