Chem. Pharm. Bull.
26(9)2793—2798(1978)

UDC 547.586.5'546.982.02.04 : 543.422.25.06

Synthesis and Properties of N-(2-Methylphenyl)- and N-(2,6-Dimethylphenyl)-β-mercaptothiocinnamamide and Their Palladium(II) Complexes

SUSUMU KITAGAWA and HISASHI TANAKA

Faculty of Pharmaceutical Sciences, Kyoto University[1]

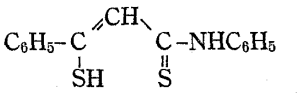
(Received March 17, 1978)

Novel dithio ligands, N-(2-methylphenyl)- and N-(2,6-dimethylphenyl)-β-mercaptothiocinnamamide were synthesized and their pK_a values in 10% EtOH aqueous solution were determined spectrophotometrically to be 3.15 ± 0.03 and 3.14 ± 0.04, respectively. Bis{N-(2-methylphenyl)- and bis{N-(2,6-dimethylphenyl)-β-mercaptothiocinnamamido}-Pd(II) were prepared and their interaction with pyridine were examined. It was observed that both complexes were capable of forming their pyridine clathrates bis{N-(2-methylphenyl)- and bis{N-(2,6-dimethylphenyl)-β-mercaptothiocinnamamido}Pd(II)bipyridine by recrystallization from their pyridine solution. These pyridine molecules were supposed to interact with the thioamido protons of the ligands.

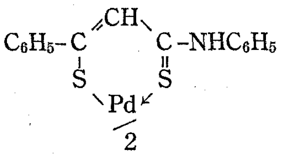
Keywords——dithio ligand; palladium(II) complex; pK_a; pyridine clathrate; hydrogen bond; NMR spectra; IR spectra

From chemical interests of metal complexes of bidentate sulfur ligands, there have been attempts to synthesize dithio metal complexes with six-membered chelate ring, and a few complexes such as dithioacetylacetonato-[2] and O-ethylthioacetothioacetato-metal complexes[3,4] have been synthesized and reported. With the similar interests we attempted to synthesize novel dithio metal complexes with six-membered chelate ring.

In the previous papers, we reported synthesis and properties of a novel dithio ligand, N-phenyl-β-mercaptothiocinnamamide, (LH),[5] and its palladium(II) complex, bis(N-phenyl-β-mercaptothiocinnamamido)Pd(II), (PdL_2).[6] It was observed that the palladium(II) complex was capable of producing a pyridine clathrate, whose composition was corresponded to PdL_2py_2, by recrystallizing from pyridine. The pyridine clathrate was found to be diamagnetic from the magnetic susceptibility measurement, and the ν_{NH} of the pyridine clathrate was observed in the lower wave-number region as compared with that of PdL_2. From these results, it may be considered that the two pyridine molecules in PdL_2py_2 are not directly coordinated to the metal ion, but interact through hydrogen bonding with the thioamide protons of PdL_2. The consideration has led us to investigate how steric hindrance around the thioamido protons affects clathrate formation. In this paper we describe synthesis and properties of dithio ligands, N-(2-methylphenyl)- and N-(2,6-dimethylphenyl)-β-mercaptothiocinnamamide, (L'H



LH



PdL_2

---

[1] Location: *Yoshida, Shimoadachi-cho, Sakyo-ku, Kyoto, 606, Japan.*

[2] R.L. Martin and I.M. Stewart, *Nature* (London), **210**, 522 (1966).

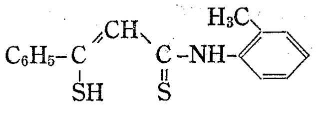
[3] A.R. Henderickson and R.L. Martin, *Aust. J. Chem.*, **25**, 257 (1972).

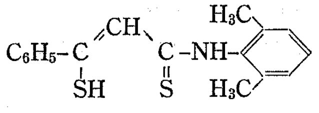
[4] A.R. Henderickson and R.L. Martin, *Inorg. Chem.*, **12**, 2582 (1973).

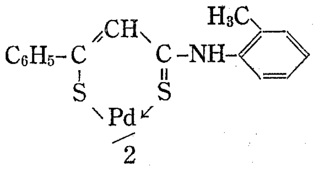
[5] S. Kitagawa and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **26**, 1021 (1978).

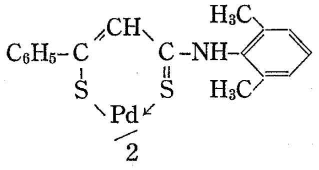
[6] S. Kitagawa and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **26**, 1026 (1978).

and L″H, respectively) and their palladium (II) complexes, bis{N-(2-methylphenyl)- and bis-{N-(2,6-dimethylphenyl)-β-mercaptothiocinnamamido}Pd(II), (PdL'_2 and PdL''_2, respectively).


L′H


L″H


PdL'_2


PdL''_2

Experimental

Materials——S-[1-Phenyl-2-(2-methylphenylthiocarbamoyl) vinyl]isothiuronium-*p*-toluenesulfonate (MITS): This salt was prepared in 22.4% yield by the same method as reported before⁵⁾ from phenylacetylene, 2-methylphenylisothiocyanate, thiourea and *p*-toluenesulfonic acid. Recrystallization from EtOH gave yellow crystals. mp 190°. *Anal.* Calcd. for $C_{24}H_{25}N_3O_3S_3$: C, 57.72; H, 5.01; N, 8.42; S, 19.24. Found: C, 58.48; H, 5.29; N, 8.42; S, 19.04.

S-[1-Phenyl-2-(2,6-dimethylphenylthiocarbamoyl)vinyl]isothiuronium-*p*-toluenesulfonate (DMITS): This salt was prepared as yellow crystal in 12.2% yield by the same method as written above by using 2,6-dimethylphenylisothiocyanate instead of 2-methylphenylisothiocyanate. mp 199°. *Anal.* Calcd. for $C_{25}H_{27}N_3O_3S_3$: C, 58.48; H, 5.26; N, 8.19; S, 18.71. Found: C, 58.67; H, 5.29; N, 8.19; S, 18.74.

N-(2-Methylphenyl)-β-mercaptothiocinnamamide: This ligand was prepared as yellow powder in 73% yield by alkaline hydrolysis of MITS according to the same direction as reported before.⁵⁾ mp 110°. *Anal.* Calcd. for $C_{16}H_{15}NS_2$: C, 67.37; H, 5.26; N, 4.91; S, 22.46. Found: C, 67.22; H, 5.23; N, 4.81; S, 22.16.

N-(2,6-Dimethylphenyl)-β-mercaptothiocinnamamide: This ligand was obtained as yellow powder in 60% yield from DMITS by the same procedure as L′H. mp 119°. *Anal.* Calcd. for $C_{17}H_{17}NS_2$: C, 68.23; H, 5.69; N, 4.68; S, 21.40. Found: C, 68.35; H, 5.79; N, 4.84; S, 21.11.

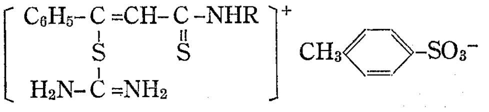
Bis{N-(2-methylphenyl)-β-mercaptothiocinnamamido}Pd(II): This complex was prepared as orange-red crystal in 85% yield from L′H and palladium ammonium chloride by the same method as reported before.⁶⁾ mp (dec.) over 260°. *Anal.* Calcd. for $C_{32}H_{28}N_2PdS_4$: C, 56.97; H, 4.15; N, 4.15; Pd, 15.73; S, 18.99. Found: C, 56.63; H, 4.18; N, 4.28; Pd, 17.17; S, 18.80.

Bis{N-(2,6-dimethylphenyl)-β-mercaptothiocinnamamido}Pd(II): This complex was obtained as orange-red crystal in 87% yield from L″H and palladium ammonium chloride by the same procedure as that for PdL'_2. mp (dec.) over 280°. *Anal.* Calcd. for $C_{34}H_{32}N_2PdS_4$: C, 58.12; H, 4.56; N, 3.99; Pd, 15.10; S, 18.23. Found: C, 57.66; H, 4.87; N, 3.85; Pd, 15.22; S, 18.17.

Apparatus——Nuclear magnetic resonance (NMR) spectra were measured on a Varian A-60 spectrophotometer at 60 MHz with tetramethylsilane as an internal standard. Infrared (IR) absorption measurements were carried out as potassium bromide disks with a Hitachi Infrared Spectrophotometer model EPI-S2. Electronic spectra were recorded on a Shimadzu multiconvertible spectrophotometer Model Double-40. Magnetic susceptibility measurements were carried out by the Gouy method at room temperature (20±1°). Electrophoretic migrations in paper were detected on a Yanagimoto Model EC-10 paper electrophoresis.

Results and Discussion

The obtained isothiuronium salts, MITS and DMITS, were examined by their NMR spectral measurements in DMSO-d_6, and their numerical data are listed in Table I with those of the non-methylated isothiuronium salt, S-[1-phenyl-2-(phenylthiocarbamoyl)vinyl]isothiuronium-*p*-toluenesulfonate (ITS).⁵⁾



ITS : R=phenyl
MITS : R=2-methylphenyl
DMITS: R=2,6-dimethylphenyl

These isothiuronium salts, MITS and DMITS, were hydrolyzed in their alkaline solution, and then acidified by hydrochloric acid to give the dithio ligands, L′H and L″H, respectively. The NMR

Table I. The NMR Spectra of the Obtained Isothiuronium Salts in DMSO-d_6 (δ ppm)

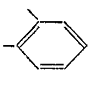
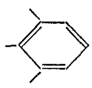
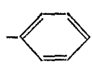
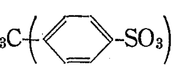
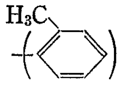
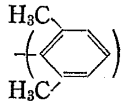
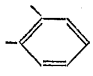
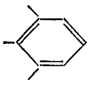
			Benzene ring proton							
Compound	-NH-	$-NH_2$	C_6H_5-				=CH-			
ITS	11.65	9.22	7.47	—	—	7.25	7.07	2.30	—	—
MITS	11.45	9.24	7.62	7.32	—	7.15	7.07	2.30	1.90	—
DMITS	11.41	9.22	7.55	—	7.37	7.05	7.18	2.29	—	1.87

Table II. The NMR Signals of the Obtained Ligands in $CDCl_3$ (δ ppm)

			Benzene ring proton				
Compound	-SH	-NH-	C_6H_5-			=CH-	CH_3-
LH	a)	8.88	7.37	—	—	6.70	—
L′H	11.07	8.70	7.35	7.23	—	6.56	2.25
L″H	11.45	8.53	7.27	—	7.15	6.22b) 6.79b)	2.23

a) Not observed. b) Either is due to CH_2 group.

measurements of these ligands were carried out in $CDCl_3$, and their numerical data were shown in Table II with those of LH. Although no SH signal was detected for LH as reported before,5) those were observed for L′H and L″H in the lower magnetic field. The NH signals of L′H and L″H shifted to the higher magnetic field on account of the shielding effect by the CH_3 groups. It was observed only for L″H that the NH signal appeared as a doublet centered at δ 8.53 ppm and the =CH- signal splitted into two, at δ 6.25 and 6.79 ppm. These observations imply that thioketo–thioenol tautomerism (Chart 1) exists in the solution of L″H. Actually, the total integral ratio of the three signals at δ 11.45, 6.79 and 6.22 ppm corresponded to two protons with a ratio of 1: 0.5: 0.5. Therefore, one of the signals at δ 6.79 and 6.22 ppm seems to be due to CH_2 group.

The electronic spectra of these ligands in their 10% EtOH aqueous solution change with pH values. Thus they showed λ_{max} around 330 nm at pH 2.00 and around 380 and 270 nm at pH 7.52 as indicated in Table III. These changes were reversible, and the spectra in pH

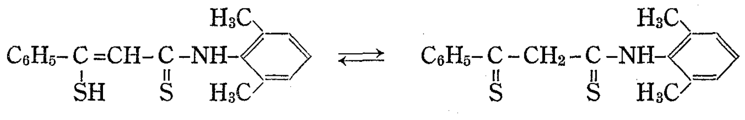
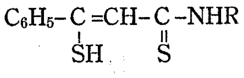


Chart 1

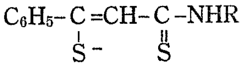
Table III. λ_{max} of the Ligands at pH 2.00 and 7.52, 2×10^{-5} M in 10% EtOH Aqueous Solution (nm)

Compound	pH		
	2.00	7.52	
LH	332	383	273
L′H	325	377	270
L″H	323	375	270

region lower than 2.00 and higher than 7.52 varied no more. Therefore, the spectra at pH 2.00 and 7.52 were regarded as those of the molecular form (1) and ionic form (2), respectively.


$C_6H_5-\underset{\substack{|\\ SH}}{C}=CH-\underset{\substack{\|\\ S}}{C}-NHR$

1


$C_6H_5-\underset{\substack{|\\ S^-}}{C}=CH-\underset{\substack{\|\\ S}}{C}-NHR$

2

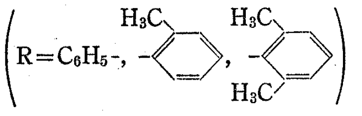


TABLE IV. Electrophoresis[a] of the Ligands 500 V, 30 min (cm)

Compound	pH		
	1.90	4.67	6.35
LH	0	0	+1.3
L′H	0	+0.2	+1.8
L″H	0	0	+1.9

a) Toyo filter paper No. 50 was used. The ligands were solved in 10% EtOH aqueous solution (5×10^{-3}M) buffered with Britton Robinson buffer.

Actually, the ligands showed the trend to move towards the anode with increasing pH in the electrophoresis as visualized in Table IV. These results will coincide with the spectral changes as described above. From the spectral changes at 377 nm of L′H and at 375 nm of L″H, their pK_a values in 10% EtOH aqueous solution were calculated by the following equation and listed in Table V.

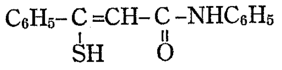
$$pK_a = pH + \log[\text{molecular form}] - \log[\text{ionic form}]$$

TABLE V. pK_a Values of the Ligands in 10% EtOH Aqueous Solution at 20°

Compound	pK_a[a]
LH	3.16±0.03
L′H	3.15±0.03
L″H	3.14±0.04

a) Mean (6 samples) ± deviation.

As is seen in the table, all the pK_a values for the three ligands showed only slight difference in each other, being fairly low values. Chikuma *et al.*⁷⁾ reported that the pK_a value was 4.51±0.06 for N-phenyl-β-mercaptocinnamamide (3). The present low pK_a values as compared with that of the monothio ligand (3) may be attributed to the electron localization on the sulfur atom of the thioamido group in the dithio ligands such as LH, L′H and L″H, and consequently to the formation of a strong hydrogen bonding between the sulfhydryl- and thioamido-group. In fact, SH signals in their NMR spectra appeared in the low magnetic field as seen in Table II, and SH stretching bands in their IR spectra also appeared in the low frequency. Martin *et al.*³⁾ reported the hydrogen bonded SH absorption at 2340 cm⁻¹ for O-ethylthioacetothioacetate,


$C_6H_5-\underset{\substack{|\\ SH}}{C}=CH-\underset{\substack{\|\\ O}}{C}-NHC_6H_5$

3

---

7) A. Yokoyama, M. Chikuma, and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), 20, 2000 (1972).

though ν_{SH} bands usually appear at 2590—2550 cm^{-1}.[8] Both L′H and L″H showed similar broad absorption with medium intensity at 2050 and 2150 cm^{-1}, respectively as shown in Fig. 1.

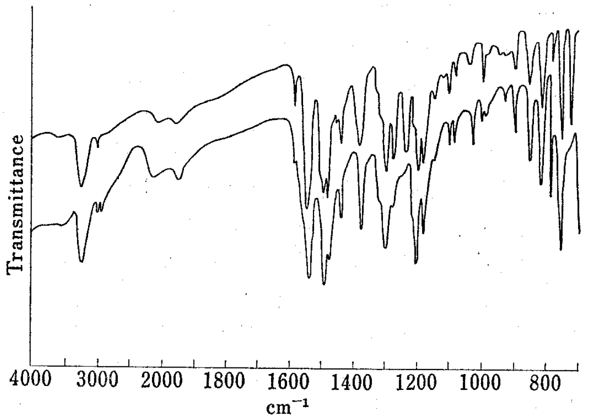


Fig. 1. IR Spectra of L′H (above) and L″H (below)

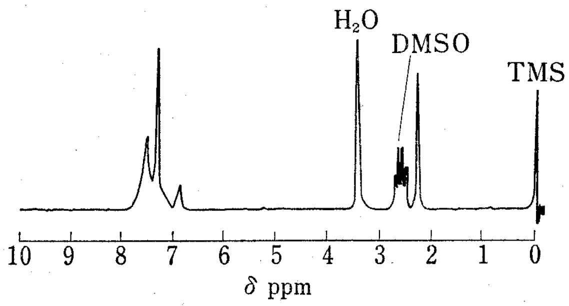
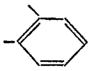


Fig. 2. NMR Spectrum of PdL′$_2$ in DMSO-d_6

Table VI. NMR Spectral Data of PdL′$_2$ and PdL$_2$ in DMSO-d_6 (δ ppm)

Compound	-NH-	Benzene ring proton		=CH-	-CH$_3$
		-C$_6$H$_5$	- 		
PdL′$_2$	n.o.[a]	7.43	7.27	6.83	2.18
PdL$_2$	n.o.[a]	7.52	—	7.08	—

[a] Not observed.

These ligands react easily with metal ions, and thus their palladium chelates, PdL′$_2$ and PdL″$_2$, were obtained. Since PdL″$_2$ were sparingly soluble in solvents, NMR measurement was carried out for PdL′$_2$, and the result was presented in Fig. 2 and Table VI with those of PdL$_2$. The signals of the two compounds bear a resemblance except that PdL′$_2$ showed additional signals due to the methyl- and *o*-phenyl-group as compared with PdL$_2$. Although the NH signal was not detected, this seems to be due to proton exchange caused by water in DMSO-d_6. In fact, their IR spectra showed NH stretching bands around 3200 cm^{-1} (Fig. 3).

It was observed that PdL′$_2$ and PdL″$_2$ gave their pyridine clathrates, PdL′$_2$py$_2$ and PdL″$_2$py$_2$, respectively, by recrystallizing from pyridine. The analytical data are in good accordance with their stoichiometries (Table VII). These two clathrates were revealed to be diamagnetic by their magnetic susceptibility measurements, which excludes the possibility that pyridine molecules are coordinated to palladium ions to form octahedral complexes.

Table VII. Analytical Data of PdL′$_2$py$_2$ and PdL″$_2$py$_2$

Compound	Color	mp (°C)	Calcd. (%)					Found (%)				
			C	H	N	Pd	S	C	H	N	Pd	S
PdL′$_2$py$_2$	Orange-red	>250	60.58	4.57	6.73	12.74	15.38	60.88	4.71	6.81	12.76	15.55
PdL″$_2$py$_2$	Orange-red	>250	61.40	4.88	6.51	12.33	14.88	61.43	4.81	6.68	13.66	14.18

---

[8] A.D. Cross, "Practical Infra-red Spectroscopy," (translated by N. Natori and G. Chihara) Tokyo Kagaku Dojin, Tokyo, 1966, p. 92.

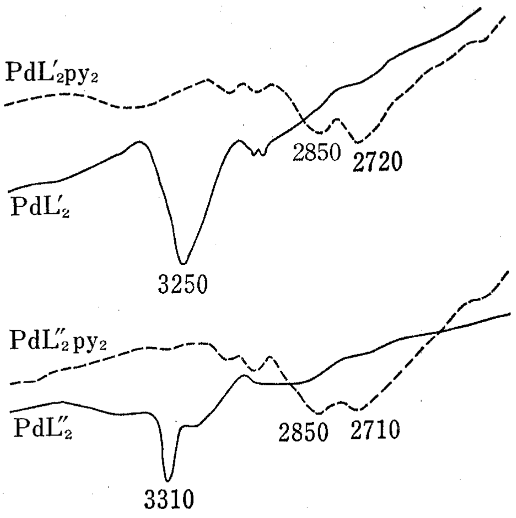


Fig. 3. The NH Stretching Bands of PdL'_2, PdL'_2py_2, PdL''_2 and PdL''_2py_2 (cm^{-1})

The IR spectra of these clathrates show quite different aspects from those of their original palladium complexes with respect to their NH bands as shown in Fig. 3. For PdL'_2 and PdL''_2 the ν_{NH} bands were observed at 3250 and 3310 cm^{-1}, respectively, whereas for PdL'_2py_2 and PdL''_2py_2 the corresponding bands were not observed around 3300—3200 cm^{-1}, but show two new bands at 2850 and 2720 cm^{-1} and 2850 and 2710 cm^{-1}, respectively. Since pyridine does not exhibit any strong absorptions in this region[9] and lowering of stretching frequencies by forming hydrogen bond is well-known,[10] the couple of the bands seem to be due to the hydrogen bonded N—H···N group, probably ν_{N-H} and $\nu_{N\cdots H}$. Lord *et al.*[11] reported similar behavior that tertiary amine chlorides such as C_5H_5NHCl showed ν_{NH} at *ca.* 2500 cm^{-1} which is about 600 cm^{-1} lower than usual ν_{NH}, and suggested that this lowering was due to the strong hydrogen bonds.

These results mentioned above coincide with those of PdL_2py_2. Therefore, it may be concluded that in spite of the steric hindrance by CH_3 groups, PdL'_2 and PdL''_2 are capable of producing their pyridine clathrates, and that in these clathrates pyridine molecules interact with the NH groups of the ligands by forming strong hydrogen bonds.

---

9) L. Corrins, B.J. Fax, and R.C. Lord, *J. Chem. Phys.*, **21**, 1170 (1953).
10) R.M. Badger, *J. Chem. Phys.*, **11**, 288 (1940).
11) R.C. Lord and R.E. Merrifield, *J. Chem. Phys.*, **21**, 166 (1953).