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Studies on New Derivatives of 8-Quinolinol as Chelating Agents. I. Syntheses, Coloration Reaction with Metal Ions and Acid Dissociation Constants of Some Azomethine and Aminomethyl Derivatives

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Azomethine derivatives of 8-hydroxyquinoline-2-carbaldehyde with aromatic and aliphatic amines and their aminomethyl derivatives were synthesized for the purpose of investigating their applications as analytical reagents. Spot tests with metal ions revealed that azomethine derivatives form intensely colored chelates, whereas aminomethyl derivatives form less intensely colored chelates. The acid dissociation constants were determined by means of potentiometric titration in 50 v/v% aqueous dioxane solution at 25±0.1°C. The values of pK_{NH^+} and pK_{OH} of 8-hydroxyquinoline-2-carbaldehyde, 2-(*o*-hydroxyphenylaminomethyl)-, 2-(*p*-chlorophenylaminomethyl)-, 2-(*p*-tolylaminomethyl)- and 2-(naphthylaminomethyl)-8-quinolinol are lower than those of 8-quinolinol. The phenyl substituent in 2 position of oxine moiety exerts an acid strengthening effect on these ligands. The basicity of the ligand *N,N'*-bis-(8-hydroxy-2-quinolylmethyl) ethylenediamine is higher than that of other oxine derivatives.

A number of derivatives of oxine have been prepared for the purpose of finding analytical reagents. However, the search has been confined to derivatives containing only the same coordinative groups as oxine, and little effort has been made to find multidentate ligands. As the ligands having additional coordinative groups, the azo derivatives,[1] 2-aminomethyl-,[2] and 2-hydroxymethyl-8-quinolinol[2] havebeen studied. In fact, 2-aminomethyl-8-quinolinol was confirmed to act as terdentate ligand with Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+} ions to produce more stable chelates than oxine.

Expecting the multidentate ligands derived from oxine to have excellent properties as analytical reagents, we attempted to synthesize 8-hydroxyquinoline-2-carbaldehyde, azomethine, and aminomethyl derivatives.

Azomethine derivatives were prepared from 8-hydroxyquinoline-2-carbaldehyde and primary amines. Condensation of the aldehyde with ethylenediamine, *o*-aminophenol, *p*-chloroaniline, *p*-toluidine, and naphthylamine in ethanol proceeded easily with gentle warming to give azomethine derivatives. Aminomethyl derivatives were prepared by the reduction of the azomethine derivatives with sodium borohydride in dioxane or ethanol at room temperature. The reaction scheme is given in Chart 1a and 1b.

We investigated the coloration reaction with metal ions and the acid dissociation constants of these derivatives in comparison with those of oxine in order to obtain information on their applicability as analytical reagents.

Experimental

Preparation. 8-Acetoxyquinoline-2-carbaldehyde: To a suspension of 5.8 g of freshly sublimed selenium dioxide in 400 m*l* of dioxane warmed with stirring on a water bath at 50—55°C, was added a solution of 11.4 g of 2-methyl-8-

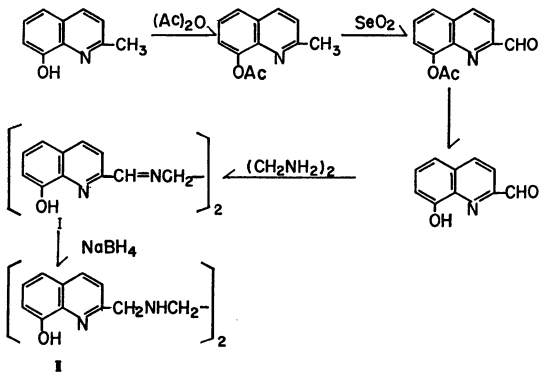

Chart 1a.

* Present address: Yoshida, Shimoadachi-cho, Sakyo-ku, Kyoto.

1) T. Boyd, E. F. Degering, and R. N. Shreve., *Ind. Eng. Chem., Anal.* **Ed.**, 10, 606 (1938).

2) R. L. Stevenson and H. Preiser, *Anal. Chem.*, **39**, 1354 (1967).

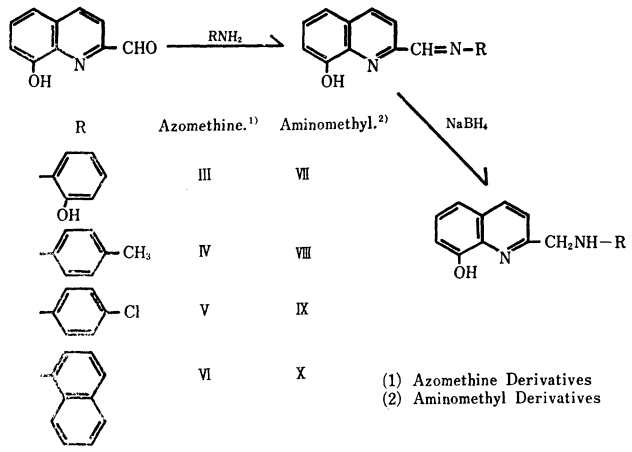

Chart 1b.

acetoxyquinoline in 50 m*l* of dioxane during the course of 3 hours. The mixture was heated to 75—80°C, allowed to stand for 2 hr, filtered, and dioxane was distilled off under reduced pressure. The residue was recrystallized from dioxane to give 9.0 g of light yellow crystals, mp 94—95°C. Found: C, 67.23; H, 4.37; N, 6.71%. Calcd for $C_{12}H_9NO_3$: C, 66.98; H, 4.21; N, 6.51%.

8-Hydroxyquinoline-2-carbaldehyde. A solution of 20 g of 8-acetoxyquinoline-2-carbaldehyde in toluene was cooled to −3°C, and stirred vigorously while 1440 m*l* of aqueous potassium hydroxide was added over 40—50 minutes. The mixture was allowed to stand at room temperature for 30 minutes, and neutralized with 20% aqueous acetic acid. The yellow powder precipitated was recrystallized from cyclohexane to give 13.5 g of yellow crystals, mp 98°C. Found: C, 69.25; H, 3.97; N, 8.26%. Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.08%.

N,N-*Bis(8-hydroxy-2-quinolylmethylene)ethylenediamine (I):* To a solution of 2 g of 8-hydroxyquinoline-2-carbaldehyde in ethanol, was added a solution of 0.35 g of ethylenediamine in ethanol. The mixture was warmed on a water bath for 30 min., cooled in an icebath, and the crystals were filterd. Recrystallization from ethanol gave 1.9 g of white crystals.

N,N′-*Bis(8-hydroxy-2-quinolylmethyl)ethylenediamine (II):* To a suspension of 2.0 g of I in 25 m*l* of ethanol, was added dropwise a solution of 0.8 g of sodium borohydride in ethanol at room temperature. The mixture was kept standing for 1 hr., filtered, and ethanol was removed under reduced pressure. Yellow powder obtained was dissolved in 30% aqueous acetic acid, neutralized with aqueous sodium carbonate. An oily substance appeared on the surface crystallized gradually on standing. Recrystallization from dioxane gave 1.2 g of light yellow crystals.

N-*(8-Hydroxy-2-quinolylmethylene)*-o-*aminophenol (III):* To a solution of 2 g of 8-hydroxyquinoline-2-carbaldehyde in boiling ethanol was added a solution of 1.26 g of *o*-aminophenol in ethanol. The mixture was cooled in an ice bath, and the crystals were filtered and recrystallized from ethanol to give 2.8 g of yellow crystals.

2-(o-Hydroxyphenylaminomethyl)-8-quinolinol (VII): To a suspension of 0.4 g of sodium borohydride in 25 m*l* of dioxane was added dropwise a solution of 1 g of III in 10 m*l* of dioxane at room temperature. The mixture was kept standing for 1.5 hr and was added to the 2—4 equivalent volume of water. This solution was concentrated and the oil separated was crystallized with chilling in an ice bath. Recrystallization from aqueous ethanol gave 0.6 g of white crystals.

The other azomethine and aminomethyl derivatives were prepared by the same method as described above. The melting points and analytical data of the synthesized derivatives are given in Table 1.

Potentiometric titration. Since all the aminomethyl derivatives synthesized are insoluble in water, the potentiometric titration was carried out in 50 v/v% aqueous dioxane solution. A solution containing the ligands (10^{-3} mol/*l*) and perchloric acid ($1.0-2.0\times10^{-3}$ mol/*l*) in 50 v/v% aqueous dioxane solution was titrated with carbonate free 0.1 N KOH solution prepared according to Armstrong's method[3] and standardized against potassium hydrogen phthalate. During the course of titration, the temperature was maintained at 25±0.1°C and a stream of CO_2 free nitrogen was passed through the titration vessel. All the potentiometric measurements of pH were carried out with a Radiometer Titrator TTT 1 and Titrigraph equipped with a Radiometer G 203 B glass electrode and K 401 saturated calomel electrode. The instrument was standardized at pH 4.01 and 6.86 using a Toa Electronics buffer solution. The pH meter correction and ion products of water for solution of 50 v/v% aqueous dioxane were determined to be −0.12 and 15.38, respectively. These values are in agreement with those reported recently by Irving,[4] and Taka-

Table 1. Azomethine and aminomethyl derivatives

Derivative No.	Mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
I	165—166	$C_{22}H_{18}N_4O_2$	71.34	4.89	15.12	71.15	5.19	15.06
II	167—168	$C_{22}H_{22}N_4O_2$	70.57	5.92	14.96	70.58	5.76	14.75
III	168—169	$C_{16}H_{12}N_2O_2$	72.71	4.58	10.60	72.71	4.79	10.44
IV	104—105	$C_{17}H_{14}N_2O$	77.84	5.38	10.68	77.93	5.52	10.56
V	135—136	$C_{16}H_{11}N_2OCl$	67.98	3.92	9.91	67.89	4.08	9.73
VI	123—124	$C_{20}H_{14}N_2O$	80.51	4.73	9.39	80.80	4.97	9.22
VII	134—135	$C_{16}H_{14}N_2O$	72.16	5.30	10.52	72.28	5.25	10.36
VIII	114—115	$C_{17}H_{16}N_2O$	77.25	6.10	10.60	76.99	6.24	10.54
IX	153—154	$C_{16}H_{13}N_2OCl$	67.48	4.60	9.84	67.52	4.34	9.72
X	164—165	$C_{20}H_{16}N_2O$	79.98	5.37	9.33	80.04	5.54	9.26

3) D. M. G. Armstrong, *Chem. Ind.*, (London) **1955**, 1405.
4) H. M. N. H. Irving and H. S. Rossoti, *J. Inorg. Nucl. Chem.*, **30**, 1215 (1968)

Table 2. Spot tests[a)]

Metal Ion	Derivative					
	oxine	I	III	IV	II	VII
Fe^{3+}	dark green(p)[b)]	brownish red(p)	black(p)	black(p)	green	brownish red(p)
Fe^{2+}	dark green(p)	black red((p)	black(p)	black(p)	green	brownish red(p)
Cu^{2+}	green(p)	brownish orange	orange(p)	orange(p)	light yellow	green
Co^{2+}	light yellow	orange(p)	orange(p)	orange(p)	light yellow	light yellow
Ni^{2+}	light yellow	red(p)	red(p)	brown(p)	light yellow	light yellow
Zn^{2+}	yellow	orange	reddish orange(p)	orange(p)	yellow	light yellow
Cd^{2+}	yellow(p)	orange	red(p)	orange(p)	yellow	light yellow
Mn^{2+}	yellow(p)	orange	red(p)	orange(p)	light yellow	light yellow

a) Metal ion solutions were added to 5% dioxane solution of oxine derivatives and the color changes of the solutions were observed at pH 6.8.
b) Precipitation occurred.

moto.[5)]

Results and Discussion

The results of the spot tests are shown in Table 2. The color reaction of the ligands obtained differs considerably from that of oxine as seen in Table 2. The results imply that the ligands may be useful as a metallochromic indicator and the reagents for colorimetric or gravimetric analysis.

The chelates of Fe^{3+}, Fe^{2+}, Cu^{2+}, Ni^{2+}, and Co^{2+} with azomethine derivatives can be extracted into the organic solvents such as isoamyl alcohol and chloroform. Among the ligands whose structures are given in Chart 1, ligands I and III form the most intensely colored chelates.

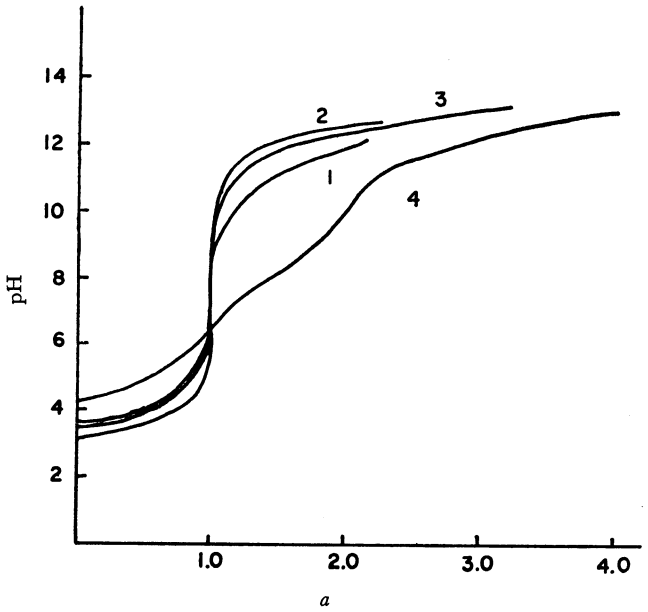

Fig. 1. Potentiometric titration curves of 8-quinolinol derivatives in 50 v/v% aqueous dioxane solution, $\mu=0.1$, 25°C; abscissa a represents moles of base added per mole of ligand.
Curve 1. 8-hydroxyquinoline-2-carbaldehyde
2. 2-(*p*-tolylaminomethyl)-8-quinolinol
3. 2-(*o*-hydroxyphenylaminomethyl)-8-quinolinol
4. *N*,*N*-bis(8-hydroxyquinolyl)ethylenediamine

Azomethine derivatives studied in this work were found to hydrolyze readily in aqueous solution and their acid dissociattion constants could not be determined. The acid dissociation constants of aminomethyl derivatives were determined in 50 v/v% aqueous dioxane solution. The potentiometric titration curves of these ligand are shown in Fig. 1.

As regards the curves of ligands VIII, IX, and X, the separation of two dissociation steps is shown clearly by the pH jump at $a=1$. The first and second steps correspond to the dissociation of proton from the quinoline nitrogen and hydroxyl groups, respectively. The titration curve of ligand VII indicates that the dissociation of proton from quinoline nitrogen occurs in acidic region and the dissociation of two hydroxyl groups overlaps in alkaline region. The titration curve of ligand II exhibits two pH jumps at $a=1$ and $a=2$. This shows that the dissociation of proton from the imino groups occurs in the neutral region and the dissociation from the hydroxyl groups overlaps in the alkaline region.

The acid dissociation constants were calculated by Schwarzenbach's[6)] method with the use of the following equations.

$$K_1 = \frac{[HL]}{[L]\cdot[H^+]},\ K_2 = \frac{[H_2L]}{[HL]\cdot[H^+]},\ \cdots,$$

$$K_j = \frac{[H_jL]}{[H_{j-1}L]\cdot[H^+]} \quad (1)$$

$$[L]_t = \sum_{j=0}^{m}[H_jL] \quad (2)$$

$$[H]_t = [H^+] - [OH^-] + \sum_{j=0}^{m} j\cdot[H_jL] \quad (3)$$

$$\sum_{j=0}^{m}(g-j)\cdot[H^+]^j\cdot\bar{K}_j = 0 \quad (4)$$

$$(\bar{K} = K_1\cdot K_2\cdot K_3\cdots K_j)$$

where

K_1, K_2, K_3, $\cdots$, K_j: the successive acid stability constants

$[L]_t$: total acid concentration

5) S. Takamoto, Q. Fernand, and H. Freiser, *Anal. Chem.*, **37**, 1249 (1965)

6) G. Schwarzenbach, *Helv. Chim. Acta*, **33**, 947 (1950)

$[H]_t$: total acid concentration

g: average number of moles of proton bound per mole of ligand

m: maximum number of moles of proton per mole of ligand

Applying Schwarzenbach's method to ligand [II] (H_4L^{2+}), Eq. (4) is modified to be

$$g + (g-1)\cdot K_1\cdot[H^+] + (g-2)\cdot\overline{K}_2\cdot[H^+]^2 + (g-3)\cdot\overline{K}_3\cdot[H^+]^3 + (g-4)\cdot\overline{K}_4\cdot[H^+]^4 = 0 \quad (5)$$

As is apparent from the titration curve 4 in Fig. 1, there exist two species H_4L^{2+} and H_3L^+ between $a=0$ and $a=1$, two species H_3L^+ and H_2L between $a=1$ and $a=2$, and three spcies H_2L, HL^-, and L^{2-} between $a=2$ and $a=4$. Thus, Eq. (5) can be approximated by the following equations in the first, second, and third buffer regions, respectively.

$$(g-3) + (g-4)\cdot K_4\cdot[H^+] = 0 \quad (6)$$

$$(g-2) + (g-3)\cdot K_3\cdot[H^+] = 0 \quad (7)$$

$$g + (g-1)\cdot K_1\cdot[H^+] + (g-2)\cdot\overline{K}_2\cdot[H^+]^2 = 0 \quad (8)$$

Since g and $[H^+]$ are determined experimentally, the acid stability constants K_3 and K_4 can be calculated from Eqs. (6) and (7), and the overlapping acid stability constants K_1 and K_2 are calculated by the least squares method from Eq. (8). The results are summarized in Tables 3 and 4, and are compared with the dissociation constant of oxine.

As shown in Table 3, the pK_{NH^+} (the dissociation constant of quinoline nitrogen) and pK_{OH} values of these ligands are lower than the corresponding values of oxine. In 8-hydroxyquinoline-2-carbaldehyde, the dissociation constants are in agreement with the values reported in literature (pK_{NH^+} <3, pK_{OH}=10.24).[2]

The pK_{OH} values of 2-(tolylaminomethyl)-, 2-(*p*-chloroaminomethyl)-, and 2-(α-naphthylaminomethyl)-8-quinolinol are almost the same and pK_{NH^+} values increase in the order IX<X<VII<oxine. Thus it is supposed that the electron-withdrawing effect of phenyl group affects the quinoline ring through the $=CH_2NH-$ group and the substituent in the phenyl ring influences 1 position to some extent, but not 8 position of quinoline. Since the methyl group in 4 position of benzene ring behaves as an electron-donating group and the chloro group as an electron-withdrawing group, the pK_{NH^+} value of ligand VIII is higher than that of ligand IX.

In the *o*-hydroxy derivative 2-(*o*-hydroxyphenylaminomethyl)-8-quinolinol (VII), assingnment of the two values of pK_{OH} is very difficult. In 5-(*o*-hydroxyphenylazo)-8-quinolinol,[5] the dissociation constant of the quinoline hydroxyl group and that of the phenyl hydroxyl group have been reported to be 8.51 and 12.0, respectively. As shown in Table 3, the pK_{OH} values of ligands VIII, IX, and

Table 3. Acid dissociation constants of aminomethyl derivatives in 50 v/v% aqueous dioxane solution at 25°C, μ=0.1 (KCL)

Substituent in 8-quinolinol	pK_{NH^+}	pK_{OH}	pK_{OH}
None	3.97	11.54	
2-formyl	<3	9.92±0.02	
2-(*p*-tolylaminomethyl)	3.62±0.02	11.11±0.03	
2-(*p*-chlorophenylaminomethyl)	3.19±0.02	11.10±0.02	
2-(naphthylaminomethyl)	3.39±0.02	11.11±0.03	
2-(*o*-hydroxyphenylaminomethyl)	3.71±0.03	10.86	11.35

Table 4. Comparison of acid dissociation constants

	$pK_{NH_2^+}$	$pK_{NH_2^+}$	pK_{OH}	pK_{OH}
ligand[a]	5.12	8.15	10.81	11.35
EDDA[b]	6.42	9.46		
EDAMP[c]	5.45	8.23		

a) 50 v/v% aqueous dioxane solution, μ=0.1 (KCl), at 25°C.
b) Aqueous solution, μ=0.1 (KCl), at 30°C.
c) Aqueous solution, μ=0.1 (KNO_3), at 25°C.

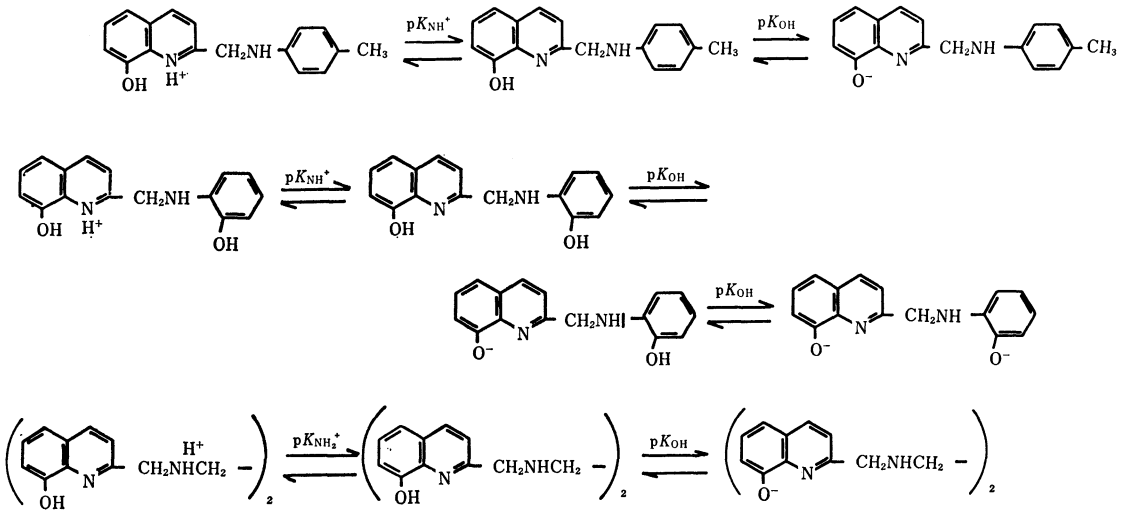

Chart 2

X are lower than those of oxine by about 0.4 log unit. Thus, we assigned the lower value (10.86) of pK_{OH} to the dissociation constant of the hydroxyl group in the quinoline ring and the higher value (11.35) to that of the hydroxyl group in the benzene ring.

In Table 4, the two $pK_{NH_2^+}$ values of ligand II corresponding to the dissociation of the imino groups are compared with those of the aliphatic analog, ethylenediaminediacetic acid (EDDA)[7] and the aromatic analog, ethylene-bis(2-aminomethyl)pyridine (EDAMP).[8] The $pK_{NH_2^+}$ values are similar to those of EDAMP and lower than those of EDDA. This suggests that the dissociation steps between $a=0$ and $a=2$ in the titration curve 4 in Fig. 1 do not correspond to the dissociation of proton from quinoline nitrogen, but to that from the imino group.

Since the basicity of ligand II is higher than that of other oxine derivatives and the ligand is expected to behave as the multidentate ligand, it is presumed that it forms more stable chelates with various metal ions than other oxine derivatives.

The equilibria involving quinoline nitrogen, hydroxyl groups and imino groups in 50 v/v% aqueous dioxane solution may be represented as shown in Chart 2. The dissociation steps of the hydroxyl groups of ligand VII are not completely clarified.

7) S. Chaberek and A. E. Martell, *J. Amer. Chem. Soc.*, **74**, 6228 (1952)

8) R. G. Lacoste and A. E. Martell, *Inorg. Chem.*, **3**, 881 (1964)