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Studies on the Sulfur-containing Chelating Agents. XXXV.[1] Determination of Acid Dissociation Constants of N-Phenyl- and N-Ethyl-β-mercaptocinnamamide and Thiodibenzoylmethane by Solvent Extraction Method

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Acid dissociation constants and partition coefficients of N-phenyl-β-mercaptocinnamamide (I), N-ethyl-β-mercaptocinnamamide (II) and monothiodibenzoylmethane (III) were determined by the solvent extraction method in various solvent systems, by the use of ^{35}S-labeled species of these chelating agents. The results are considerably different from those obtained spectrophotometrically. The hydrolysis and the oxidation were found to occur in aqueous organic solvent in parallel with the dissociation in I and II, and III respectively. The solvent extraction method was regarded to be preferable than the spectrophotometric method, because the influences of the side reactions can be made very little by the use of solvent extraction method.

In the previous papers, the syntheses of a number of thio-β-diketones and β-mercaptocinnamamides which form stable metal chelates were reported,[3] and some of them were found to be useful as analytical reagent.[4] It was also found that some β-mercaptocinnam amides have fairly strong antimicrobial activities, and their chelating abilities seem to have close relation to their antimicrobial activities.[5] In the preliminary survey of their reactions with metal ions considerable differences have been found in the behavior towards metal ions among these chelating agents, in spite of that they have same coordinating groups, namely mercapto and carbonyl groups. These results gave us the interest to study the reaction of these chelating agents with metal ions in detail, especially on the effect of the amide group toward the chelate formation. In recent years, metal chelates of thio-β-diketones have been actively studied, whereas the chelating agents which involve amide groups have not been studied. N-Phenyl-β-mercaptocinnamamide (I), N-ethyl-β-mercaptocinnamamide (II) and 3-mercapto-1,3-diphenylprop-2-en-1-one(thiodibenzoylmethane) (III) were adopted for this study. This paper deals with the study on the acid dissociation of these chelating agents. The metal chelates produced from them are usually insoluble in water and extractable into some organic solvents, and the solvent extraction method is regarded to be as a suitable method for the study of the property of the metal chelates. Accordingly, solvent extraction method was adopted for these chelating agents among various methods for the determination of the acid dissociation constant.

1) Part XXXIV: A. Yokoyama, N. Nakanishi, and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **20**, 1856 (1972).
2) Location: *Yoshida, Shimoadachi-cho, Sakyo-ku, Kyoto.*
3) *a*) A. Yokoyama, S. Kawanishi, M. Chikuma, and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **15**, 540 (1967); *b*) A. Yokoyama and H. Tanaka, *ibid.*, **12**, 683 (1964); *c*) A. Yokoyama, K. Ashida, and H. Tanaka, *ibid.*, **12**, 690 (1964).
4) *a*) A. Yokoyama, M. Chikuma, H. Hayashi, and H. Tanaka, *Bunseki Kagaku*, **18**, 24 (1969); *b*) H. Tanaka, N. Nakanishi, Y. Sugiura, and A. Yokoyama, *ibid.*, **17**, 1428 (1968); *c*) H. Hashitani and K. Katsuyama, *ibid.*, **19**, 355 (1970); *d*) K. Itsuki and H. Komuro, *ibid.*, **19**, 1214 (1970); *e*) E.W. Berg and K.P. Reed, *Anal. Chim. Acta*, **36**, 372 (1966); *f*) E. Uhlemann and H. Müller, *ibid.*, **41**, 311 (1968); *g*) *idem*, *ibid.*, **48**, 115 (1969); *h*) A.K.De, S.M. Khopkar, and R.A. Chalmers, "Solvent Extraction of Metals," Van Nostrand Reinhold Company Ltd, London, 1970, p. 65.
5) Unpublished.

In order to determine the acid dissociation constant by the solvent extraction method, radioactivity of sulfur-35 of the labeled compounds of the chelating agents in both organic and aqueous phases was measured to know the distribution ratio. For this purpose, sulfur-35 labeled chelating agents were prepared by the application of the synthetic method which we reported previously for the syntheses of β-mercaptocinnamamides.[3c] The synthetic methods reported by Uhlemann[6] and Chaston[7] for the preparation of thio-β-diketones are not favorable for the preparation of sulfur-35 labeled compounds. The method adopted here is shown in Chart 1.

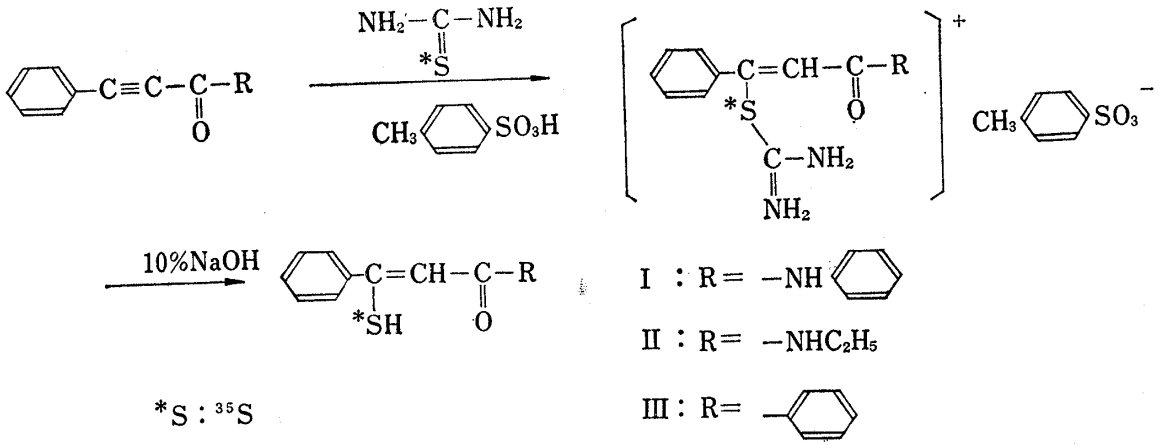

Chart 1

Experimental

Materials——^{35}S-[1-Phenyl-2-(phenylcarbamoyl)vinyl]isothiuronium *p*-Tluenesulfonate (IV): A mixture of 5 mmole of N-phenyl-phenylpropiolamide, equimolar *p*-toluenesulfonic acid and ^{35}S-thiourea (2.4 mCi/mmole) in 10 ml of EtOH was refluxed for 3 hr. After cooling, ether was added and crystals separated out were collected and used in next procedure without further purification. Yield 90%.

^{35}S-N-Phenyl-β-mercaptocinnamamide (I): To about 5 mmole of IV, 10% NaOH aqueous solution was added and warmed at 60—70° for 2 hr. After cooling, the reaction mixture was extracted with ether. Aqueous phase was separated and acidified with 20% HCl under ice-cooling. The precipitate separated out was collected and recrystallized from absolute EtOH to give yellow needles, yield 60% (9.7×10^7 cpm/mmole). Melting point (107°) coincided with that of the product obtained by cold run.[3c] Purity was checked by thin-layer chromatography.

^{35}S-[1-Phenyl-2-(ethylcarbamoyl)vinyl]isothiuronium *p*-Toluenesulfonate (V): V was obtained from 5 mmole of N-ethyl-phenylpropiolamide, equimolar *p*-toluenesulfonic acid and ^{35}S-thiourea (1.8 mCi/mmole) by the same treatment as in IV, with the yield of 87%, and used in next procedure without further purification.

^{35}S-N-Ethyl-β-mercaptocinnamamide (II): From 5 mmole of V, II was obtained as pale yellow needles, by the same treatment as in I, with the yield of 60%. Melting point (138°) coincided with that of the product obtained by cold run.[3c] Specific activity was 4.6×10^7 cpm/mmole. Purity was checked by thin layer chromatography.

^{35}S-(1-Phenyl-2-benzoylvinyl)isothiuronium *p*-Toluenesulfonate (VI): To 3 mmole of 1,3-diphenyl-prop-2-yn-1-one[8] in 10 ml EtOH equimolar *p*-toluenesulfonic acid and ^{35}S-thiourea (1.3 mCi/mmole) were added. Yellow needles precipitated on standing for 30 min at room temperature. Yellow needles collected were recrystallized from EtOH, mp 197—198°. Yield, 95%. *Anal.* Calcd. for $C_{23}H_{22}O_4N_2S_2$: C, 60.79; H, 4.85; N, 6.17. Found: C, 60.80; H, 4.80; N, 6.07. The elemental analyses were carried out with the product obtained by cold run.

^{35}S-3-Mercapto-1,3-diphenylprop-2-en-1-one (III): To 40 ml of 10% NaOH aqueous EtOH solution, about 3 mmole of VI was added and refluxed for 2 hr. After cooling the reaction mixture was poured into

6) E. Uhlemann and H. Müller, *Angew. Chem.*, **77**, 172 (1965).
7) S.H.H. Chaston, S.E. Livingstone, T.N. Lockyer, V.A. Pickles, and J.S. Shannon, *Australian, J. Chem.*, **18**, 673 (1968).
8) J.V. Nef, *Ann.*, **308**, 264 (1899).

50 ml of H_2O and extracted with ether. Aqueous phase was separated and acidified with 20% HCl under ice-cooling. The precipitate separated out was collected and recrystallized from EtOH to give red needles, mp 85°. Yield, 85% (1.2×10^8 cpm/mmole). *Anal.* Calcd. for $C_{15}H_{12}O_2S$: C, 75.00; H, 5.00; S, 13.33. Found: C, 75.02; H, 5.19; S, 13.04. The elemental analyses were carried out with the product obtained by cold run.

N-Phenyl-benzoylacetamide (VII): To N-phenyl-β-mercaptocinnamamide (0.5 g) in EtOH, 3% HCl (2 ml) was added. The reaction mixture was allowed to stand for 7 days and the solvent was evaporated under diminished pressure. The residual colorless crystals were recrystallized from EtOH, mp 106°. Yield 30%. *Anal.* Calcd. for $C_{15}H_{13}ON_2$: C, 75.31; H, 5.44; N, 5.86. Found; C, 75.46; H, 5.55; N, 5.88.

N-Ethyl-benzoylacetamide (VIII): To N-ethyl-β-mercaptocinnamamide (0.5 g), in EtOH was treated as described above. mp 91°. Yield 25%. *Anal.* Calcd. for $C_{11}H_{13}ON_2$: C, 69.11; H, 6.81; N, 7.33. Found C, 69.38; H, 6.80; N, 7.32.

1,3,6,8-Tetraphenyl-4,5-dithiaocta-2,6-diene-1,8-dione (IX): To 3-mercapto-1,3-diphenylprop-2-en-1-one (1 g) in EtOH solution, aqueous solution of iodine (0.5 g) containing KI was added. Yellow needles separated out were collected and washed with H_2O and EtOH. mp 141—142°. Yield 43.5%. *Anal.* Calcd. for $C_{30}H_{22}O_2S_2$; C, 75.31; H, 4.60. Found C, 75.48; H, 4.81.

Reagents——^{35}S-Thiourea was obtained from Radiochemical Center, Amersham, England. The peroxide-free dioxane was obtained by the following procedure. To 1000 g of dioxane were added 15 ml of conc. HCl and 70 ml of H_2O. The solution was stirred for 3 hr, 15 g of KI was added, and the mixture was stirred well. KOH pellets were added until the solution was saturated. The supernatant was removed and allowed to stand over pellets of KOH for 1 day, and distilled after refluxing with Na for 1 day. All other organic solvents were purified by distillation. All other chemicals were of analytical reagent grade. The following buffer solutions were used; HCl–KCl (pH 1.0—2.2), HCl–potassium acid phthalate (pH 2.2—3.6), HOAc–NaOAc (pH 3.6—6.0), KH_2PO_4–$Na_2B_4O_7$ (pH 6.0—9.2), Na_2CO_3–$Na_2B_4O_7$ (pH 9.2—11.2).

Apparatus——Beta-radioactivities were measured by a Fujitsu 2π gas flow counter Model EA-102A. The pH value of equilibrated aqueous phase was measured by a Hitachi-Horiba Model F-5 type pH meter with a combination electrode. Absorption spectra were measured by a Hitachi EPS-2 spectrophotometer and a Shimadzu QV-50 type spectrophotometer. Solvent extraction equilibrations were performed in a Iwaki mechanical shaker at 22 ± 0.5°.

Determination of Acid Dissociation Constants——Solvent Extraction Method: Four ml of solution of the chelating agents in an organic solvent (5×10^{-4}—2×10^{-2} M) was shaken mechanically with an equal volume of buffer solution (ionic strength; 0.1, $NaClO_4$) of various pH values in glass tubes stoppered with caps. To avoid volume change in both phases the experiments were carried out by the use of the organic solvent and the aqueous solution which had been pre-equilibrated. After shaken for 30 min for attaining the extraction equilibrium, the mixture was allowed to stand for about 1 hr. Centrifugation was often needed for the phase separation in high distribution range. After phase separation 1 ml aliquots of both phases were taken and poured into the dish of stainless steel and dried with a lamp. Radioactivity was measured and the remaining aqueous phase was applied to pH measurement. The precision of pH measurements was ±0.01. The distribution ratio was defined as follows.

$$D = \frac{\text{Activity of } ^{35}\text{S in organic phase}}{\text{Activity of } ^{35}\text{S in aqueous phase}}$$

The distribution ratio (D) is expressed in equation 1, provided that undissociated species is only the species present in the organic phase and no polymerized species is present in both phases.

$$D = \frac{[HR]_0}{[HR]_w+[R^-]_w} = \frac{P}{1+\frac{K_a}{[H^+]_w}} \qquad (1)$$

In equation 1, HR, R^-, P, and K_a represent undissociated form of mono basic acid (chelating agent), anionic form, partition coefficient ($P=[HR]_o/[HR]_w$) and dissociation constant ($K_a=[H^+]_w[R^-]_w/[HR]_w$), respectively. The subscripts 'o' and 'w' designate the organic and the aqueous phases respectively. The acid dissociation constant (pK_a) and the partition coefficient (log P) were determined from the relationship between log D and pH by Dyrrsen's graphical method,[9] as shown in Fig. 1.

Spectrophotometric Method: An 1 ml of aliquot of the chelating agents in pure dioxane (5×10^{-4} M) was pipetted into 9 ml of dioxane solution containing the buffer solution, (ionic strength; 0.1, $NaClO_4$). The absorbances of these solutions at wave-lengths corresponding to λ_{max} of the chelating agents (I: 312 mμ, II: 292 mμ and III: 332 mμ) were measured respectively as soon as possible after the preparations of the solutions. As the absorbances of these solutions decrease considerably with time, absorbances were measured at appropriate time intervals to get the absorbances at zero time by the extrapolation. The acid

9) D. Dyrrsen, *Acta Chem. Scand.*, **11**, 1771 (1957).

dissociation constants (pK_a) in aqueous solution containing various volume of dioxane were calculated from the following equation 2.

$$pK_a = pH + \log \frac{\varepsilon_L - \varepsilon}{\varepsilon - \varepsilon_{HL}} \quad (2)$$

Where ε_{HL} and ε_L are the extinction coefficients of the molecule and the anion of the chelating agent at the analytical wavelength and ε is the extinction coefficient of the mixture of molecule and anion at the same wavelength. In the cases of I and II, the same experiments were repeated in aqueous solutions containing various amount of dioxane (10, 20 and 30 v/v %), and the values of pK_a in zero concentration of dioxane were obtained by the extrapolation procedure from the plots of pK_a against the percentage of dioxane, while the value of pK_a of III was measured in 50 v/v % dioxane solution because of the low solubility.

Result and Discussion

The distribution ratios were determined with various organic solvents such as chloroform, benzene and carbon tetrachloride. The relationships between pH and log D in each solvent system are shown in Figs. 1, 2, and 3, respectively. The values of log P and pK_a obtained are shown in Table I. As shown in Table I, the pK_a value obtained in carbon tetrachloride system was found to be lower than those obtained in chloroform and benzene systems. In connection with this fact, it should be pointed out that the solvent effect on the equilibrium between thioketo and thioenol forms was remarkably observed.[10] If the partitions between organic and aqueous phases were different between the thioketo and thioenol forms it would be possible to anticipate that the pK_a values obtained were considerably influenced by the solvents. On the other hand, standing on a macroscopic view point, the apparent pK_a values

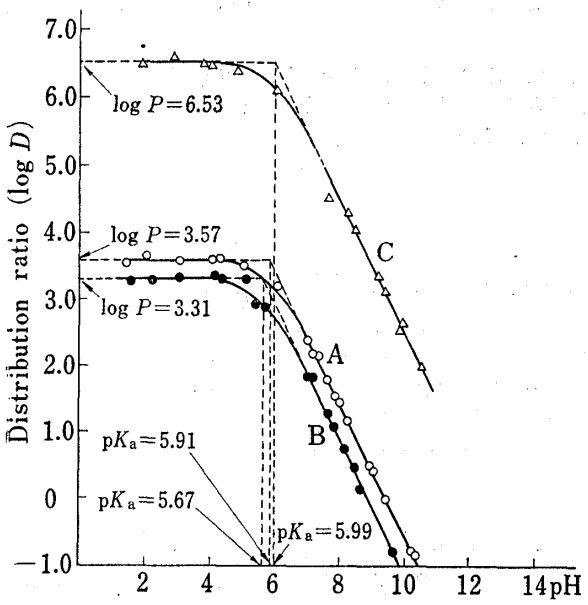

Fig. 1. Distribution Ratio of Chelating Agents as a Function of pH in $CHCl_3$–Water System

ionic strength : 0.1 ($NaClO_4$)
A: N-phenyl-β-mercaptocinnamamide, initial concentration 8.2×10^{-4}M
B: N-ethyl-β-mercaptocinnamamide, initial concentration 4.4×10^{-3}M
C: thiodibenzoylmethane, initial concentration 5.0×10^{-3}M

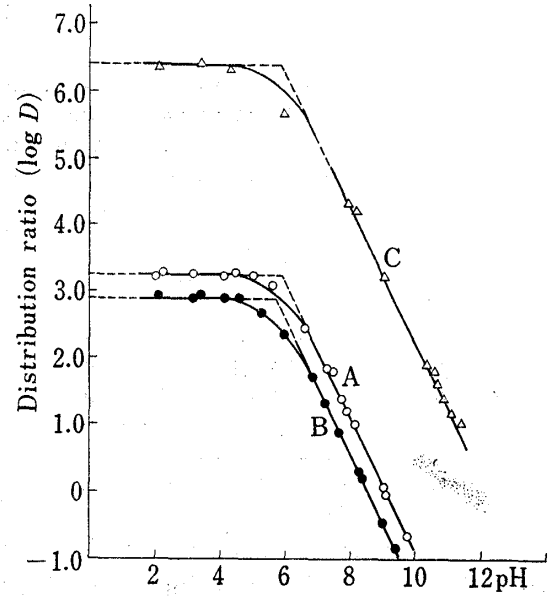

Fig. 2. Distribution Ratio of Chelating Agents as a Function of pH in Benzene–Water System

ionic strength : 0.1 ($NaClO_4$)
A: N-phenyl-β-mercaptocinnamamide, initial concentration 8.2×10^{-4}M
B: N-ethyl-β-mercaptocinnamamide, initial concentration 4.4×10^{-3}M
C: thiodibenzoylmethane, initial concentration 5.0×10^{-3}M

10) A. Yokoyama and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **15**, 290 (1967).

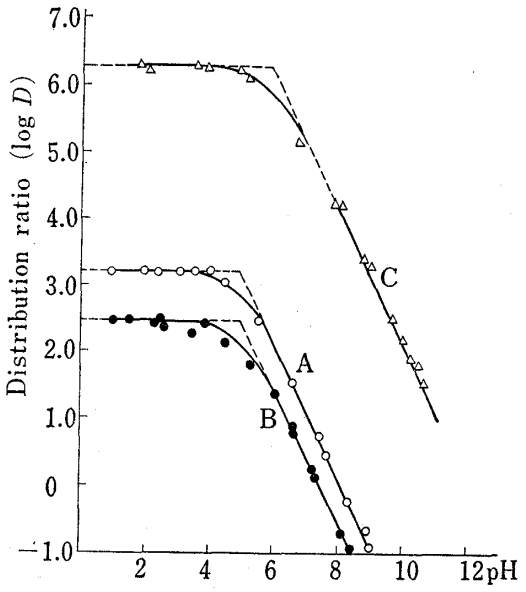

Fig. 3. Distribution Ratio of Chelating Agents as a Function of pH in CCl_4–Water System

ionic strength: 0.1 ($NaClO_4$)
A: N-phenyl-β-mercaptocinnamamide, initial concentration 8.2×10^{-4}M
B: N-ethyl-β-mercaptocinnamamide, initial concentration 4.4×10^{-3}M
C: thiodibenzoylmethane, initial concentration 5.0×10^{-3}M

in Table I may possibly be used practically in the succeeding study on the chelate formation reaction in the same solvent system, as the carefully repeated experiments gave the reproducible results.

In the cases of I and II, an attempt to obtain pK_a values by the potentiometric method was unsuccessful. In the course of the titration in an aqueous dioxane solution, it was practically impossible to measure the value of pH after each addition of a drop of titrant, because the pH value changed gradually. Accordingly, the dissociation constants of I and II could not be determined potentiometrically. In addition, the similar phenomena were also observed when the absorption spectra of I and II were measured, for the determination of the dissociation constants spectrophotometrically in aqueous dioxane solution. The absorbances at λ_{max} changed gradually as shown in Fig. 4. Therefore, the extrapolation treatment described in experimental part was necessary to obtain the pK_a values listed in Table I. The observations mentioned above and the fact that the values of pK_a obtained by solvent ex-

Table I. Acid Dissociation Constants (pK_a) and Partition Coefficients (log P) of N-Phenyl-β-mercaptocinnamamide (I), N-Ethyl-β-mercaptocinnamamide (II), and Thiodibenzoylmethane (III)

	pK_a				log P		
	Extraction			Spectrophotometry			
	$CHCl_3$	C_6H_6	CCl_4		$CHCl_3$	C_6H_6	CCl_4
I	5.91±0.09	5.90±0.10	5.00±0.07	4.51±0.06	3.57±0.05	3.25±0.06	3.23±0.03
II	5.67±0.10	5.75±0.09	5.15±0.11	4.73±0.06	3.31±0.05	2.90±0.04	2.45±0.06
III	5.99±0.14	5.91±0.13	5.82±0.12	8.17±0.03[a]	6.53±0.08	6.40±0.07	6.32±0.07

a) determined in 50% aqueous dioxane

traction method were considerably different from that obtained by other methods gave us a doubt that some other reactions other than dissociation may take place in aqueous organic solvent in parallel with the dissociation. In an attempt to know the behaviors of the chelating agents in aqueous solution, spectral changes on standing in solution were measured under various conditions. Figure 4 shows the spectral change of I with time in acidic 50% dioxane solution. Remarkable shift of λ_{max} (from 315 mμ to 243 mμ) was observed with an isosbestic point at 263 mμ. The absorption spectrum on standing over night agreed completely with that of N-phenyl-benzoylacetamide (VII). These spectral changes together with the fact that in pure dioxane solution the absorption spectrum of I remains unchanged for a long time, suggest that I is hydrolyzed to VII. The evidence that the product of the reaction was VII, was made from the thin-layer chromatography. When the reaction mixture was chromatographed over the silica gel, two spots corresponding to original compound (I) and hydro-

lyzed compound (VII) were observed and any other product was not detected on the chromatogram as shown in Fig. 8. *Rf* values of two spots agreed completely with those of authentic samples of I and VII, respectively. It was found that I and VII react with ferric ions to form green[3c] and violet[11] complexes respectively with extremely high sensitivity. These colorations helped us to confirm the spots of I and VII on the chromatogram without difficulties. Hydrolysis product was isolated from the reaction mixture as described in experimental part and was identified with VII by elemental analysis and nuclear magnetic resonance spectra.

When II was allowed to stand in acidic 50% dioxane solution, the similar result as seen in I was observed. The spectral change was shown in Fig. 5. On the thin-layer chromatogram, we found only two spots corresponding to II and the hydrolysis product, N-ethyl-benzoylacetamide (VIII) as shown in Fig. 8. In both cases, the hydrolyses were also observed in an alkaline region, however it was not so remarkable, compared with that in the acidic region. The spectral change of III was observed in the similar experimental condition as in I and II. In this case, the spectral change, as shown in Fig. 6, suggests that the reaction does not proceed to form hydrolyzed compound, dibenzoylmethane, but to form a oxidized compound, disulfide (IX), and the reaction proceeds further from disulfide to an unknown compound after a long standing. On standing of IX, which was prepared as described in experimental part, showed the same spectral change. As shown in Fig. 7, the decrease of λ_{max} at 335 mμ of IX and the shift of λ_{max} (from 265 mμ to 250 mμ) were observed. The reaction product other than disulfide was detected on thin-layer chromatogram as shown in Fig. 8. However any effort to identify this final product was unsuccessful. As a whole, III is more stable than I and II, since the rate of oxidation of III is much slower than that of

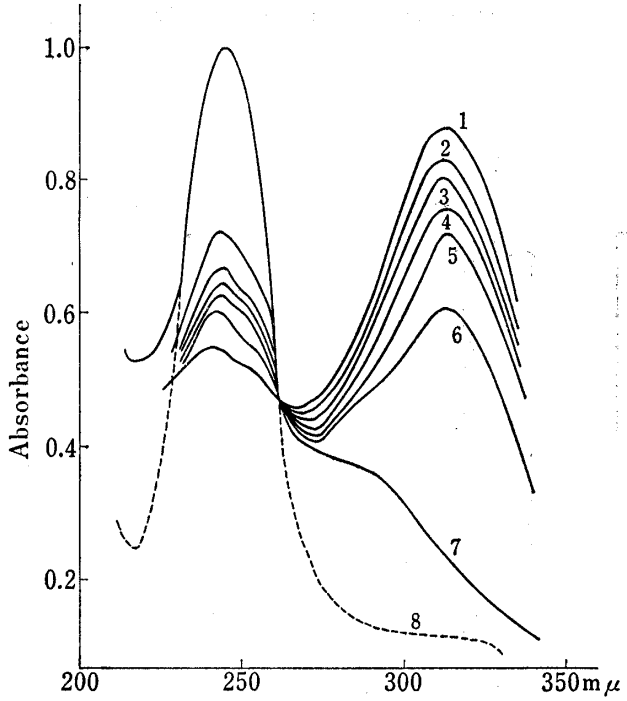

Fig. 4. Absorption Spectra of N-Phenyl-β-mercaptocinnamamide and N-Phenyl-benzoylacetamide in 50% Aqueous Dioxane

N-phenyl-β-mercaptocinnamamide: 10^{-4}M dioxane solution, 5 ml
$HClO_4$: 10^{-2}M, 4 ml
$NaClO_4$: 6×10^{-1}M, 1 ml
1: 20 min, 2: 60 min, 3: 120 min, 4: 180 min, 5: 240 min,
6: 420 min, 7: 24 hr, 8: N-phenyl-benzoylacetamide

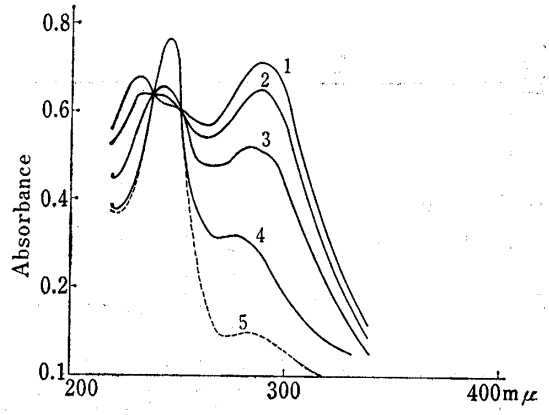

Fig. 5. Absorption Spectra of N-Ethyl-β-mercaptocinnamamide and N-Ethyl-benzoylacetamide in 50% Aqueous Dioxane

N-ethyl-β-mercaptocinnamamide: 8×10^{-5}M dioxane solution, 5 ml
$HClO_4$: 10^{-2}M, 4 ml $NaClO_4$: 6×10^{-1}M, 1 ml
1: 5 min, 2: 50 min, 3: 220 min, 4: 24 hr,
5: N-ethyl-benzoylacetamide

11) A. Syamal, *Can. J. Chem.*, **47**, 1963 (1969).

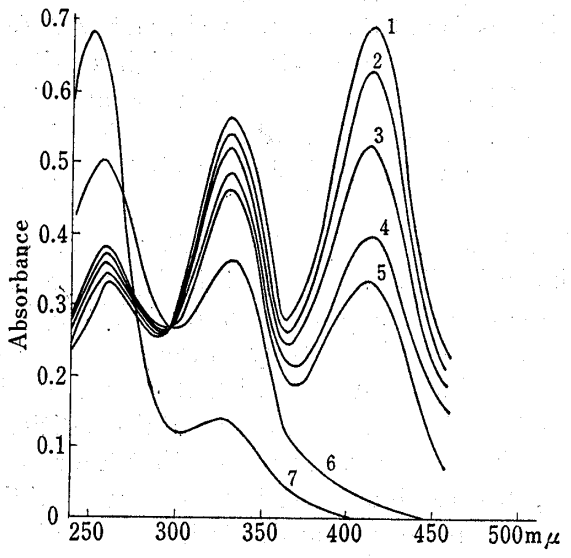

Fig. 6. Absorption Spectra of Thiodibenzoylmethane in 50% Aqueous Dioxane

thiodibenzoylmethane: 8×10^{-5}M dioxane solution 5 ml
$HClO_4$: 10^{-2}M, 4 ml
$NaClO_4$: 6×10^{-1}M, 1 ml
1: 3 min, 2: 80 min, 3: 180 min, 4: 300 min,
5: 350 min, 6: 24 hr, 7: 48 hr

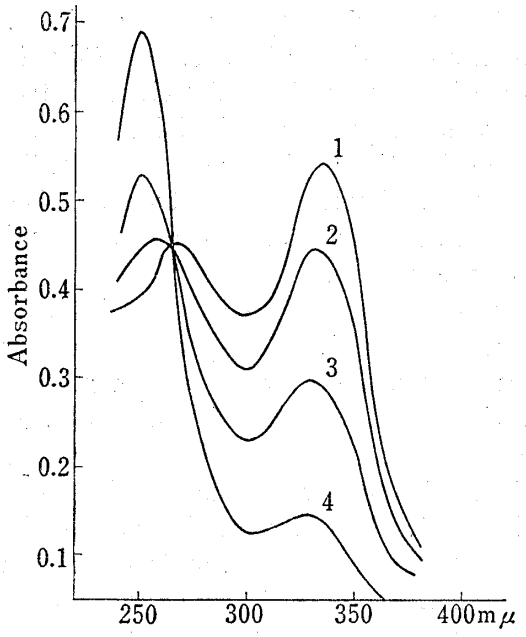

Fig. 7. Absorption Spectra of 1,3,6,8-Tetraphenyl-4,5-dithiaocta-2,6-diene-1,8-dione in 50% Aqueous Dioxane

1,3,6,8-Tetraphenyl-4,5-dithiaocta-2,6-diene-1,8-dione: 4×10^{-5}M
dioxane solution, 5 ml, $HClO_4$, : 10^{-2}M, 4 ml,
$NaClO_4$: 6×10^{-1}M, 1 ml
1: 2 min, 2: 32 min, 3: 145 min, 4: 24 hr

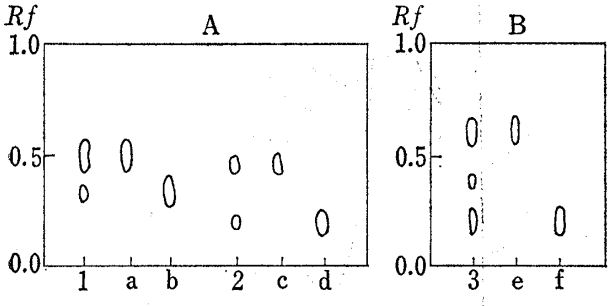

Fig. 8. Thin-layer Chromatograms of N-Phenyl-β-mercaptocinnamamide, N-Ethyl-β-mercaptocinnamamide and Thiodibenzoylmethane in Aqueous Dioxane Solutions

1: N-phenyl-β-mercaptocinnamamide,
2: N-ethyl-β-mercaptocinnamamide,
3: Thiodibenzoylmethane
conditions: 50 v/v % aqueous dioxane (pH 1.6) after 1 day
plate: silica gel (wakogel B-10 treated with HCl)
developing solvent: A; $CHCl_3$–C_2H_5OAc (10: 1), B; benzene
color-producing reagent A; Fe^{3+}, B; iodine
reference substance in dioxane solution
a: N-phenyl-β-mercaptocinnamamide
b: N-phenyl-benzoylacetamide
c: N-ethyl-β-mercaptocinnamamide
d: N-ethyl-benzoylacetamide
e: thiodibenzoylmethane
f: 1,3,6,8-tetraphenyl-4,5-dithiaocta-2,6-diene-1,8-dione

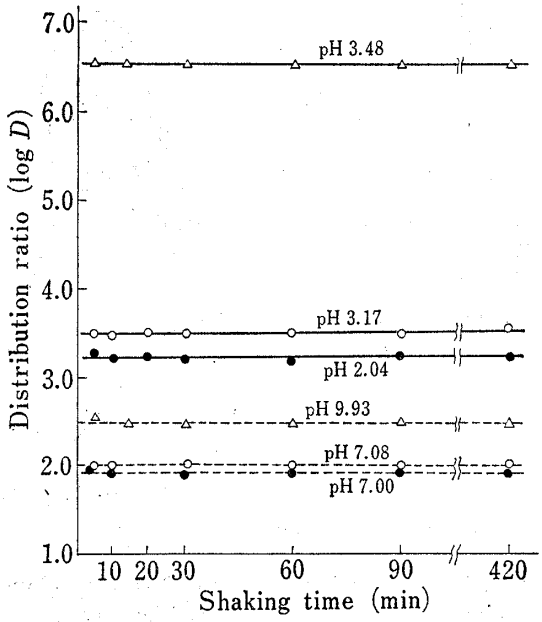

Fig. 9. Effect of Shaking Time on Distribution Ratio

ionic strength: 0.1 solvent: $CHCl_3$
—○—, ---○---: N-phenyl-β-mercaptocinnamamide 1.5×10^{-3}M
—●—, ---●---: N-ethyl-β-mercaptocinnamamide 5.0×10^{-3}M
—△—, ---△---: thiodibenzoylmethane 1.0×10^{-3}M

hydrolyses of I and II. In addition, it was found that III is less stable in an aqueous dioxane solution than in pure dioxane or other organic solvents such as chloroform, benzene and tetrachloromethane.

To evaluate the pK_a values in Table I, it is necessary to keep in mind these experimental results involve the hydrolyses of I and II, and the oxidation of III, together with the dissociation reaction in aqueous organic solvent. When other reactions such as hydrolysis and oxidation take place in pararell with the dissociation at unnegligible rate, their influences are inevitable to the pK_a values obtained potentiometrically and spectrophotometrically even if the experimental techniques such as extrapolation were applied to minimize the errors, whereas, the values obtained by the solvent extraction method may be significantly distinguished from the values obtained by other methods through the following considerations. The equilibria of solvent extraction and hydrolysis are schematically expressed in Chart 2. As the equilibrium of distribution in solvent extraction is considered to be attained very rapidly in general,[12] its rate may be considered to be much faster than that of hydrolysis or oxidation. Accordingly, in the chelating agents presented here, the equilibrium system with a rapid attainment together with the large P values means that the large part of the chelating agent is kept unchanged in the organic phase, in other words in the solvent extraction system, the concentration of undissociated species of reagent is always kept constant in the aqueous phase even in the condition that the hydrolysis or oxidation takes place in parallel with the dissociation. In fact, log D was found to be constant on shaking over a period of 7 hr as shown in Fig. 9. Hence the dissociation constants obtained by the solvent extraction method may be considered to reflect more properly the dissociation reaction of the chelating agent in aqueous solution, than those obtained by other methods. These results and discussions gave us the conclusion that the pK_a values obtained by the solvent extraction method can possibly be evaluated as more reliable and suitable ones than those obtained by other methods for the study of the metal complexes of these chelating agents, although they are macroscopic ones as described above. The kinetic study on the hydrolyses of these chelating agents is now under way, and the results obtained so far show a support for the conclusion mentioned above. The details of the study of the hydrolysis reaction will be reported later.

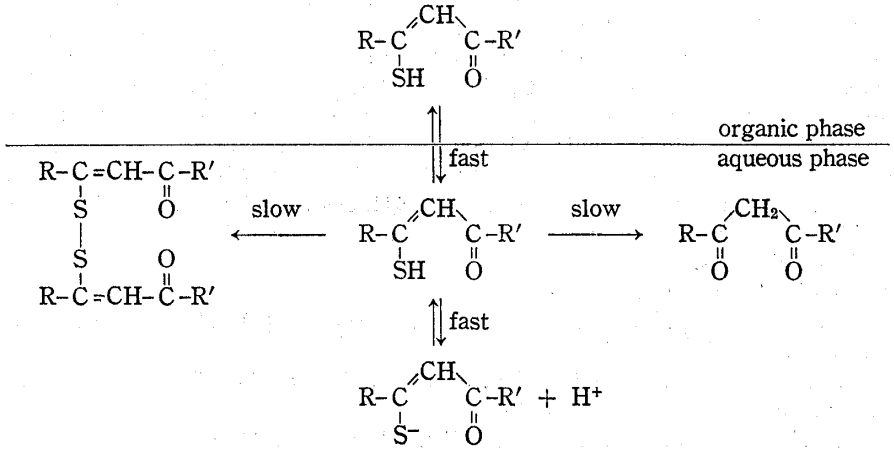

Chart 2

12) G.H. Morrison and H. Freiser, "Solvent Extraction in Analytical Chemistry," John Wiley and Sons, Inc., New York, N.Y., 1957; J. Stary, "Solvent Extraction of Metal Chelates," Pergamon Press, New York, N.Y., 1964, p. 37.