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Syntheses and Chelating Properties of Sulfonamidoquinolines

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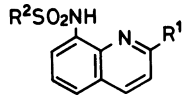
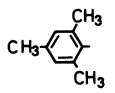
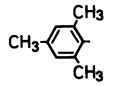
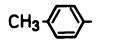
Seven chelating agents were synthesized. The complexation properties of these reagents with divalent metals (Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}) were investigated in dioxane-water (75% dioxane, 25% water), and the complex formation constants were compared with those of 8-quinolinol as a reference chelating agent. These sulfonamidoquinoline reagents formed ML and ML_2 type complexes, and the order of complex stabilities followed Irving-Williams' order except for 2-methyl substituted derivatives. With 2-methyl derivatives, Ni^{2+} complexes were less stable than Co^{2+} complexes. Structural characteristics of sulfonamides as chelating agent were discussed in detail.

We have synthesized a series of new sulfonamide reagents, and studied their properties as regards the complexation and the solvent extraction of metal ions.[1-4] The acidity of an amide proton of sulfonamide is comparable to that of phenol, and in this respect sulfonamide-type chelating agents are expected to show a similar complex-forming ability to ordinary phenol-based chelating agents. Experimental studies showed that this is in fact the case.[1-7]

8-Sulfonamidoquinoline derivatives extract transition metal ions as 8-quinolinol do, but they strongly prefer the extraction of copper(II) and do not extract iron(III).[1,3,8,9] To understand somewhat unusual metal extraction behavior of 8-sulfonamidoquinoline as compared with phenolic or β-diketone-type extractants, a measurement of complex formation constants of this series of chelating agents is highly desirable.

In this study, the complex formation constants with divalent metals of sulfonamidoquinolines, 8-(methanesulfonamido)quinoline (**MQ**), 8-(2,4,6-trimethylbenzenesulfonamido)quinoline (8-(mesitylenesulfonamido)quinoline; **MsQ**), 8-(trifluoromethanesulfonamido)-quinoline (**FQ**), 8-(*p*-toluenesulfonamido)quinoline (*p*-**TQ**), 2-methyl-8-(methanesulfonamido)quinoline (**MMQ**), 2-methyl-8-(mesitylenesulfonamido)quinoline (**MMsQ**), and 2-methyl-8-(trifluoromethanesulfonamido)-quinoline (**MFQ**), were investigated by potentiometric method.



R^1	R^2	Abbrev.
H	CH_3	MQ
CH_3	CH_3	MMQ
H		MsQ
CH_3		MMsQ
H	CF_3	FQ
CH_3	CF_3	MFQ
H		p-TQ

Experimental

Syntheses of Sulfonamide Reagents. *2-Methyl-8-methanesulfonamidoquinoline (**MMQ**).* To a pyridine solution (15 ml) of 8-amino-2-methylquinoline (1.0 g, 6.32 mmol) was added dropwise a benzene solution of methanesulfonyl chloride (0.793 g, 6.92 mmol) in an ice bath during 1 h. The reaction mixture was gradually warmed to 60 °C, and 1 ml of water was added. After stirring for 30 min, the reaction mixture was evaporated under reduced pressure. The residue was dissolved in chloroform, and was washed with diluted sulfuric acid, water, 5% sodium carbonate solution and water, successively. The chloroform solution was dried with sodium sulfate, concentrated, and was chromatographed on a silica-gel column (WAKOGEL C-200, 17×40 mm) with chloroform as an eluent. The main band was collected, and the product was recrystallized from methanol. Yield, 0.83 g (55%). Pale yellow needles. Mp 142.5—143.5 °C. IR (KBr disk) 3300 (NH), 1328, 1147 cm^{-1} (SO_2). ^1H NMR (δ ppm from TMS; $CDCl_3$); δ=2.70 (3H, s, CH_3-2), 3.00 (3H, s, CH_3SO_2-), 7.35—8.12 (5H, m, Ar-H). Found: C, 55.90; H, 5.16; N, 11.77%. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86%.

*8-(Trifluoromethanesulfonamido)quinoline (**FQ**).* To a dichloromethane solution (70 ml) of 8-aminoquinoline (7.2 g, 50 mmol) was slowly added a dichloromethane solution (10 ml) of freshly distilled trifluoromethanesulfonic anhydride (15.3 g, 54 mmol) in the period of 30 min. The mixture was stirred for 1.5 h in an ice bath, and then gradually warmed to 60 °C (1h). After the removal of solvent under reduced pressure, the reaction mixture was dissolved in chloroform, and was washed with water. The chloroform solution was dried with sodium sulfate, concentrated, and was chromatographed on a silica-gel column (WAKOGEL C-200, 20×40 mm) with chloroform as an eluent. The main band was collected and the product was recrystallized from chloroform. Yield, 10.8 g (78%). Yellow prisms. Mp 146—147 °C. IR (KBr disk) 3140 (NH), 1295, 1145 cm^{-1} (SO_2). ^1H NMR ($CDCl_3$); δ= 7.30—7.75 (3H, m, H-3, -5, and -6), 7.90 (1H, dd, H-7, J=2.6, 6.0 Hz), 8.23 (1H, dd, H-4, J=1.6, 7.8 Hz), 8.81 (1H, dd, H-2, J=4.1, 1.6 Hz). Found: C, 43.35; H, 2.60; N, 10.17%. Calcd for $C_{10}H_7F_3N_2O_2S$: C, 43.38; H, 2.55; N, 10.14%.

*2-Methyl-8-(trifluoromethanesulfonamido)quinoline (**MFQ**).* This compound was prepared in a similar manner to **FQ**. Recrystallized from methanol-chloroform. Yield, 80%. Yellow needles. Mp 137.0—137.5 °C. IR (KBr disk) 3165 (NH), 1290, 1154 cm^{-1} (SO_2). ^1H NMR ($CDCl_3$); δ=2.75 (3H, s, CH_3-), 7.37 (1H, d, H-3, J=8.0 Hz), 7.40—7.70 (2H, m, H-5 and -6), 7.85 (1H, dd, H-7, J=6.5, 2.5 Hz), 8.10 (1H, d, H-4, J=8.0 Hz). Found: C, 45.54; H, 3.21; N, 9.65%. Calcd for $C_{11}H_9F_3N_2O_2S$: C, 45.52; H, 3.13; N, 9.65%.

*8-Mesitylenesulfonamidoquinoline (**MsQ**) and 2-Methyl-8-mesitylenesulfonamidoquinoline (**MMsQ**).* These compounds were prepared in a similar manner to **MMQ**. Recrystallized from methanol-chloroform.

MsQ: Yield, 90%. Colorless prisms. Mp 178—179 °C. IR (KBr disk) 3305 (NH), 1359, 1150 cm^{-1} (SO_2). ^1H NMR ($CDCl_3$); δ=2.15 (3H, s, CH_3-4'), 2.74 (6H, s, CH_3-2' and -6'),

6.81 (2H, s, H-3′ and -5′), 7.25—7.70 (4H, m, H-3, -5, -6, and -7), 8.11 (1H, dd, H-4, J=2.0, 8.5 Hz), 8.80 (1H, dd, H-2, J=5.0, 2.0 Hz). Found: C, 65.67; H, 5.67; N, 8.48%. Calcd for $C_{12}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58%.

MMsQ: Yield 71%. Pale yellow needles. Mp 169—170.5 °C. IR (KBr disk) 3295 (NH), 1157 cm^{-1} (SO_2). ^1H NMR ($CDCl_3$); δ=2.16 (3H, s, CH_3-4′), 2.67 (6H, s, CH_3-2′ and -6′), 2.74 (3H, s, CH_3-2), 6.79 (2H, s, H-3′ and -5′), 7.17—7.68 (4H, m, H-3, -5, -6, and -7), 7.92 (1H, d, H-4, J=8.2 Hz). Found: C, 66.84; H, 6.03; N, 8.22%. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23%.

*8-(Methanesulfonamido)quinoline (**MQ**) and 8-(p-Toluenesulfonamido)quinoline (p-**TQ**).* These compounds were prepared according to the reported procedure.[7]

Measurement of Acid Dissociation Constants and Complex Formation Constants. Reagent: Dioxane was used immediately after purification. Standard potassium hydroxide (0.1 M (1 M=1 mol dm^{-3})) solution was prepared by the Albert's method.[10] Metal nitrate solutions (0.01 M) were prepared by dissolving the metal nitrate (guaranteed reagents) in distilled water. The concentration was determined by chelatometric titration.[11] Other reagents were of guaranteed grade.

Measurement. Two milliliters of 0.01 M perchloric acid, 2 ml of 0.1 M potassium nitrate, 1 ml of 0.01 M metal nitrate aqueous solution, 2 ml of 0.01 M ligand solution in dioxane, and 13 ml of dioxane were taken in a titration vessel (75% dioxane solution). When acid dissociation constants were determined, 1 ml of water was taken instead of 1 ml of 0.01 M metal nitrate solution. The titration vessel was maintained at 30±0.1 °C. Nitrogen gas which was pre-passed through 75% dioxane-water was slowly passed over the solution throughout the titration. The standard potassium hydroxide solution was added to the stirred solution with small portions together with three times volume of pure dioxane in order to keep the solvent composition constant. All pH measurements were made with GC-195C combined pH electrode (TOA Elect. Ltd.) on HM-15A digital pH meter (TOA Elect. Ltd.).

Evaluation of Acid Dissociation Constants. Since the sulfonamide ligand has one dissociable amide proton and one quinolinic nitrogen, two proton dissociation constants are defined as in Eqs. 1 and 2. Ka_1 and Ka_2 correspond to the dissociation of quinolinium and amide protons, respectively.

$$H_2L^+ \rightleftarrows HL + H^+ : \quad Ka_1 = \frac{[HL][H^+]}{[H_2L^+]}, \tag{1}$$

$$HL \rightleftarrows L^- + H^+ : \quad Ka_2 = \frac{[L^-][H^+]}{[HL]}. \tag{2}$$

First, the pH meter was calibrated in a usual manner against phthalate and phosphate buffers. Then, a standard solution of perchloric acid in 75% dioxane was titrated by standard potassium hydroxide solution while keeping the composition of the solvent constant. A certain constant value (0.55) was found to be added in order to convert the measured (apparent) pH values to $-\log [H^+]$ values, *i.e.*,

$$-\log [H^+] = pH_{app} + 0.55. \tag{3}$$

A titration of standard perchloric acid solution beyond an equivalence point or of pure mixed solvent (with added potassium perchlorate) by standard potassium hydroxide gave an estimation of "conditional" ionic product Kw for the dissociation of water. Thus, for known concentrations of OH^- ion, $-\log [H^+]$ values were obtained according to Eq. 3 from the measured pH_{app} values for the solution. The relationship between $[OH^-]$ and $[H^+]$ was found to be

$$Kw = [H^+][OH^-] = 10^{-17.4}. \tag{4}$$

The conditional Kw value is close to the value of $10^{-17.70}$ reported for the similar solvent (30% water −70% dioxane (v/v)) without added salt.[12]

A conventional treatment of mass balance and equilibrium in solution leads to the following expressions (under conditions, $Ka_1 \gg Ka_2$) which relate proton dissociation constants to the experimentally observable variables. When $0<a<1$,

$$T_{OH} = \frac{-[H^+]^3 - Ka_1[H^+]^2 + (Kw + Ka_1 \cdot T_L)[H^+] + Ka_1 \cdot Kw}{[H^+](Ka_1 + [H^+])}, \tag{5}$$

and when $1<a<2$,

$$T_{OH} = \frac{-[H^+]^3 - Ka_2[H^+]^2 + (Kw + Ka_2 \cdot T_L)[H^+] + Ka_2 \cdot Kw}{[H^+](Ka_2 + [H^+])} + T_L, \tag{6}$$

where T_{OH} is a total concentration of added potassium hydroxide, T_L is a total concentration of ligand, and a is equal to T_{OH}/T_L.

Ka_1 and Ka_2 values were calculated from titration data of ligands in the absence of metal ions (Figs. 1a—1h) by using Marquardt nonlinear least squares method[14] according to Eqs. 5 and 6.

Evaluation of Complex Formation Constants. The complex formation equilibria of sulfonamide reagents in this study with divalent metal ion are generally formulated as follows:

$$M^{2+} + L^- \rightleftarrows ML^+ : \quad K_1 = \frac{[ML^+]}{[M^{2+}][L^-]}, \tag{7}$$

$$ML^+ + L^- \rightleftarrows ML_2 : \quad K_2 = \frac{[ML_2]}{[ML^+][L^-]}. \tag{8}$$

In this study, however, the second proton dissociation constant Ka_2 was sometimes too low to be measured accurately, and it is generally inconvenient to treat the complex formation in terms of the concentration of L^- species. Thus, the equilibria were described in a different way as follows:

$$M^{2+} + HL \rightleftarrows ML^+ + H^+ : \quad K_1' = \frac{[ML^+][H^+]}{[M^{2+}][HL]}, \tag{9}$$

$$ML^+ + HL \rightleftarrows ML_2 + H^+ : \quad K_2' = \frac{[ML_2][H^+]}{[ML^+][HL]}. \tag{10}$$

Then, K_1 and K_2 are related to K_1' and K_2', respectively, as follows:

$$K_1 = K_1'/Ka_2, \tag{11}$$

$$K_2 = K_2'/Ka_2. \tag{12}$$

A treatment of complex formation equilibria leads to Eq. 13, and K_1' and K_2' were calculated from the titration data by nonlinear least squares method in a usual manner.

$$T_{OH} = T_L - A - [H^+] + Kw/[H^+], \quad (13)$$

where,

$$A = \frac{-C+\sqrt{C^2-4BD}}{2B}, \quad (14)$$

$$B = K_1' \cdot K_2'(Kw - T_{OH}[H^+] - [H^+]^2 + 2T_M[H^+]), \quad (15)$$

$$C = K_1'[H^+](Kw - T_{OH}[H^+] - [H^+]^2 + T_M[H^+]), \quad (16)$$

$$D = [H^+]^2(Kw - T_{OH}[H^+] - [H^+]^2). \quad (17)$$

Results and Discussion

Acid Dissociation Constants. Titration curves of sulfonamide ligands in 75% dioxane-water are illustrated in Figs. 1a—1h including 8-quinolinol (**HQ**) as a reference ligand. The ligand concentration could not be increased over 10^{-3} M because of the solubility limitation of the ligand itself or metal complexes derived. At such relatively low concentrations, the proton dissociation constants (p*K*a) lower than 3 or higher than 14 can not be accurately determined by pH measurement; a computer simulation study indicated that pH measurement error of 0.02 pH unit can result in artificial proton dissociation constants of that order of acid strength. Thus, such low or high p*K*a values numerically obtained were not adopted as real constants.

Few equilibrium data have been reported on the complex formation in 75% dioxane-water medium. 8-Quinolinol (**HQ**) and 2-methyl-8-quinolinol (**MHQ**)

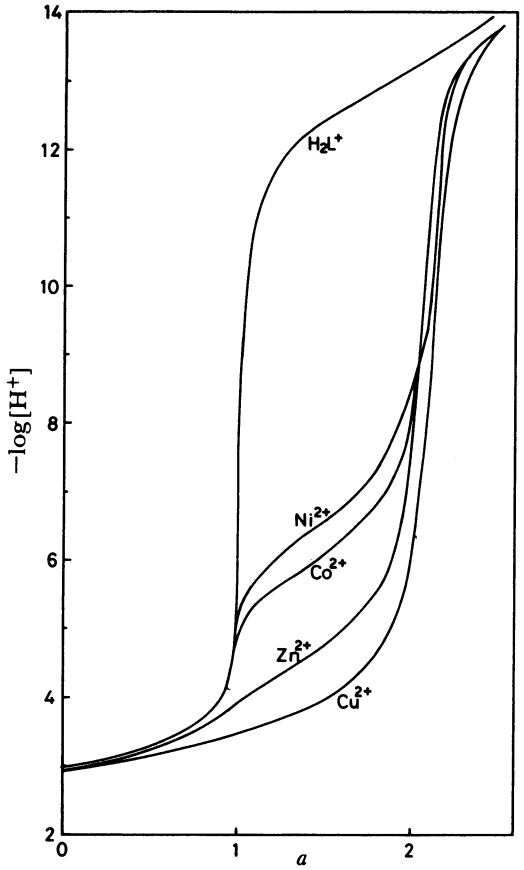


Fig. 1b.

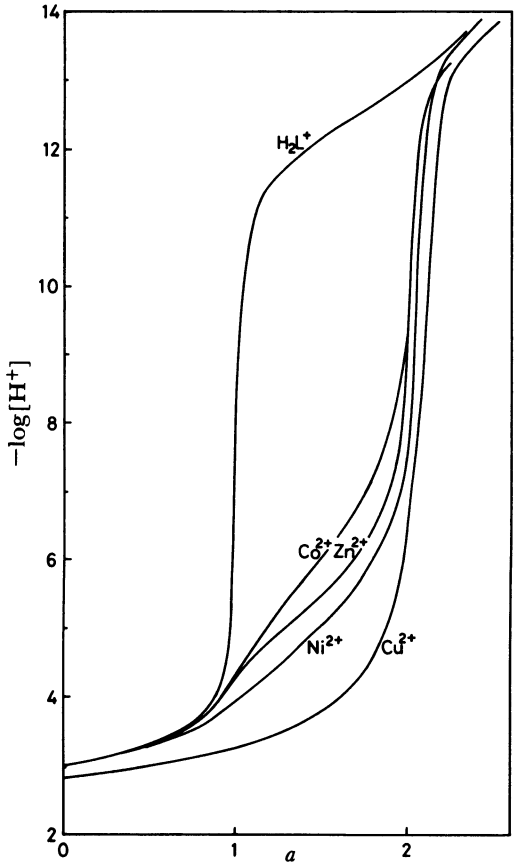


Fig. 1a.

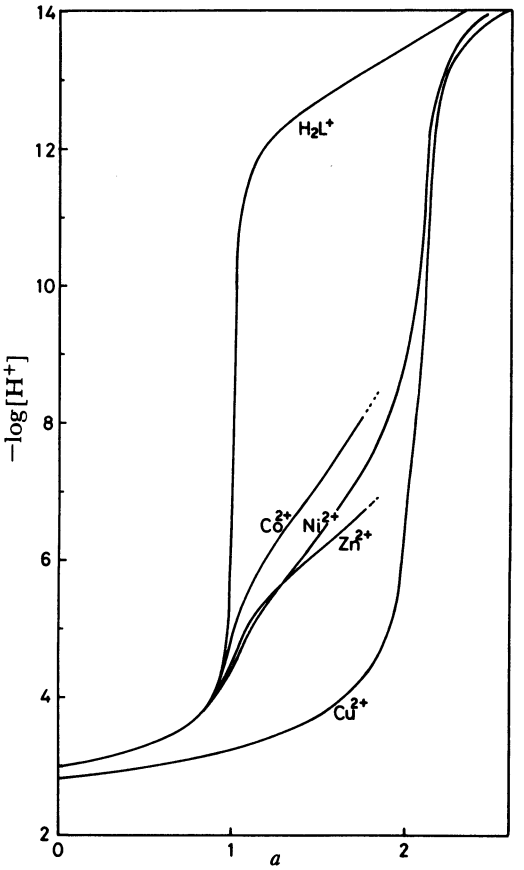


Fig. 1c.

Fig. 1. Titration curves for sulfonamidoquinolines in the absence and presence of metal ions in 75% dioxane-water (v/v) at 30°C: a) **MQ**; b) **MMQ**; c) **MsQ**; d) **MMsQ**; e) **FQ**; f) **MFQ**; g) *p*-**TQ**; h) **HQ**. $[M^{2+}]=[H_2L^+]=1\times10^{-3}$ M, μ=0.1 (KNO_3).

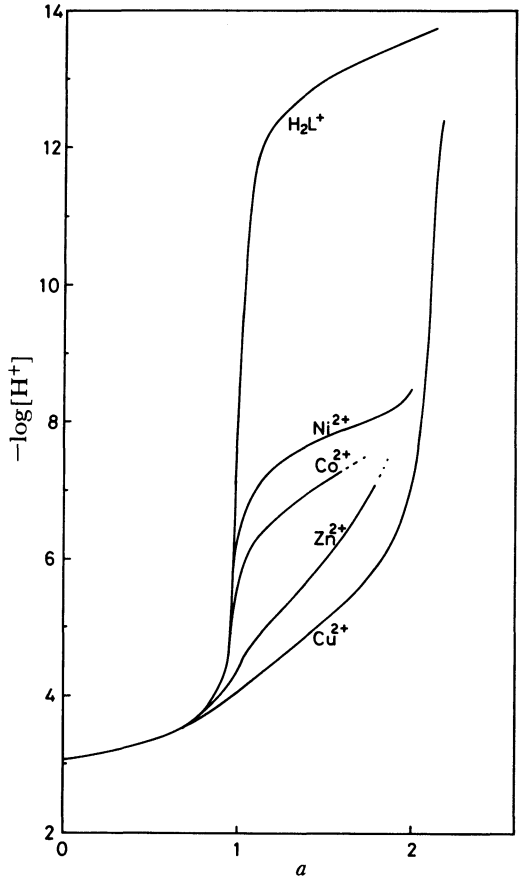


Fig. 1d.

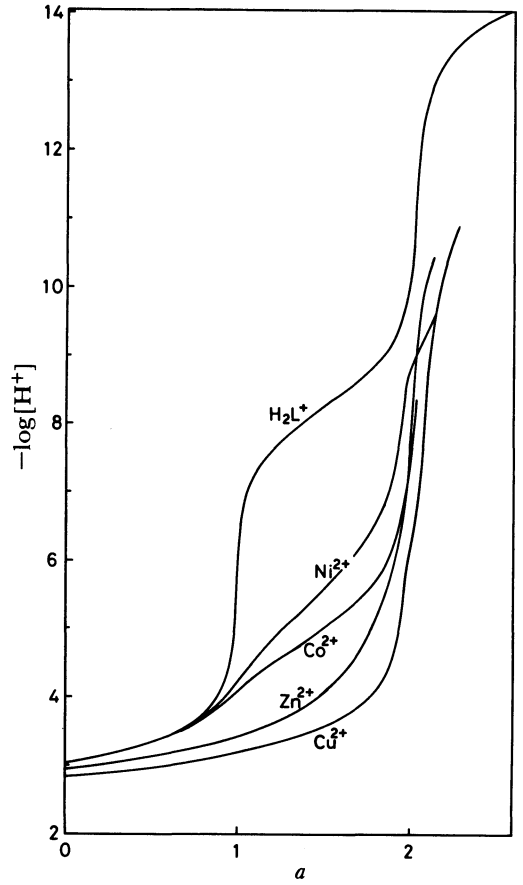


Fig. 1f.

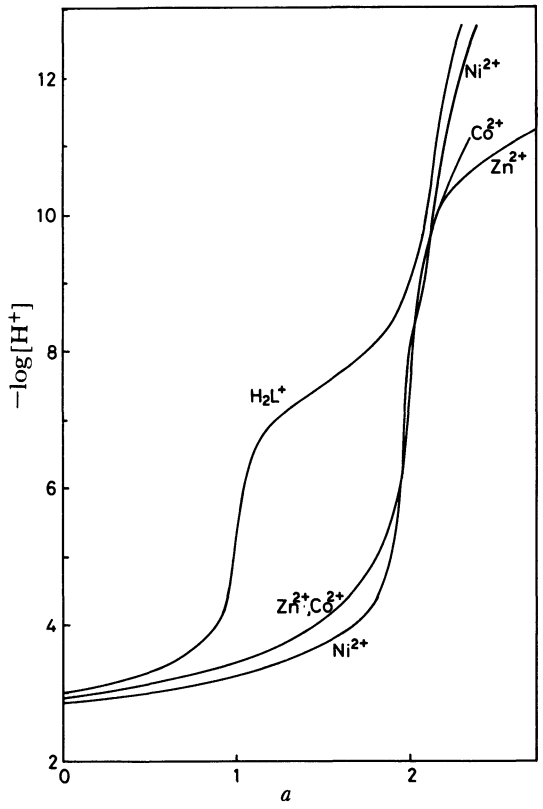


Fig. 1e.

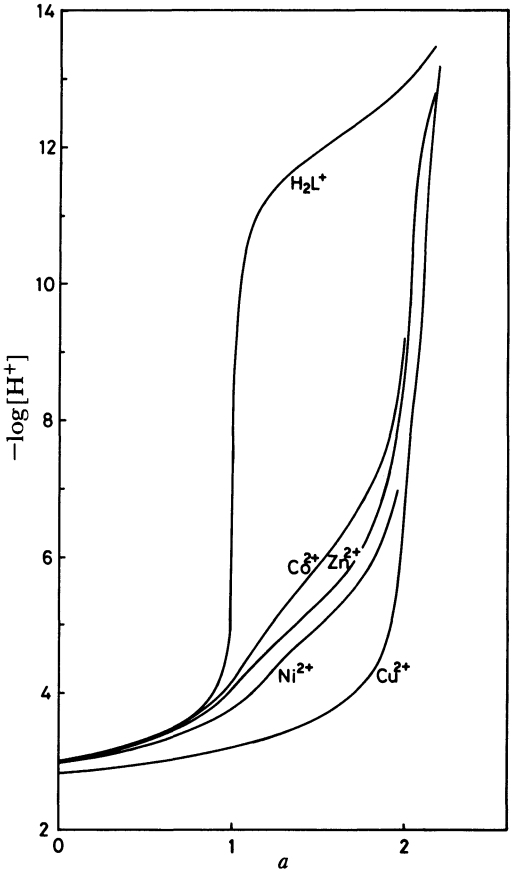


Fig. 1g.

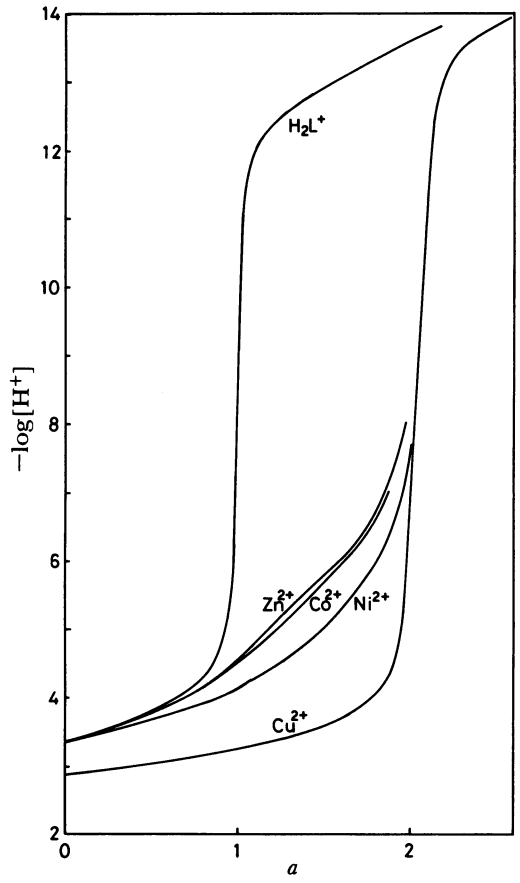


Fig. 1h.

were studied in 50% dioxane-water,[9] and the reported constants are listed in Table 1 for comparison. In the case of 8-quinolinol, the change of 50 to 75% for the volume fraction of dioxane in the medium caused a decrease of 0.56 in pKa_1 and an increase of 1.8 in pKa_2. This is explained that charged species, H_2L^+ and L^- are less stable in organic-rich medium than in water rich solvent.

Complex Formation Constants. Titration curves of the chelating agents in the presence of divalent metal ions are illustrated in Figs. 1a—1h. It is evident from these curves that most ligands including 8-quinolinol form ML and ML_2 type, stable complexes with divalent metal cations. The complex formation constants calculated from these data are summarized in Table 1, K_1 and K_2 values rather than K_1' and K_2' are shown. As mentioned before, the latter values are experimentally more reliable for ligands with high pKa_2 values (log K_2 values for proton association)(>13) since they are free from the ambiguity in the determination of Ka_2. K_1 and K_2 values are obtained by using Eqs. 11 and 12.

The formation constants suffer a considerable medium effect (composition of solvent). Thus, except for Cu^{2+} all of log K_1, log K_2, and log β value are greater in 75% dioxane-water than in 50% dioxane-water. This may be explained in a usual manner that the complex state M-L is more stable than the free metal cation plus L^- state which is more stabilized by hydration in water-rich medium. The increased stability of the complexes in 75% dioxane-water probably holds in sulfonamide ligands.

The orders of stabilities, log K_1, log K_2, log β of 8-sulfonamidoquinolines which do not carry 2-methyl group all follow Irving-Williams' order (*i.e.* $Cu^{2+}>Ni^{2+}>Co^{2+}$). Since **FQ** and Cu^{2+} formed a complex insoluble in 75% dioxane, the stability constants could not be obtained.

The order of metal complex stabilities of 2-methylquinoline derivatives (including 2-methy-8-quinolinol) are $Cu^{2+}>Co^{2+}>Ni^{2+}$, the order of Ni^{2+} and Co^{2+} being reversed from that of Irving-Williams. The difference of log K_1 between Ni^{2+} and Co^{2+} is smaller than that of log K_2. This may be considered that the ML_2 type Co^{2+} complex can assume either tetrahedral or octahedral configuration (chelating ligands of square planar configuration, with coordinated water molecules in axial position), while Ni^{2+} complex takes (distorted) octahedral configuration.[15]

If two 8-sulfonamidoquinoline chelating ligands take square planar configuration around a metal ion, a steric interaction between 2-methyl group of one ligand and 8-sulfonamide group of the other is expected from a molecular model consideration. 2-Methyl group may interact with a coordinated water in the same plane even when a single chelating ligand is bound to the metal. The complex formation constants (log β) for Cu^{2+} and Ni^{2+} are unanimously lowered on introduction of 2-methyl group in 8-sulfonamidoquinoline or 8-quinolinol, inspite of the increased basicity of L^- associated with the methyl substitution. For **MMsQ** where an extremely bulky mesitylenesulfonyl group comes close to the ligand on the opposite side of the plane, nickel complex is expected to become especially unstable. The titration curve (Fig. 1d), however, indicates a considerable pH depression at *a* value above 1. Around this pH region, however, proton dissociation from coodinated water is also expected to take place as a side reaction. In accordance with this, the titration data did not give well-defined K_1 and K_2 values.

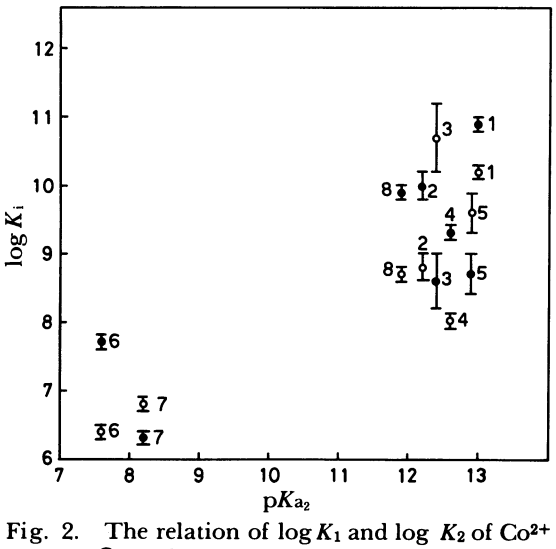


Fig. 2. The relation of log K_1 and log K_2 of Co^{2+} *vs.* pKa_2: ● K_1, ○ K_2; 1) **HQ**, 2) **MQ**; 3) **MMQ**; 4) **MsQ**; 5) **MMsQ**; 6) **FQ**; 7) **MFQ**; 8) *p*-**TQ**.

TABLE 1. COMPLEX FORMATION CONSTANTS

Ligand		H^{+} [a]	Cu^{2+}	Zn^{2+}	Co^{2+}	Ni^{2+}
MQ	log K_1	<2	13.6±0.2	10.1±0.1	10.0±0.2	10.8±0.1
	log K_2	12.2±0.1	11.4±0.2	9.8±0.2	8.8±0.2	9.9±0.1
	log β		24.7±0.4	19.7±0.3	18.6±0.4	20.6±0.2
MMQ	log K_1	<2	11.7±0.1	10.9±0.1	8.6±0.4	8.8±0.1
	log K_2	12.4±0.1	12.0±0.2	11.0±0.3	10.7±0.5	9.4±0.1
	log β		23.9±0.3	22.0±0.4	19.3±0.9	18.3±0.2
MsQ	log K_1	<2	14.7±0.3	10.0±0.1	9.3±0.1	10.0±0.1
	log K_2	12.6±0.1	12.1±0.1	9.4±0.2	8.0±0.1	8.7±0.1
	log β		26.9±0.4	19.5±0.3	17.5±0.2	18.8±0.2
MMsQ	log K_1	<2	11.3±0.2	10.7±0.2	8.7±0.3	—[c]
	log K_2	12.9±0.2	11.0±0.2	9.8±0.2	9.6±0.3	—[c]
	log β		22.3±0.4	20.6±0.4	18.3±0.6	—[c]
FQ	log K_1	<2	—[d]	7.7±0.1	7.7±0.1	8.8±0.1
	log K_2	7.6±0.1	—[d]	6.4±0.1	6.4±0.1	7.2±0.1
	log β		—[d]	14.0±0.2	14.1±0.2	16.0±0.2
MFQ	log K_1	<2	9.3±0.2	8.5±0.3	6.3±0.1	6.3±0.1
	log K_2	8.2±0.1	8.4±0.1	7.2±0.2	6.8±0.1	5.5±0.1
	log β		17.7±0.3	15.7±0.4	13.1±0.2	11.8±0.2
***p*-TQ**	log K_1	<2	13.6±0.1	10.2±0.1	9.9±0.1	10.7±0.1
	log K_2	11.9±0.1	11.7±0.1	9.5±0.2	8.7±0.1	9.8±0.1
	log β		25.3±0.2	19.8±0.3	18.6±0.2	20.5±0.2
HQ	log K_1	3.6±0.1	13.0±0.6	10.8±0.1	10.9±0.1	11.6±0.1
	log K_2	13.0±0.1	13.7±0.2	10.2±0.2	10.2±0.1	10.7±0.2
	log β		27.0±0.8	21.0±0.3	21.2±0.2	22.3±0.3
HQ[b]	log K_1	4.16	13.29	9.45	9.65	10.50
	log K_2	11.2	12.61	8.70	8.40	9.77
	log β		25.90	18.15	18.05	20.27
MHQ[b]	log K_1	4.68	11.92	9.06	8.59	8.96
	log K_2	11.3	10.90	8.84	8.79	7.98
	log β		22.82	17.90	17.38	16.94

a) These values listed in the row of log K_1 and log K_2 are for pKa_1 and pKa_2, respectively. b) Data in 50% dioxane-water (v/v), μ=0.1 (Ref. 13). c) The value could not be calculated. d) Precipitated.

TABLE 2. COMPLEX FORMATION EQUILIBRIUM CONSTANTS ACCORDING TO EQUATION 18—20

Ligand		Cu^{2+}	Zn^{2+}	Co^{2+}	Ni^{2+}
MQ	log K_1'	1.4±0.2	−2.1±0.1	−2.2±0.1	−1.4±0.1
	log K_2'	−0.8±0.2	−2.3±0.2	−3.4±0.1	−2.2±0.1
	log β'	0.6	−4.4	−5.6	−3.6
MMQ	log K_1'	−0.7±0.1	−1.5±0.1	−3.8±0.4	−3.6±0.1
	log K_2'	−0.4±0.2	−1.4±0.3	−1.7±0.5	−3.0±0.1
	log β'	−1.1	−2.9	−5.5	−6.6
MsQ	log K_1'	2.1±0.3	−2.6±0.1	−3.2±0.1	−2.5±0.1
	log K_2'	−0.5±0.1	−3.2±0.2	−4.5±0.1	−3.8±0.1
	log β'	1.6	−5.8	−7.7	−6.3
MMsQ	log K_1'	−1.6±0.1	−2.2±0.1	−4.3±0.3	—[a]
	log K_2'	−1.9±0.1	−3.1±0.1	−3.3±0.3	—[a]
	log β'	−3.5	−5.3	−7.6	
FQ	log K_1'	—[b]	0.1±0.1	0.1±0.1	1.2±0.1
	log K_2'	—[b]	−1.2±0.1	−1.2±0.1	−0.4±0.1
	log β'		−1.1	−1.1	0.8
MFQ	log K_1'	1.1±0.2	0.2±0.3	−1.9±0.1	−2.0±0.1
	log K_2'	0.1±0.1	−1.2±0.1	−1.5±0.1	−2.8±0.1
	log β'	1.2	−1.0	−3.4	−4.8
***p*-TQ**	log K_1'	1.7±0.1	−1.8±0.1	−2.1±0.1	−1.3±0.1
	log K_2'	−0.2±0.1	−2.4±0.2	−3.2±0.1	−2.1±0.1
	log β'	1.5	−4.2	−5.3	−3.4
HQ	log K_1'	0.1±0.5	−2.2±0.1	−2.1±0.1	−1.4±0.1
	log K_2'	0.7±0.2	−2.8±0.2	−2.7±0.1	−2.3±0.2
	log β'	0.8	−5.0	−4.8	−3.7
HQ[c]	log K_1'	2.1	−1.75	−1.55	−0.70
	log K_2'	1.4	−2.50	−2.80	−1.43
	log β'	3.5	−4.25	−4.35	−2.13
MHQ[c]	log K_1'	0.6	−2.24	−2.71	−2.34
	log K_2'	−0.4	−2.46	−2.51	−3.32
	log β'	0.2	−4.70	−5.22	−5.66

a) The value could not be calculated. b) Precipiated. c) Data in 50% dioxane-water (v/v), μ= 0.1 (Ref. 13).

The plots of log K_1 or log K_2 against pKa_2 are shown in Fig. 2. The points are classified in two groups, trifluoromethane-sulfonamides and the rest of the sulfonamides. Both log K_1 and log K_2 decrease as pKa_2 decreases when the two groups are compared, indicating that a large decrease in basicity of the ligand inevitably leads to a decrease in nucleophilicity toward metal cations. However, there is no obvious correlation between the complex formation constants and the second proton dissociation constants within the individual group. Similar trends were observed for other metal ions when log K_1 and log K_2 values were plotted against pKa_2.

It is more convenient to consider the structural factors of complex formation in terms of the ion exchange-type equilibria formulated in Eqs. 9 and 10, the equilibrium constants of which do not involve the contribution from the second proton dissociation constants, *i.e.*,

$$\log K_1' = \log K_1 - \mathrm{p}Ka_2, \quad (18)$$

$$\log K_2' = \log K_2 - \mathrm{p}Ka_2, \quad (19)$$

$$\log \beta' = \log K_1 + \log K_2 - 2\mathrm{p}Ka_2. \quad (20)$$

In other words, log K_1' (or log K_2') is expected to reflect the contribution of (i) nucleophilicity of quinoline nitrogen and (ii) steric factors to the free energy of 1:1 (or 1:2) complex formation. In addition, log K_1' and log K_2' can be an indirect measure of an ease of solvent extraction, since the reagents with higher K_1' and K_2' values can extract metal ions under lower pH conditions. Table 2 summarizes these constants.

One first can compare the simplest sulfonamide homologue **MQ** with **HQ**. For clarity, log K_1' and log K_2' values for **MQ** and **HQ** are shown in Fig. 3. The constants K_1' almost parallel in the two chelating agents (for the four metal ions studied). The magnitude of the constants are also quite close to each other. This suggests the chelating behavior of the agents **MQ** and **HQ** toward the four metal ions are similar in nature toward the four metal ions in spite of the difference in the coordinating atoms.

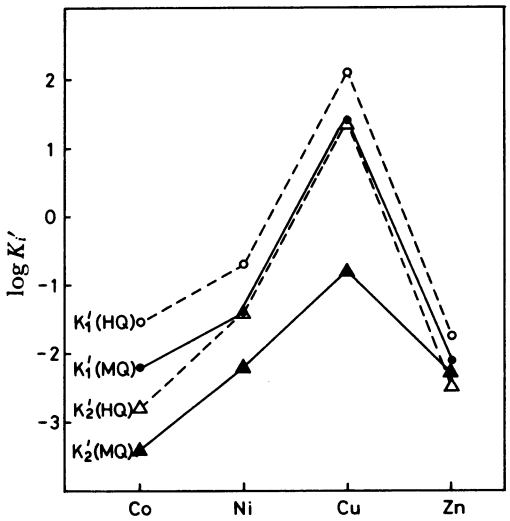


Fig. 3. Comparison of complex formation equilibrium constants K_i' between 8-(methanesulfonamido)quinoline (**MQ**) and 8-quinolinol (**HQ**).

One now looks in Fig. 3 at the log K_2' values of **HQ**, and finds that they almost parallel with the log K_1' values. On the other hand, however, there is no such parallelism in **MQ** metal chelates, *i.e.*, for Cu^{2+} the K_2' value is too low and for Zn^{2+} the value is too high. This suggests that there are some structural factors which lower the formation constant of 1:2 copper(II)-**MQ** chelate. Such structural factors are not easily foreseeable from the analogy between **MQ** and **HQ** mentioned just above. In the same notion, there seems to be some stabilizing factor for the 1:2 zinc(II)-**MQ** chelate as compared with the corresponding **HQ** chelate. A destabilizing effect in 1:2 copper(II) chelate has already been noticed for the sulfonamide chelating agents derived from 2-(aminomethyl)pyridine,[2] and a steric bulkiness of sulfonamido group may be the reason of the destabilization. As to the stabilizing effect in 1:2 zinc(II) chelate (as compared with the corre-

Table 3. Effect of substituents on the stability of metal complexes of 8-sulfonamidoquinolines and 8-Quinolinol[a]

Difference	Constant(K) concerned	Cu^{2+}	Zn^{2+}	Co^{2+}	Ni^{2+}
log K(**MQ**)-log K(**MMQ**)	K_1'	2.1	−0.6	1.6	2.2
	K_2'	−0.4	−0.9	−1.7	0.8
	β'	1.7	−1.5	−0.1	3.0
log K(**MsQ**)-log K(**MMsQ**)	K_1'	3.7	−0.4	1.1	—
	K_2'	1.4	−0.1	−1.2	—
	β'	5.1	−0.5	−0.1	—
log K(**FQ**)-log K(**MFQ**)	K_1'	—	−0.1	2.0	3.2
	K_2'	—	0.0	0.3	2.4
	β'	—	−0.1	2.3	5.6
log K(**p-TQ**)-log K(**MsQ**)	K_1'	−0.4	0.8	1.1	1.2
	K_2'	0.3	0.8	1.3	1.7
	β'	−0.1	1.6	2.4	2.9
log K(**HQ**)-log K(**MHQ**)[b]	K_1'	1.5	0.49	1.16	1.64
	K_2'	1.8	−0.04	−0.29	1.89
	β'	3.3	0.45	0.87	3.53

a) Calculated from the data in Table 2. b) Data in 50% dioxane-water.

sponding 8-quinolinol chelate), there is no reasonable explanation at present.

Table 3 summarizes the effect of substituent (mainly 2-methyl substitution on quinoline ring) on the stability of metal complexes. The positive values indicate destabilization of the complex on methyl-substitution, and the negative values, stabilization. The major effect of substitution shown in the table may be assumed to be those of steric interaction and not those of electronic effect, since, as discussed before, K' value does not include a contribution from the basicity of sulfonamide anion or the proton dissociation constant Ka_2. Electron-donating effect of methyl group which increases the basicity of quinoline nitrogen (see Table 1 for pKa_1 values of **HQ** and **MHQ**) should not be treated lightly, but the net effect of the increase in basicity is to increase the stability of the metal complex in rather a uniform manner irrespective of the nature of metal ion.

It is seen in Table 3 that 2-methyl group on quinoline ring causes a strong overall destabilizing effect (large positive value for β' row in Table 3) on copper(II) and nickel(II) chelates of both 8-sulfonamidoquinoline and 8-quinolinol. A moderate to none destabilizing effect is observed with cobalt(II) chelates, while a stabilizing effect is noticed for zinc(II) chelates of sulfonamides. The increase of stability in zinc(II) chelates of 2-methyl-substituted sulfonamide reagents is at least partially due to the increase in basicity (nucleophilicity) of quinoline nitrogen, since no steric constraints due to methyl substitution are expected in tetrahedral configuration of zinc(II) chelates. However, **HQ** and **MHQ** chelates in Table 3 indicate that the introduction of methyl group causes a decrease in stability even for zinc(II) chelate (though small as compared with copper(II) and nickel(II)). A stabilization of zinc(II) complex with 8-sulfonamide chelating agent as compared with 8-quinolinol has been pointed out earlier. It may deserve further study.

It is important to note that the destabilization by 2-methyl substitution is already pronounced at the formation of 1:1 complex for some metal-ligand combination (Cu-**MMsQ** and Ni-**MFQ** in Table 3). This means that the effect of methyl substitution —whether it can be purely steric or not— is operating not only between the coordinated chelating ligands but also between the chelating ligand and the water both coordinated on the metal.

A change from *p*-toluenesulfonyl to mesitylenesulfonyl group causes a moderate over-all destabilization of the complex except for copper(II) (see β' row in Table 3). In this case, a steric interaction between the chelating ligands seems to be an important factor, since contributions from K_2' term (the value of K_2' row, Table 3) are positive for all the metal ions.

In summary, it is concluded that (i) the coordination behavior toward Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} of 8-sulfonamidoquinoline chelating agents quite resemble 8-quinolinol, but (ii) a steric bulkiness of sulfonamido group exerts a destabilizing effect when the configuration of the complex is not tetrahedral. An introduction of methyl group on 2-position of quinoline ring further amplifies the latter effect through a chelating ligand-ligand interaction and through a chelating ligand-coordinated water interaction, leading to destabilization in zinc(II) chelates. The point (ii) above seems to be the most notable feature of sulfonamide reagents, but it is likely that the effect did not work in full for the metal ions herein studied. For metal cations of smaller ionic radius such as Fe^{3+}, a destabilizing effect is expected to be more pronounced. Unfortunately, rather unusual medium used in the present work (75% dioxane) hampered a detailed study on iron(III) chelates.

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