Journal of Organometallic Chemistry, 162 (1978) 239—252

ORGANOTIN(IV) DERIVATIVES OF L-CYSTEINE AND DL-PENICILLAMINE

by G. Domazetis, R.J. Magee and B.D. James,
Department of Inorganic and Analytical Chemistry,
La Trobe University, Bundoora, Victoria, 3083, Australia.
(Received August 31st, 1978)

SUMMARY

The preparations of chlorodimethyl- and chlorodi-*n*-butyl tin(IV) derivatives of L-cysteine, L-cysteine ethyl ester and DL-pencillamine are described. Infrared, n.m.r. and mass spectral data are presented. The compounds contain Sn-S bonds and suggestions for structures are made.

INTRODUCTION

In their studies of the biochemistry of organotin compounds, Aldridge and Cremer showed that diethyltin dichloride had a high affinity for the -SH groups of glutathione and dimercaprol (BAL), but that bis(triethyltin) sulfate did not[1]. ESCA studies, on the other hand, indicated that complexes were formed between tri-*n*-butyltin chloride and amino acids which contained free thiol groups[2]. Mitochondrial oxidative phosphorylation is inhibited *in vitro* by very low concentrations of trialkyltin compounds[3]. In view of the fact that organomercury and -arsenic compounds exert their general inhibitory effects *via* metal-sulfur bond formation[1], we felt it would be valuable to determine whether Sn-S bond formation could be involved in the case of organotin compounds. Consequently, the syntheses and characterization of a series of organotin(IV) derivatives of L-cysteine, DL-pencillamine, glutathione reduced, and other related compounds, were undertaken. Here we report the first preparations of such compounds, present data showing the presence of Sn-S bonds, and postulate possible structures.

EXPERIMENTAL

All compounds used in the syntheses were obtained commercially and employed without further purification.

L-Cysteinato S-(chlorodimethyl)stannane hydrate.

Dimethyltin(IV) oxide (1.66 g, 0.01 mol) was added slowly to a solution of L-cysteine hydrochloride hydrate (1.76 g, 0.01 mol) in 100 mL of 80% ethanol/water solvent. The mixture was stirred for 3 h until a clear solution resulted. The solvent was removed with a rotary evaporator and the resulting oil was placed in a vacuum desiccator for 3 days. A hard, clear glassy solid was obtained in essentially quantitative yield. Mp > 156°C (subl). Thin layer chromatography using aluminium oxide plates and ethanol/water developing solvent showed only one peak. Anal. Calcd. for $C_5H_{14}O_3ClSNSn$: C, 18.63; H, 4.37; S, 9.94; Cl, 11.0. Found: C, 18.93; H, 4.21; S, 10.0; Cl, 11.1. The compound is soluble in alcohol, water and acetone; insoluble in chloroform, hexane and benzene.

The derivative L-Cysteinato S-(chlorodi-*n*-butyl) stannane hydrate was prepared in a similar manner, except that the reactants were kept at 35-40°C. The clear, glassy solid (mp 90.0-92.1°C) is soluble in chloroform, ethanol and acetone.

Ethyl L-Cysteinato S-(chlorodimethyl) stannane.

L-cysteine ethyl ester hydrochloride (3.72 g, 0.02 mol) was dissolved in 150 mL of absolute alcohol and dimethyltin(IV) oxide (3.32 g, 0.02 mol) was added with stirring over 2 h. The clear solution was allowed to stand for 2 days and the large crystals which formed were filtered off then dried in a vacuum desiccator. Yield 60%. Anal. Calcd. for $C_7H_{16}O_2ClSNSn$: C, 25.20; H, 4.83; S, 9.6; N, 4.20; Sn, 35.58. Found: C, 25.47, H, 4.99; S, 9.3; N, 4.06; Sn, 35.68. Mp 93.5-96.1°C. The product is soluble in ethanol and chloroform but is insoluble in water. The colorless crystals slowly turn yellow over *ca.* 3 weeks.

Prepared in a similar manner was Ethyl L-Cysteinato S-(chlorodi-*n*-butyl) stannane. Anal. Calcd. for $C_{13}H_{28}O_2ClSNSn$: C, 37.48; H, 6.77; Sn, 28.49. Found: C, 37.49; H, 6.83; Sn, 28.12.

DL-Penicillamino S-(chlorodimethyl)stannane.

DL-penicillamine (1.49 g, 0.01 mol) was dissolved in 100 mL 70:30 alcohol/water mixture and dilute hydrochloric acid added until pH 2.8. Dimethyltin(IV) oxide (1.66 g, 0.01 mol) was slowly added with stirring over 2½ h, the pH of the solution being maintained at 3.6-3.8 with dil. HCl. The solvent was then completely removed on a rotary evaporator and the solid so obtained maintained under the vacuum at 100°C for a further ¾ h. The product was removed from the flask and stored overnight in a vacuum desiccator. Yield 90%. Mp 140°C (dec). Anal. Calcd. for $C_7H_{16}O_2ClSNSn$: C, 25.30; H, 4.85; S, 9.64; Sn, 35.71. Found: C, 24.97; H, 5.00; S, 9.2; Sn, 36.2.

DL-Pencillamino S-(chlorodi-*n*-butyl)stannane hydrate was prepared in a somewhat similar manner, except that the solvent was removed quickly and no drying was carried out at 100°C. This is a clear, viscous oil which is soluble in acetone, chloroform and ethanol. Anal. Calcd. for $C_{13}H_{30}O_3ClSNSn$: C, 36.01; H, 6.97; S, 7.38. Found: C, 36.35; H, 6.90; S, 7.4.

S-(chlorodimethylstannyl)2-thioethylamine.

Dimethyltin(IV) oxide (1.66 g, 0.01 mol) was added to a solution of 2-aminoethanethiol hydrochloride (1.14 g, 0.01 mol) in ethanol and the mixture stirred for 6 h at 60°C. On cooling, crystals of the product formed. Yield 76%. Anal. Calcd. for $C_4H_{12}ClSNSn$: C, 18.45; H, 4.64; Sn, 45.59. Found: C, 18.47; H, 4.62; Sn, 46.6. Mp 199.8°C.

^1H NMR spectra were recorded at ambient temperature with a Perkin-Elmer R32 spectrometer, using D_2O and $CDCl_3$ as solvents. The ^{13}C spectra were obtained with a JEOL-PFT-100FT instrument operating at 25.15 MHz, and coupled to a JEOL EC-100 data collection system. Infrared spectra were obtained from KBr pressed disks (solids) or from films between KBr windows (oils) using a Perkin-Elmer 457 grating spectrophotometer calibrated with polystyrene film. Ultraviolet spectra were obtained using a Varian 634 instrument. Mass spectra were recorded with a JEOL D-100 Mass Spectrometer.

The pH measurements were obtained using a Jones Labstaph pH meter,

calibrated with pH 7.0 and pH 9.2 buffers and further checked against a pH 4 buffer. Melting points were obtained with a Mettler FP2 melting point microscope. Microanalyses were performed by the Australian Microanalytical Service, C.S.I.R.O., Melbourne.

RESULTS AND DISCUSSION

In the preparation of compounds where the formation of a tin-carboxylate bond was possible, a water-alcohol solvent mixture was employed. Under these conditions the carboxylate group does not react with the tin compound, and the formation of a tin-sulfur bond is favored. The infrared spectra of the complexes (Table 1) shows the presence of the ν(Sn-S) mode near 400 cm^{-1} (with a corresponding absence of the ν(S-H) frequency) and the mass spectra (Table 2) contain peaks such as $Sn\text{-}SCH_2CHNH_2^+$ which indicate the presence of Sn-S bonds. Thus, formation of Sn-S bonds can be regarded as established and the formulae of the compounds confirmed by microanalysis.

The behaviour of the L-cysteinato S-(chlorodimethyl) stannane complex in solution appears fairly complicated. A 0.01 M solution in water has a pH of 3.8 and titration with sodium hydroxide produces two end points corresponding to the consumption of one and two mole equivalents of base, respectively. This appears to correspond to titration of the protons on the carboxylate and amino groups.

The ultraviolet spectrum of the compound at pH 3.8 contains two maxima, whereas at pH 1.3 only one peak is present - as is the case at pH > 12. (see Table 3). The pH dependence of the spectrum indicates that ionic species are formed in solution: protonation of the ligand and coordination at the tin atom being the likely possibilities. It is not possible to postulate from the U/V spectrum which species are present - but it is clear from the absence of a peak at 236 nm that the cysteinate anion is not present at pH > 12. Likewise, the absence of a peak at 256 nm (pH 1.3) indicates that a chlorodimethyltin ion is not present. Thus, a simple dissociation into dimethyltin and cysteinate ions is not indicated by the U/V spectrum. The

(continued on p. 247)

TABLE 1

I.R. SPECTRA

Compound*	$\nu(NH_2)$ cm^{-1}	ν(C=O) cm^{-1}	ν(Sn-C) asym. cm^{-1}	ν(Sn-C) sym. cm^{-1}	ν(Sn-S) cm^{-1}	ν(Sn-Cl) cm^{-1}
L-Cysteine[a]	3012(s.br.)	1590(s)				
L-Cysteine.HCl.H_2O[b]	2940(s.v.br.)	1740(s)				
Me_2SnCl Cyst.H_2O[c]	3000(s.v.br.)	1614[d] (v.s.br.)	562(s)	530(s)	390(sh)	355(s.br.)
Me_2SnCl Pen[c]	3060(v.br.)	1620(s)	560(m)	530(m)	412(m)	323(m)
Me_2SnCl Cyst-Et	(3309(s) (3243(s) (3105(w)	1733(v.s.)	560(s)	532(s)	392(w)	367(s)
$Me_2SnClS(CH_2)_2NH_2$	(3263(s) (3212(s) (3140(s)	-	562(s)	530(s)	394(s)	331(s)
$Bu_2SnClCyst.H_2O$[c]	3120(s.v.br.)	1640[d] (s.sh)	-	535(m)	-	350(w.br.)
Bu_2SnCl Pen.H_2O[c]	*ca.* 3100(v.br.)	1619[e] (v.s.)	600(m)	525(s)	410(s)	321(m)
Bu_2SnCl Cyst-Et	(3300(s) (3230(s) (3150(sh)	1742(v.s.)	555(w)	515(w)	-	360(w)

*Abbreviations used in this and the following tables are:
Cyst = L=cysteine; Pen = DL-penicillamine; Cyst-Et = L-cysteine ethyl ester; Me = methyl; Bu = *n*-butyl.

(a) Also 2568(s), ν(S-H); 1615(vs), NH_3^+ deg. def. mode (ref. 10).

(b) 2548(w), ν(S-H); 1618(m), NH_3^+ deg. def.; 1560(s), $\delta(NH_2)$. A band is also present at 355 cm^{-1}.

(c) A band *ca.* 3450 cm^{-1}(s,br) is found for all these compounds; ν(O-H).

(d) A band at 1614 cm^{-1}(s,br) is also present, NH_3^+ deg. def.?

(e) Only one very strong, broad peak is observed. This probably contains the NH_3^+ def. mode.

TABLE 2

MASS SPECTRA*

$(CH_3)_2Sn(Cl)SCH_2CH(NH_2)COOH.H_2O$ (a)			$(CH_3)_2Sn(Cl)SCH_2CH(NH_2)COOC_2H_5$ (b)		
m/z	Int.	Assignment	m/z	Int.	Assignment**
529	5	$Me_2Sn(Cl)(SCH_2CHCO)_2Sn(Cl)Me^+$	529	1	$Me_2Sn(SCH_2CHCO)_2SnClMe^+$
499	0.5	$MeSn(Cl)(SCH_2CHCO)_2SnCl^+$	499	0.1	$MeSnCl(SCH_2CHCO)_2SnCl^+$
362	5	$[ClSnSCH_2CHCOSn]^+$	333	0.1	P^+
346	20	$MeSnSCH_2CH_2NH_2SnMe^+$	318	10	$CH_3Sn(Cl)L^+$
316	2	$SnSCH_2CH_2NH_2Sn^+$	298	5	$(CH_3)_2SnL^+$
226	2	$Me_2SnSCH_2CH_2NH_2^+$	260	5	$(CH_3)_2Sn(Cl)SCH_2CHNH_2^+$
220	10	$Me_2SnCl_2^+$	245	10	$CH_3Sn(Cl)SCH_2CHNH_2^+$
205	90	$MeSnCl_2^+$	225	20	$(CH_3)_2SnSCH_2CHNH_2^+$
196	10	$SnSCH_2CH_2NH_2^+$	205	30	$(CH_3)SnCl_2^+$
185	100	Me_2SnCl^+	185	30	$(CH_3)_2SnCl^+$
167	60	$MeSnS^+$	155	25	$SnCl^+$
135	10	$MeSn^+$	135	15	CH_3Sn^+
103	10	$[SCH_2CHCOO]^+$	120	15	Sn^+
			103	70	SCH_2CHCOO^+
			76	100	CS_2^+

$(n\text{-}C_4H_9)_2Sn(Cl)SCH_2CH(NH_2)COOC_2H_5$ [c]			$(n\text{-}C_4H_9)_2Sn(Cl)SCH_2CH(NH_2)CO_2H.H_2O$ [d]		
m/z	Int.	Assignment**	m/z	Int.	Assignment
417	1	$Bu_2Sn(Cl)L^+$	531	0.1	$Bu_2Sn(Cyst)SnBu^+$
382	5	Bu_2SnL^+	474	2	$(BuSn)_2Cyst^+$
360	30	$BuSn\text{-}Cl.L^+$	417	1	$BuSn(Cyst)Sn^+$
344	2	$Bu_2Sn(Cl)SCH_2CHNH_2^+$	360	0.5	$Sn(Cyst)Sn^+$
325	15	$BuSnL^+$	269	10	Bu_2SnCl^+
309	15	$Bu_2Sn\text{-}SCH_2CHNH_2^+$	247	10	$BuSnCl_2^+$
296	10	?	177	1	$BuSn^+$
287	10	$BuSn(Cl)SCH_2CHNH_2^+$	165	20	$SnSCH_2^+$
268	10	Bu_2SnCl^+	121	10	SnH^+
252	8	$BuSnSCH_2CHNH_2^+$	120	5	$Cyst^+$
248	10	$BuSnSCH_2CH{=}CH^+/BuSnCl_2^+$	103	10	SCH_2CHCOO^+
222		$BuSn\text{-}SCH_2^+$	76	30	CS_2^+
212		$BuSnCl^+$	57	100	$C_4H_9^+$
195		$SnSCH_2CHNH_2^+$			

* Not all peaks are listed. Intensities are approximate.

[a] Probe temperature 260°C, ionizing voltage 20V.
[b] Probe temperature 160°C, ionizing voltage 75V.
[c] Probe temperature 100°C, ionizing voltage 25V.
[d] Probe temperature 155°C, ionizing voltage 75V.

** L refers to Cyst-Et.

TABLE 3

ULTRAVIOLET SPECTRA

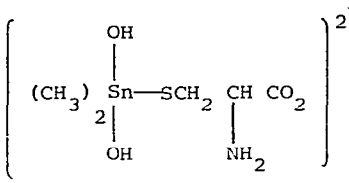
Compound	pH	λ_{max}(nm)	ϵ_{max}	
Me_2SnCl Cyst.[a]	1.3	215	2.0×10^3	
	3.8	196	4.0×10^3	
		227	750	$[Me_2Sn]^{2+}$ has peak at 220 nm
	>12	222	1.8×10^3	Me_2SnCl_2 in H_2O has λ_{max} at 195 and 256 nm.
Cysteine[b]	0.4	190	2.5×10^3	
Cysteinate anion[b]	*ca.*12	236	4.3×10^3	

(a) $Me_2SnClS(CH_2)_2NH_2$ in neutral solution has two peaks: 198, 224 nm.

(b) From ref. 11.

ε_{max} values at both ends of the pH scale contrast sharply with those observed for cysteine at pH 0.4 and pH 12.

The ^{1}H n.m.r. spectra are given in Table 4. In aqueous solution (pH 3.8), the cysteinato complex displays a simple AB pattern similar to the one shown by cysteine itself near this pH. At pD > 11, the spectrum of the organotin compound becomes a complex ABC type, which is also similar behavior to that of free cysteine[4]. In view of the observations made from the U/V spectrum, the species present at high pH may be formed by replacement of the chloride by hydroxyl to give a species such as:



The similar $^{2}J(^{119/117}Sn\text{-}CH)$ values found for $[Me_2Sn(OH)_4]^{2-}$ (5) and the cysteine complex, at high pH values, support the species proposed, as does the reduced shift value of the methyltin protons.

^{1}H and ^{13}C n.m.r. spectra of the cysteine and penicillamine complexes are indicative of pentacoordinate tin species. However, the spectra were obtained for D_2O solutions, and it is difficult to know whether coordination by water molecules is responsible for the pentacoordination.

I.R. spectra can distinguish between coordination by H_2O, $-NH_2$ and -COOH groups, all of which have the potential to coordinate to tin. The spectra of both the cysteine and penicillamine complexes (Table 1) contain broad peaks centered at 3450 cm^{-1} and 3000 cm^{-1}, which are characteristic of H_2O and $-NH_2$ groups involved in hydrogen bonding[6]. The strong peaks at *ca.* 1620 cm^{-1} are assigned to ν(C=O) which may coordinate to the tin atom. It is noted that organotin complexes of some aminoacids which contain Sn-O bonds, also show the carbonyl frequencies in this region, but coordination to tin is not proposed[7]. It has been shown that the ν(C=O) frequency may

(continued on p. 250)

TABLE 4

N.M.R. SPECTRA

^1H Spectra

Chemical shifts are relative to external TMS = 0 ppm for D_2O solutions or internal TMS for $CDCl_3$ solutions. (The shift of Me_3SnCl under identical conditions was 1.07 ppm).

Coupling constants taken at 300 Hz width, and are the average of 3-5 readings.

Compound	$^2J(^{119}Sn-CH)$	$^2J(^{117}Sn-CH)$	δ(SnMe)	δ(CH)	δ(CH_2)	Other
$Me_2Sn(Cl)Cyst.$ [a]	80.1	77.2	1.44	4.48	3.59	δ(DHO) = 5.16
$Me_2Sn(Cl)Pen.$ [a]	79.1	75.3	1.42	4.51	1.96	δ(DHO) = 5.15
$Me_2Sn(Cl)S(CH_2)_2NH_2$ [a]	78.0	73.8	1.39	complex		δ(DHO) = 5.15
$Me_2Sn(Cl)Cyst.-Et.$ [b]	72.0	68.7	1.30	3.98	3.02	δ(CH_2) = 4.24 δ(CH_3) = 1.30 δ(NH_2) = 2.89
$Me_2Sn(Cl)Cyst.$ [a] pD > 11	81.6	77.8	0.78*			δ(DHO) = 5.14
$[Me_2Sn(OH)_4]^{2-}$ [c]	82.7	78.4	-			

^{13}C Spectra

Chemical shifts are given to ±0.1 ppm and coupling constants to ±2.5 Hz.

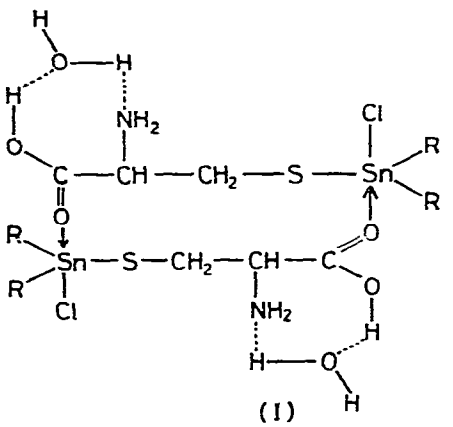
Compound	Chemical Shifts αC	βC	γC	δC	Coupling Const. ^1J	^2J	^3J	C=O Shift	Other Shifts
$Bu_2Sn(Cl)Cyst.-Et$[b]	26.0	28.1	26.5	13.7	539.6 512.7	-	68.4	171.0	(SCH_2) = 55.7; (NCH) = 62.3; (CH_2) = 30.9; (CH_3) = 14.2.
$Me_2Sn(Cl)Cyst.Et$[b]	7.1				581.1 551.6			170.9	(SCH_2) = 55.8; (NCH) = 62.5; (CH_2) = 30.9; (CH_3) = 14.2.
$Me_2Sn(Cl)Pen$[a]	5.2				600.6†			173.1	(NCH) = 68.5; $C(CH_3)_2$ = 46.4; (CH_3) = 31.5, 29.5.

[a] D_2O solvent. [b] $CDCl_3$ solvent. [c] From ref. 9

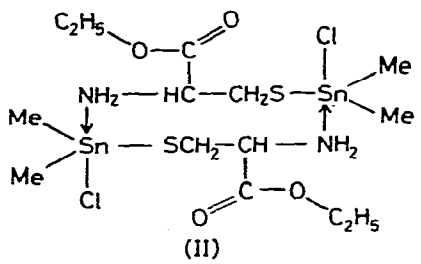
* Chemical shift relative to dissolved $(CH_3)_3SnCl$ = 0.90 (pH>11).

† Separate peaks could not be resolved.

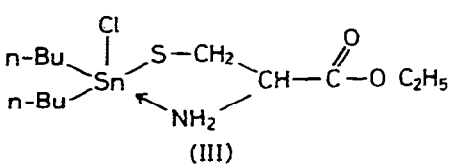
fall in the region 1630-1570 cm^{-1} for a series of organotin complexes which contain C=O groups coordinated to tin, and the strength of the coordination, along with possible mass effects, can influence the position of this band[8,9]. The mass spectra of these complexes indicate that coordination is possible *via* the free carboxylate group. The spectrum of $(n\text{-}C_4H_9)_2Sn(Cl)SCH_2CH(NH_2)COO$ shows the presence of di-tin species, while that of $(CH_3)_2Sn(Cl)SCH_2CH(NH_2)COO$ shows a number of peaks which arise from the $[(CH_3)_2Sn(Cl)SCH_2CO]_2^+$ dimer. At the temperatures employed to obtain the mass spectra, decomposition of the complexes occurs, and this may make structural assignments less straightforward. However, we have compared the mass-spectra with that of $(CH_3)_3SnSCH_2COOH$, taken over temperatures where decomposition does not occur and have observed the species $(CH_3)_3SnSCH_2COOSn(CH_3)_3^+$,



(I) R=Me, n-Bu



(II)



(III)

$(CH_3)_3SnSCH_2COSn(CH_3)_3^+$ and $[(CH_3)_3SnSCH_2CO]_2^+$ therein. The data therefore indicate a dimeric five-coordinate structure in the solid, involving coordination by C=O to tin, and the presence of hydrogen bonding, as shown in structure I. A monomeric structure containing $R_2Sn(Cl)SCH_2CH(NH_3^+)CO_2^-$. H_2O cannot, however, be completely excluded at this stage.

Structural inferences may be drawn quite readily from the spectra of the L-cysteine ethyl ester complexes. The coupling constants $^1J(^{119/117}Sn-^{13}C)$ and $^2J(^{119/117}Sn-CH_3)$ in $CDCl_3$ solutions are also indicative of five-coordinate tin (Table 4). The $\nu(NH_2)$ bands in the i.r. spectra are typical of coordinated $-NH_2$ groups, whereas the $\nu(C=O)$ groups are not coordinated[9]. Coordination of the NH_2 group has also been postulated for a series of organotin(IV) amino acid derivatives[7]. The i.r. spectrum of the compound $(CH_3)_2Sn(Cl)SCH_2CH_2NH_2$ is similar in the $\nu(N-H)$, $\nu(Sn-S)$ and $\nu(Sn-Cl)$ regions to the spectra of the L-cysteine ethyl ester derivatives. The mass spectrum of the dimethyltin cysteine ethyl ester derivative suggests the presence of dimeric species and a structure such as (II). However, in the case of the dibutyltin complex, all the spectral evidence indicates a monomeric structure (III). This apparent discrepancy may be explained because a thermogram of the dimethyltin complex shows that considerable decomposition occurs at the mass spectral probe temperature which was employed. Hence, dimeric species may be formed by decomposition and association in the solid. In any event, preliminary X-ray crystallographic data (R = 0.069) indicates that this complex does exist with a structure analogous to (III).

ACKNOWLEDGEMENT

G.D. acknowledges receipt of a Commonwealth of Australia Postgraduate Research Award.

REFERENCES

1. W.N. Aldridge and J.E. Cremer, Biochem. J., 61, 406, (1955).
2. Y. Limouzin and P. Llopiz, J. Organomet. Chem., 122, 41, (1976).
3. W.N. Aldridge and B.W. Street, Biochem. J., 91, 287, (1964).
4. K.G.R. Pachler, Spectrochim. Acta., 19, 2085, (1963).
5. R.S. Tobias, I. Ogrins, and B.A. Nevett, Inorg. Chem., 1, 638 (1962).
6. C.A. McAuliffe, J.V. Quagliano and L.M. Vallarino, Inorg. Chem., 5, 1996, (1966).
7. B.Y.K. Ho and J.J. Zuckerman, Inorg. Chem., 12, 1552 (1973).
8. G. Domazetis, R.J. Magee and B.D. James, Submitted for publication.
9. C.A. McAuliffe, J. Chem. Soc., (A), 641, (1967).
10. H. Shindo and T.L. Brown, J. Am. Chem. Soc., 87, 1904 (1965).
11. P.C. Jocelyn, "Biochemistry of the SH Group", Academic Press Inc., London, 1972, p.50.