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Preparation of a New Dithioligand

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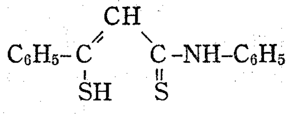
A new dithio ligand containing sulfhydryl and thioamido group, N-phenyl-β-mercaptothiocinnamamide, was prepared and its properties were studied. Although the nuclear magnetic resonance (NMR) spectrum did not show the SH signal, the ν(SH) was observed in the infrared (IR) spectrum. The mass spectrum and the molecular weight estimation revealed that the ligand has a monomer structure. The λ_{max} (ε) in EtOH are as follows; 347 nm (15600), 265 and 229 sh. The pK_a value in 10% EtOH aqueous solution was determined spectrophotometrically to be 3.16 ± 0.03. The low pK_a value was supposed to be an existence of a strong hydrogen bond.

Keywords——new dithioligand; sulfhydryl group; thioamido group; isothiuronium salt; NMR spectrum; mass spectrum; infrared spectrum; pH dependency of electronic spectrum; pK_a determination; strong hydrogen bond

1,3-Dithio chelating agents which are capable of forming six-membered chelating ring with metal ions are expected to have many interesting properties. Attempted syntheses of free dithioacetylacetone have been unsuccessful.[2–4] However, recently Martin *et al.* have succeeded in the synthesis of O-ethylthioacetothioacetate which is the only example of 1,3-dithio ligand isolated in pure and monomeric state.[5,6] The synthetic difficulties of 1,3-dithio ligands are partly due to the reason SH group usually has high reactivity into dimer or polymer sometimes with formation of gummy products. On the other hand, monothio-β-diketones[7] and N-phenyl-β-mercaptocinnamamides[8] which have oxygen and sulfur as donor atoms were synthesized easily and have widely been studied.[9] Since N-phenyl-β-mercaptocinnamamides are promising compounds as analytical reagents[10,11] and antimicrobial pharmaceuticals,[12] we intended to prepare a novel dithio chelating ligand, N-phenyl-β-mercaptothiocinnamamide shown by (I). This paper deals with the preparation, some spectroscopic properties and acid dissociation of (I).



$C_6H_5-C(SH)=CH-C(=S)-NH-C_6H_5$

I

Experimental

Materials——S-[1-Phenyl-2-(phenylthiocarbamoyl)vinyl]isothiuronium *p*-Toluenesulfonate(II): A mixture of 0.1 mol of N-phenyl-phenylpropiolamide,[13] equimolar *p*-toluenesulfonic acid and thiourea were dissolved in 200 ml of EtOH and the solution was allowed to stand overnight. The yellow crystals separated

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[1] Location: *Yoshida, Shimoadachi-cho, Sakyo-ku, Kyoto, 606, Japan.*
[2] E. Fromm and P. Ziersch, *Chem. Ber.*, 39, 3599 (1906).
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out were collected and recrystallized from MeOH, mp 200°. Yield 70%. *Anal.* Calcd. for $C_{23}H_{23}O_3N_3S_3$: C, 56.91; H, 4.74; N, 8.66; S, 19.80. Found: C, 56.76; H, 4.81; N, 8.53; S, 19.78.

N-Phenyl-β-mercaptothiocinnamamide (I): (II) was dissolved in 10% NaOH aqueous solution and acidified with 10% HCl aqueous solution under ice cooling. The yellow precipitate separated out was collected and recrystallized from EtOH, mp 108°. Yield 75%. *Anal.* Calcd. for $C_{15}H_{13}NS_2$: C, 66.42; H, 4.80; N, 5.17; S, 23.62. Found: C, 66.38; H, 4.44; N, 5.26; S, 23.58.

Apparatus——Electronic spectra were recorded on a Shimadzu multiconvertible spectrophotometer Model Double-40. Infrared spectrum (IR) absorption measurements were carried out as potassium bromide disks in the range 4000—650 cm^{-1} with a Hitachi infrared spectrophotometer Model EPI-S2. Nuclear magnetic resonance (NMR) was measured on a Varian A-60 spectrophotometer at 60 MHz with tetramethylsilane as an internal standard. The pH values were measured with a Hitachi-Horiba Model F5 pH meter. Mass spectra were recorded with a Hitachi RMU-6C mass spectrometer. Molecular weight estimation by vapour pressure osmometry in benzene was performed with a Mechrolab Model 301A vapour pressure osmometer using benzil as a standard substance. Electrophoretic migrations in paper were detected on a Yanagimoto Model EC-10 paperelectrophoresis.

Results and Discussion

The process for the preparation of the ligand are shown in Chart 1. Although isothiuronium salt (II) is stable, the ligand is very unstable and is easily oxidized into disulfide. It can be stocked under N_2 for a few days without decomposition.

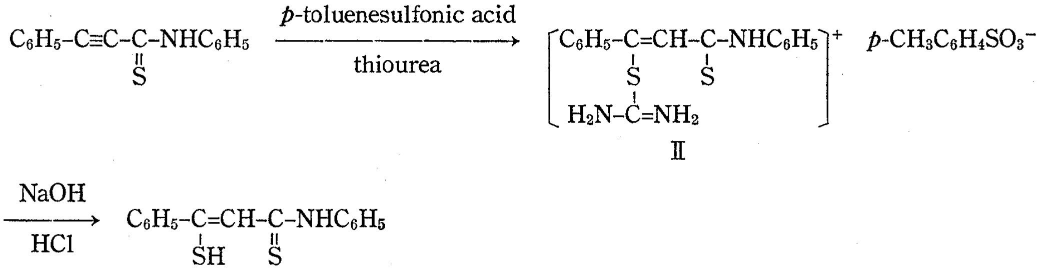

Chart 1

NMR spectrum of the ligand in $CDCl_3$ is indicated in Fig. 1. The NH signal is usually broad because of the proton exchange and therefore the broad signal in the lowest magnetic field seems to be that of thioamido proton. The chemical shift of the methine proton was observed at δ 6.70 ppm, while that of N-phenyl-β-mercaptocinnamamide was found at 6.3 ppm[8] and that of O-ethylthioacetothioacetate, at 6.42 ppm.[5] The signal at 7.37 ppm has integrated area corresponding to ten protons and this indicates that the signal consists of the two phenyl groups. The SH proton, however, was not detected in any tested solvent such as acetone, benzene, pyridine, dimethyl sulfoxide (DMSO) and $CDCl_3$.

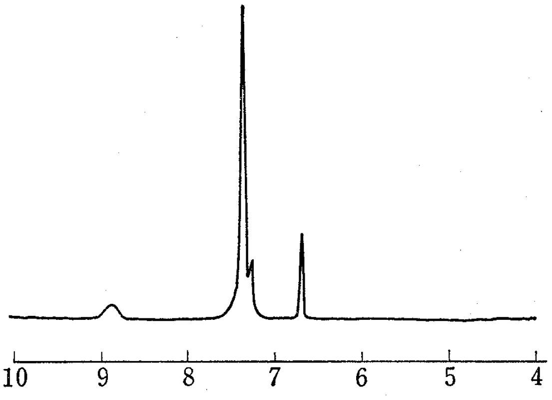

Fig. 1. NMR Spectrum of the Ligand

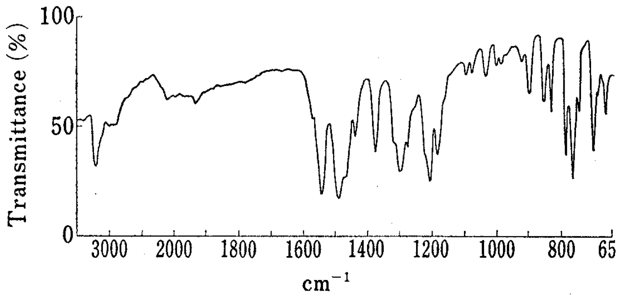

Fig. 2. The Infrared Spectrum of the Ligand (KBr Disk)

The IR spectrum of the ligand is represented in Fig. 2. The band at 3240 cm^{-1} is assigned to NH stretching mode. The SH stretching bands are usually observed in the 2500 cm^{-1} region. Martin *et al.*, however, reported a broad absorption with medium intensity at a fairly low wave number, 2340 cm^{-1} in O-ethylthioacetothioacetate and assigned it to a chelated SH stretching mode.[5] They explained that the low frequency is due to a strong hydrogen bond formation between SH and CS group. In the ligand (I) a similar broad band was detected at 2200 cm^{-1} which disappeared on chelation and this fairly low frequency shows the existence of a very strong hydrogen bond between the sulfhydryl and thiocarbonyl group. The band at 1560 cm^{-1} was assigned to be a C$\doteq$C stretching mode by its shift lower frequency on chelation. Rao *et al.*[14] reported that in compounds where $>$N–C=S unit is present, three bands due to the mixed vibrations by ν(C–N), ν(C$\doteq$S) and δ(NH) appear in the regions, 1395—1570, 1260—1420 and 960—1140 cm^{-1} which were tentatively designated as NCS I, II and III band, respectively. In the ligand (I) three strong absorption bands are found at 1500, 1310 and 1190 cm^{-1} corresponding to the NCS I, II and III, respectively, although the band III appears in a little higher region than that reported by Rao *et al.*

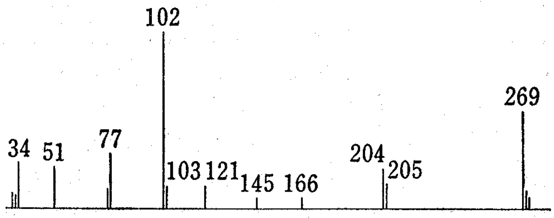

Fig. 3. Mass Spectrum of the Ligand

Peaks with intensity <5% of the *m/e* 102 peak have been omitted.

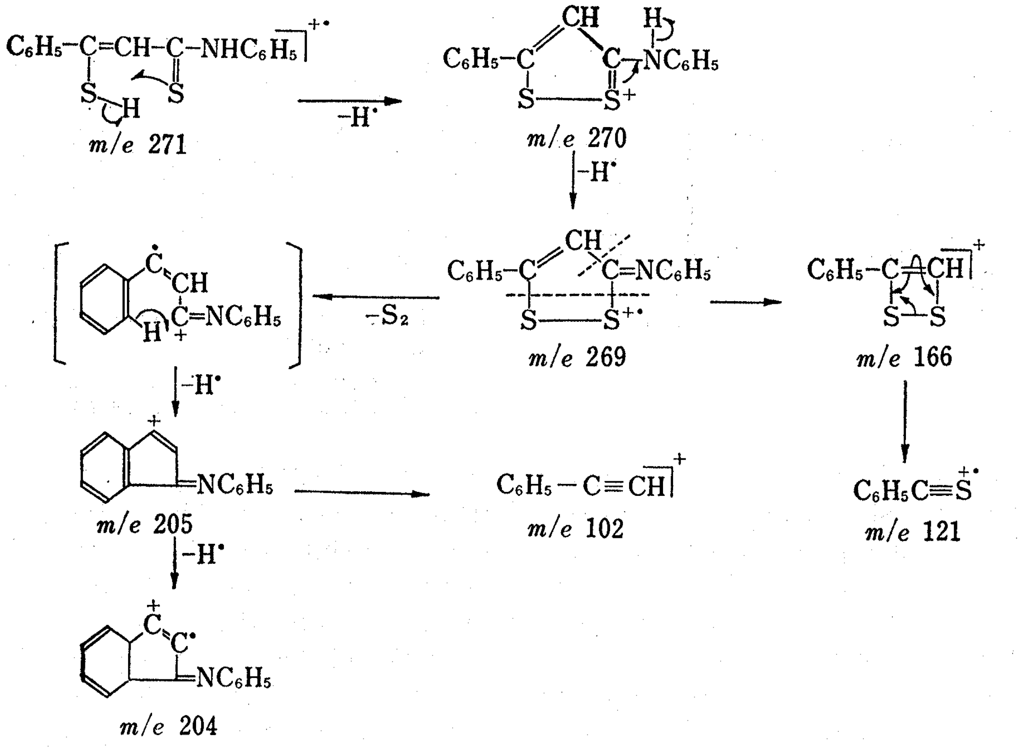

Chart 2

The mass spectrum of the ligand is given in Fig. 3. The proposed ion reactions are shown in Chart 2 and their metastable peaks are presented in Table I. The parent compound lost two hydrogen atoms and gave a secondarily abundant fragment at *m/e* 269 and such a stable intramolecular disulfide sometimes appears as "the resonance stabilized dithiolium cation" in

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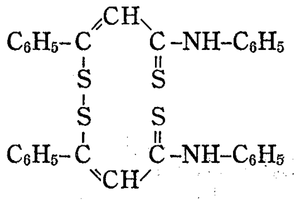
14) C.N.R. Rao and R. Venkataraghavan, *Spectrochim. Acta*, **18**, 541 (1962).

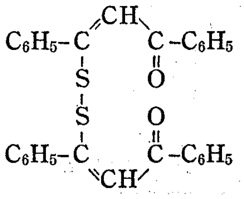
Table I. Metastable Peaks in the Mass Spectrum of the Ligand

Reaction m_1	$\longrightarrow m_2$	Metastable peak $m^*=(m_2)^2/m_1$ Calcd.	Found	Reaction m_1	$\longrightarrow m_2$	Metastable peak $m^*=(m_2)^2/m_1$ Calcd.	Found
271	270	269.0	269.0	205	204	203.0	203.8
270	269	268.0	268.0	205	102	50.8	51.2
269	205	156.2	156.0	166	121	88.2	88.6
269	166	102.4	102.5				

the literatures.[5, 15–17] The disulfide, then, decomposes in two ways. The ions at *m/e* 205 and 204 show the formation of 3*H*-indene derivatives by losing two sulfur atoms from the disulfide. The fragment at *m/e* 166 changes into the fragment at *m/e* 121 which indicates that one sulfur atom of the ligand is attached to the carbon atom of the β-position. Only from the result of the elemental analysis of the ligand, the intermolecular disulfide (III) similar to 1,3,6,8,-tetraphenyl-4,5,-dithiaocta-2,6-diene-1,8-dione (IV) may be possible in (I). Chaston *et al.* reported the mass spectrum of the compound (IV) whose parent ion appears at *m/e* 478.[15] In case of (I), however, no fragments are found in the region, *m/e* 272—542, which denies the existence of the dimer (III). In fact, the molecular weight estimation of (I) in benzene by vapour pressure osmometry gave 272 for the calculated molecular weight 271, which supports the ligand has a monomer structure.



III



IV

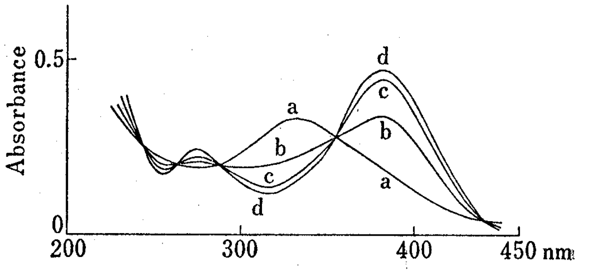


Fig. 4. The pH Dependency of the Electronic Spectra of the Ligand

2×10^{-5}M in 10% of ethanol aqueous solution.
pH: a, 2.00; b, 3.25; c, 4.81; d, 7.52

The electronic spectrum of the ligand was recorded in EtOH. λ_{max} nm(ε) are as follows: 347 (15600), 265 sh and 229 sh. The spectral pH dependency of the ligand is given in Fig. 4. At the low pH the spectrum shows λ_{max} at 332 nm and it shifts to 383 nm with an increase of pH. The latter λ_{max} reversibly shifts to the former by reacidification, which leads us to understanding that these spectral changes are due to the proton dissociation of the SH group of the ligand. The spectra at the lower pH than 2.00 and those at the higher pH than 7.52 change no more. Therefore, the spectrum at pH 2.00 and that at 7.52 were regarded as that of the molecular form and that of the ionic form, respectively. Actually, the ligand stays at the original point at pH 1.90 and moves to the anode side at pH 6.35 in the electrophoreisis.

The obtained pK_a value is 3.16±0.03. Tanaka *et al.* determined the pK_a value of N-phenyl-β-mercaptocinnamamide, monothio derivative of (I), to be 4.51±0.06 by spectro-

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15) S.H.H. Chaston, S.E. Livingston, T.N. Lockyer, V.A. Pickles, and J.S. Shannon, *Aust. J. Chem.*, **18**, 673 (1965).
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photometry.⁹⁾ The low pK_a value compared with that of the oxygen analogue seems to arise partly from the strong hydrogen bond between the sulfhydryl group and the sulfur atom of the thiocarbonyl group, which weakens the SH bond of the sulfhydryl group and consequently makes the dissociation of the hydrogen atom easier.

The ligand shows characteristic reactions with some metal ions. Although the ligand is not stable, its intermediate, isothiuronium salt which is very stable and releases the ligand easily by the treatment with NaOH aqueous solution, can be used as a reagent, instead of the unstable ligand.