Reactions of Hydrogenated Thiamine Derivatives with $K_2[MX_4]$, where M is Pd^{II} or Pt^{II} and X is Cl or Br

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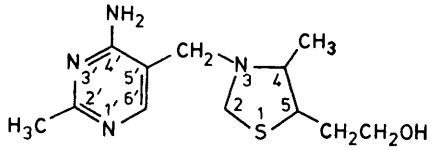
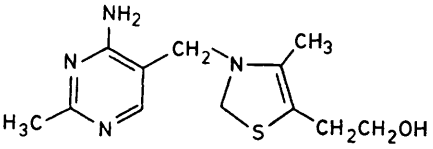
The reactions of $K_2[MX_4]$, where M is Pd^{II} or Pt^{II} and X is Cl or Br, with the hydrogenated thiamine derivatives L, 3-[(4'-amino-2'-methyl-5'-pyrimidinyl)methyl]-5-(β-hydroxyethyl)-4-methylthiazolidine (L^1), 3-[(4'-amino-2'-methyl-5'-pyrimidinyl)methyl]-5-(β-hydroxyethyl)-4-methylthiazoline (L^2), 3-[(4'-amino-2'-methyl-5'-pyrimidinyl)methyl]-4-methyl-5-(β-monophosphatoethyl)thiazolidine (L^3), 3-[(4'-amino-2'-methyl-5'-pyrimidinyl)methyl]-4-methyl-5-(β-pyrophosphatoethyl)thiazolidine (L^4) and their deuteriated derivatives, have been studied in aqueous solutions at pH *ca.* 1 and 5.5. The products, $[ML_2X_2].2HX$ and $[ML_2X_2]$, have been isolated from these studies and characterized by elemental analyses, conductivity measurements, pH-metric titrations, i.r., ^1H n.m.r., and ^{13}C n.m.r. spectra. A complete assignment of the ^1H and ^{13}C n.m.r. spectral resonances is presented for both the ligands and the complexes. The results show that the ligands are protonated primarily at the $N^{1'}$ atom of the pyrimidine moiety, while the metallation site is either the N^3 or the S atom of the thiazoline or thiazolidine ring.

RECENTLY [1,2] we reported the reactions of $K_2[MX_4]$ (M = Pd^{II} or Pt^{II}; X = Cl or Br) with thiamine and its phosphate esters. The isolated complexes, from these reactions, were possibly the first examples of metal–thiamine complexes presenting a direct metal–ligand bond, *via* the $N^{1'}$ atom of the pyrimidine moiety. The thiazole ring was found not to react with the metals, due to the positive charge on nitrogen and the contribution to the ring resonance of the lone electron pairs of sulphur.[1,2] Continuing our studies on interactions of $K_2[MX_4]$ with thiamine derivatives, we now present the reactions of the di- and tetra-hydrogenated thiamine derivatives with Pt^{II} and Pd^{II}.

The di- and tetra-hydrothiamine derivatives 3-[(4'-amino-2'-methyl-5'-pyrimidinyl)methyl]-5-(β-hydroxyethyl)-4-methylthiazolidine (L^1) and 3-[(4'-amino-2'-methyl-5'-pyrimidinyl)methyl]-5-(β-hydroxyethyl)-4-



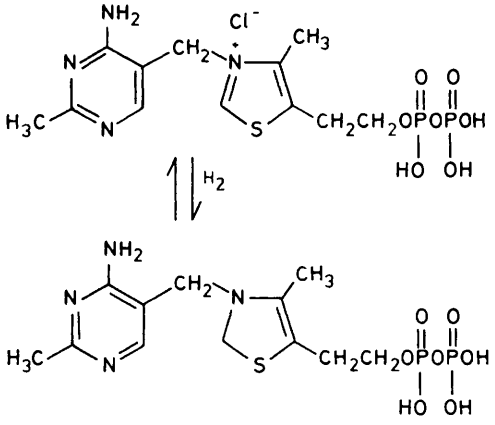
L^1



L^2

methylthiazoline (L^2) were first prepared and characterized by Hirano [3] and Bonvicino and Hennessy [4] by reduction of thiamine with $Na[BH_4]$ and $Li[AlH_4]$ respectively. The tetrahydrothiamine monophosphate (L^3) and tetrahydrothiamine pyrophosphate (L^4) were prepared analogously.[3,4]

In 1937, Lipmann [5,6] proposed that the enzymatic action of thiamine pyrophosphate, in the lactic acid bacteria *B. delbrücki*, was due to its ability to act as an oxidation–reduction system. He also showed [7] that thiamine pyrophosphate could be reduced in the presence of Pt black or sodium dithionate, as shown in equation (1).



(1)

Although the model of Lipmann is now known to be incorrect,[8] both hydrogenated derivatives are interesting as ligands. They both contain a pyrimidine ring and a thiazoline or thiazolidine ring. The nitrogen atom of the latter ring no longer bears a net positive charge as in thiamine, which makes a comparison of the donor properties of the three rings towards Pt^{II} and Pd^{II} possible. It is also interesting to compare the donor properties of the thiazoline and thiazolidine rings with those of thiazole, where the sulphur atom does not appear to co-ordinate with metals.[9] The thiazolidine ring is also interesting as a ligand, since it is a part of the penicillin antibiotic. A preliminary account of this work has already been published.[10]

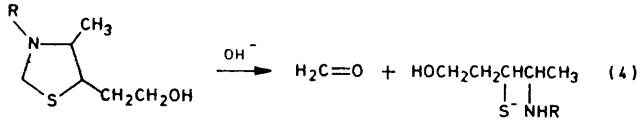
RESULTS AND DISCUSSION

The reactions of L^1, L^2 and their phosphate esters with $K_2[MX_4]$ were carried out in aqueous neutral and

acidic (pH *ca.* 1) solutions, equations (2) and (3) respectively, since in alkaline media the ligands are unstable and decompose, as shown [11] in equation (4). The

$$K_2[MX_4] + 2L \xrightarrow{H_2O} [ML_2X_2] \quad (2)$$

$$K_2[MX_4] + 2L \xrightarrow{0.1\ \text{mol dm}^{-3}\ \text{HX}} [ML_2X_2]\cdot 2HX + 2KX \quad (3)$$



(4)

complexes with the deuteriated derivatives of L^3 and L^4 were not prepared, due to the low yield obtained from the preparations of these ligands.

The two complexes $[ML_2X_2]$ and $[ML_2X_2]\cdot 2HX$ could be interconverted reversibly, depending on pH [equation (5)]. The ligands L^1 and L^2 are soluble in acidic aqueous solutions, with retention of one HX molecule [equation (6)]. The products L·HX, together with the complexes

$$[ML_2X_2]\cdot 2HX \underset{\text{pH } ca.\ 1,\ 0.1\ \text{mol dm}^{-3}\ \text{HX}}{\overset{\text{pH } ca.\ 5.5,\ 0.1\ \text{mol dm}^{-3}\ \text{Na[OH]}}{\rightleftharpoons}} [ML_2X_2] \quad (5)$$

$$L \underset{0.1\ \text{mol dm}^{-3}\ \text{Na[OH]}}{\overset{0.1\ \text{mol dm}^{-3}\ \text{HX}}{\rightleftharpoons}} L\cdot HX \quad (6)$$

$[ML_2X_2]\cdot 2HX$ and $[ML_2X_2]$, were characterized by elemental analyses, conductivity measurements, pH-metric titrations (see Table 1), and i.r., ^1H n.m.r., and ^{13}C n.m.r. spectra.

The analytical results agree with the assigned formulae. The conductivity measurements indicate that the ligands L and the complexes $[ML_2X_2]$ are non-electrolytes, while the products L·HX and $[ML_2X_2]\cdot 2HX$ are 1 : 1 and 1 : 2 electrolytes respectively, in dimethylformamide (dmf) or water solutions. These observations confirm that there is retention of one HX molecule by the ligands

TABLE 1

Analytical and physical data of the compounds

Compound	Analysis (%) [a] C	H	N	M	X	Conductance [b] / S cm² mol⁻¹	M.p. (θc/°C)	pK_1, pK_2
L^2						7.5 [c]	145	3.2, 7.2
L^2·HCl					11.55 (11.75)	56.7 [c] 118.7 [d]	105	
$[PtL^2_2Cl_2]\cdot 2HCl$	32.85 (33.05)	4.30 (4.15)	13.25 (12.85)	22.15 (22.4)	15.95 (16.3)	202.1 [d] 81 [c]	244 [e]	3.0, 5.5
$[PdL^2_2Cl_2]\cdot 2HCl$	36.25 (36.8)	4.45 (4.60)	14.9 (14.3)	14.0 (13.6)	17.95 (18.15)		173 [e]	3.0, 5.7
$[PtL^2_2Cl_2]$	35.8 (36.1)	3.95 (4.50)	14.15 (14.05)	24.35 (24.45)	8.95 (8.90)	6.3 [c]	200 [e]	
$[PdL^2_2Cl_2]$	39.2 (40.6)	4.95 (5.05)	15.15 (15.8)	14.9 (15.0)	10.35 (10.0)	7.8 [c]	193 [e]	
L^1						8.0 [c]	150	3.1, 7.1
L^1·HCl					11.7 (11.65)	54.8 149.4 [d]	102	
$[PtL^1_2Cl_2]\cdot 2HCl$	32.15 (32.9)	4.95 (4.80)	12.3 (12.8)	22.25 (22.3)	16.05 (16.2)	78.0 [c] 194.2 [d]	245 [e]	3.0, 5.6
$[PdL^1_2Cl_2]\cdot 2HCl$	36.4 (36.4)	5.00 (5.10)	14.05 (14.25)	13.1 (13.55)	18.2 (18.05)		210 [e]	3.0, 5.8
$[PtL^1_2Cl_2]$	35.1 (35.9)	4.70 (5.00)	13.0 (13.95)	24.4 (24.3)	8.50 (8.85)	6.5 [c]	240 [e]	
$[PdL^1_2Cl_2]$	39.8 (40.35)	5.10 (5.60)	16.0 (15.7)	14.5 (14.9)	9.25 (9.95)	7.3 [c]	220 [e]	
$[PtL^1_2Br_2]$	32.1 (32.3)	4.50 (4.50)		22.2 (21.90)			238 [e]	
$[PdL^1_2Br_2]$	36.3 (35.90)	5.10 (5.00)		13.55 (13.25)			215 [e]	
$[PtL^3_2Cl_2]\cdot 2HCl$	27.4 (27.8)	4.20 (4.05)			14.0 (13.7)		216 [e]	
$[PdL^3_2Cl_2]\cdot 2HCl$	30.95 (30.45)	4.65 (4.45)			14.85 (15.0)		185 [e]	
$[PtL^3_2Cl_2]$	29.8 (29.95)	4.10 (4.35)			7.50 (7.40)		202 [e]	
$[PdL^3_2Cl_2]$	32.45 (33.0)	4.55 (4.80)			8.20 (8.15)		176 [e]	
$[PtL^4_2Cl_2]\cdot 2HCl$	24.15 (24.1)	3.95 (3.70)			12.15 (11.90)		172 [e]	
$[PdL^4_2Cl_2]\cdot 2HCl$	26.85 (26.05)	4.10 (4.00)			13.1 (12.85)		148 [e]	
$[PtL^4_2Cl_2]$	25.8 (25.65)	3.50 (3.90)			6.45 (6.30)		206 [e]	
$[PdL^4_2Cl_2]$	28.05 (27.85)	4.15 (4.25)			6.55 (6.85)		178 [e]	

[a] Calculated values are given in parentheses. [b] 10^{-3} mol dm^{-3} solution at 20 °C. [c] In dmf. [d] In water. [e] Decomposes.

TABLE 2

Infrared spectral data (cm^{-1}) of the compounds

Compound	ν(OH),ν($\overset{+}{N}$H) ν(NH_2),ν(CH)		ν(OD), ν(ND_2)	δ(NH_2) + ν(pyrimidine ring)	ν(pyrimidine ring)	ν(M–X)	δ(OH) + δ(CH)
L^2	3 360s	2 935s		1 640vs	1 560s		1 738
	3 300w	2 860s					
	3 140s	2 835s		1 590 (sh)			
	2 975s						
L^2·HCl	3 400br	2 920m					
	3 200br	2 680br		1 650s	1 580 (sh)		1 740s
	3 060br			1 605m			
L^2·DCl			2 470br	1 600s	1 585 (sh)		
L^1	3 400s	2 930br		1 642s			
	3 300w	2 880w			1 545s		1 741m
	3 150br	2 830w		1 603s			
	2 980w						
L^{1D}			2 545s	1 615s	1 555s		
			2 310s				
L^1·HCl	3 380br	2 920br					
	3 160br	2 700br		1 660s	1 550 (sh)		1 735s
				1 603m			
L^1·DCl			2 400br	1 645s	1 560m		
L^3	3 400br	2 970w		1 640s			
	3 140br	2 920w		1 600m	1 570m		1 738s
L^4	3 400br	2 950br		1 635s			
	3 160br			1 600 (sh)	1 560m		1 738s
$[PtL^2{}_2Cl_2]$	3 400br	2 920w					
	3 300br	2 820w		1 650s	1 540 (sh)	330m	1 735 (sh)
	3 200br			1 608w			
$[PtL^{2D}{}_2Cl_2]$			2 500br	1 600s	1 560w		
$[PtL^2{}_2Cl_2]$·2HCl	3 400br	2 760br					
	3 300s br	2 650w		1 662s	1 575 (sh)	320m	1 735 (sh)
	3 130s	2 620w					
	2 900br			1 603s			
$[PdL^2{}_2Cl_2]$·2HCl	3 400br	2 900br					
	3 260br	2 800br		1 655s		310m	1 738m
	3 120br	2 620m			1 580m		
				1 602s			
$[PtL^3{}_2Cl_2]$·2DCl			2 500s br	1 650s	1 570m		
$[PtL^1{}_2Cl_2]$	3 400br	3 160br		1 642s			
	3 310br	2 930m		1 593 (sh)	1 555 (sh)	335m	1 738s
$[PdL^1{}_2Cl_2]$	3 350br	2 920m					
	3 080m br	2 890w		1 650s br	1 560s (sh)	320w	1 738s
				1 605s			
$[PtL^{1D}{}_2Cl_2]$			2 500s br	1 605s	1 560s	330m	
$[PtL^1{}_2Cl_2]$·2HCl	3 400br	2 860w					
	3 200br	2 650br		1 650s	1 580m	315w	1 740s
	2 930w			1 605m			
$[PdL^1{}_2Cl_2]$·2HCl	3 360br	2 900br					
	3 200br	2 600br		1 650s	1 575s	320w	1 738s
	3 060m br			1 605m			
$[PtL^1{}_2Cl_2]$·2DCl			2 500br	1 650s	1 565m		
$[PtL^3{}_2Cl_2]$	3 300br	2 940br		1 650s br	1 570w	340m	1 732m
	3 150br			1 605 (sh)			
$[PtL^3{}_2Cl_2]$·2HCl	3 350br	2 920s br					
	3 200br	2 650br		1 650s	1 580m	320w	1 738m
	3 060m br			1 610w			
$[PdL^3{}_2Cl_2]$·2HCl	3 300br	2 900br					
	3 070br	2 700br		1 650s	1 580m	320w	1 735m
				1 610 (sh)			
$[PtL^4{}_2Cl_2]$	3 350br	2 940br		1 655s	1 560s (sh)	340m	1 735m
	3 150br			1 620 (sh)			
$[PtL^4{}_2Cl_2]$·2HCl	3 300br	2 930br					
	3 070br	2 700br		1 650s	1 580m	320w	1 735m
				1 610 (sh)			
$[PdL^4{}_2Cl_2]$·2HCl	3 350br	2 920m br					
	3 060br	2 650br		1 650s	1 580m	330w	1 735m
				1 610 (sh)			

L and two HX molecules by the complexes $[ML_2X_2]$. Since the complexes $[ML_2X_2]$ are non-conducting, the ligands should be bonded to the metals through only one bonding site in a square-planar arrangement. Therefore the HX molecules are retained by only one position of the ligands, which should be different from the metallation site.

The pH-metric titrations performed in aqueous solutions (see Table 1), give the first indication of the protonation and metallation sites. Although the pK_2 values cannot be considered as very accurate, since at pH > 5.5 the complexes decompose with subsequent precipitation, they can be assigned to the C_2–H ionization of the thiazoline and thiazolidine rings [reaction (4)]. Bonvicino and Hennessy [4] report two pK values for the ligands L^1 and L^2 in the alkaline region (7.8 and 11.5). It is characteristic that the pK_2 value is reduced by 1.5—2 units on passing from the ligands to the complexes. If therefore pK_2 is due to the C^2 hydrogens, the metals should be bonded near this carbon atom. The pK_1 values, which are almost unchanged in the ligands and the complexes, can be assigned to $N^{1'}$ of pyrimidine, since it is close to the pK values of other natural pyrimidine derivatives.[12] The pK value of the $N^{1'}$ site of thiamine [13] is about 5.

Infrared Spectra.—All the ligands and the complexes show strong bands in the region 2 900—3 500 cm^{-1}, due to the ν(OH), $\nu(NH_2)$, and ν(CH), aliphatic or aromatic, vibrational modes or couplings of these.[14] The detailed positions of the bands are shown in Table 2.

In the hydrohalogenated ligands and complexes ($L \cdot HX$ or $[ML_2X_2] \cdot 2HX$) there is one very broad absorption in this region, which extends to *ca.* 2 500 cm^{-1} and indicates the existence of hydrogen bonding of the type $\overset{+}{N}H \cdots X$.[14-17] All these bands shift to lower frequencies upon deuteriation according to the ratios ν(OH)/ν(OD) and ν(NH)/ν(ND) which lie in the range 1.3—1.4 (see Table 2).

The normal values of the ν(OH) and $\nu(NH_2)$ frequencies show that these functional groups are not involved in bonding with the metals. Furthermore the extension of the i.r. absorptions to *ca.* 2 500 cm^{-1} in the hydrohalogenated derivatives indicates the retention of the HX molecules by a ring nitrogen.

Further evidence for the non-involvement in bonding of the NH_2 group and the protonation and metallation sites is given by an examination of the i.r. spectra in the 1 600 cm^{-1} region. Ligand L^1 shows an absorption at 1 642 and 1 603 cm^{-1}, $L^1 \cdot HCl$ at 1 660 and 1 603 cm^{-1}, the complex $[PtL^1_2Cl_2]$ at 1 642 and 1 593 cm^{-1}, and the complex $[PdL^1_2Cl_2]$ at 1 645 and 1 601 cm^{-1}. In the complexes $[PtL^1_2Cl_2] \cdot 2HCl$ and $[PdL^1_2Cl_2] \cdot 2HCl$, these bands appear at 1 650 and 1 605 cm^{-1} (see Table 2 and Figure 1). In the deuteriated derivatives of these compounds (L^{1D} represents deuteriated L^1 *etc.*), these two bands are replaced by one of intermediate frequency, at 1 615 cm^{-1} in L^{1D}, at 1 645 in the $L^{1D} \cdot DCl$, at 1 605 cm^{-1} in $[PtL^{1D}_2Cl_2]$, and at 1 650 cm^{-1} in $[PtL^{1D}_2Cl_2] \cdot 2DCl$ (see Figure 1). The two bands shown in the non-deuteriated derivatives can therefore be assigned to ring stretching and $\delta(NH_2)$ (bending), while the unique bands of the deuteriated ones are due to ring stretching only.[18,19] The $\delta(ND_2)$ bands appear at *ca.* 1 200 cm^{-1} [$\nu(NH)/\nu(ND) = 1.35$] (see Table 2). This again indicates that the amino-group is free.[18,19]

The first ring stretching mode of pyrimidine [17,20] appears at a frequency higher than 1 600 cm^{-1}. Rao and Venkataraghavan [21] and Chouteau *et al.*[22] assigned a band in this region to ring stretchings of thiazole, thiazoline, and thiazolidine. However, Sbrana *et al.*[23] assigned the 1 610 cm^{-1} band to a combination of thiazole fundamentals 862 + 750 = 1 612 cm^{-1}. We may therefore assign the higher frequency band, in the present case, to a pyrimidine rather than thiazoline or thiazolidine ring stretching. Note also that the unique band of the deuteriated derivatives in this region is shown at higher frequencies in $L^{1D} \cdot DCl$ and $[PtL^{1D}_2Cl_2] \cdot 2DCl$, than in L^{1D} and $[PtL^{1D}_2Cl_2]$. This indicates that in the former compounds the HCl is retained by the pyrimidine rings.[15] The complex $[PtL^{1D}_2Cl_2]$ shows this band at 1 605 cm^{-1}, while in the ligand L^{1D}, it appears at 1 615 cm^{-1}. This is evidence that the pyrimidine ring is not bonded to the metals, as in the case of thiamine itself,[1,2] since the opposite effect would be expected otherwise. Therefore

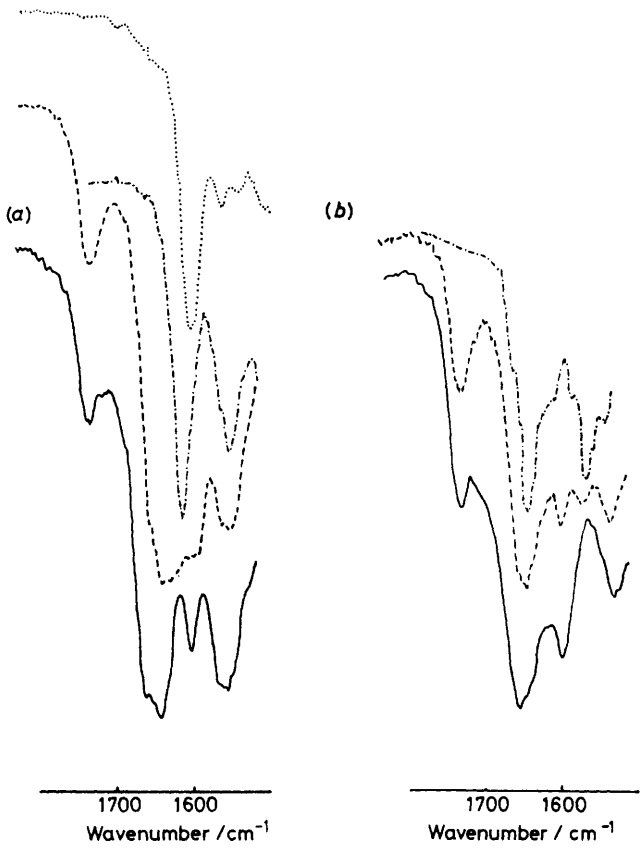


FIGURE 1 Infrared spectra in the 1 500—1 700 cm^{-1} region of (*a*) L^1 (——), $[PtL^1_2Cl_2]$ (— — —), L^{1D} (— · — · —), $[PtL^{1D}_2Cl_2]$ (· · · ·), and (*b*) $L^1 \cdot HCl$ (——), $[PtL^1_2Cl_2] \cdot 2HCl$ (— — —), $L^{1D} \cdot DCl$ (— · — · —)

the metal must be bonded through the thiazoline or thiazolidine rings. Similar observations for ν(C=O) of 2-benzoylpyridine [24] and d(+)-biotin [25] have been made in their complexes with metals, bonded through nitrogen and sulphur respectively. The other ligands and complexes also show similar behaviour (see Table 2).

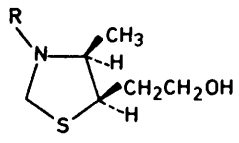
A medium intensity band, shown at *ca.* 1 740 cm^{-1} in all the ligands and the complexes, may be assigned to a combination of a CH out-of-plane deformation and an OH or NH_2 deformation mode [23] since it disappears upon deuteriation (see Figure 1).

The ν(M–Cl) stretching vibrations are assigned to the medium intensity bands in the region 310—340 cm^{-1} for the different complexes (see Table 2). They shift to *ca.* 230 cm^{-1} in the bromo-analogues. In the hydrochloride complexes $[ML_2Cl_2]\cdot 2HCl$, this vibration appears at lower frequencies and is less intense than in the $[ML_2Cl_2]$ complexes. This is possibly due to intramolecular hydrogen bonding.[26,27] The unique ν(M–X) band may indicate a *trans* rather than a *cis* square-planar structure.

Hydrogen-1 N.M.R. Spectra.—In their improved preparation of L^1, Clark and Sykes [28] obtained this ligand in two diastereoisomeric forms, *syn* and *anti*. They observed two doublets in the ^1H n.m.r. spectra, which were assigned to different C^4–CH_3 groups, at $\delta = 1.05$ p.p.m. and $\delta = 1.29$ p.p.m., with $J = 6.4$ Hz. With many recrystallizations, these workers [28] succeeded in obtaining the isomer with $\delta = 1.05$ p.p.m., which was in excess (2.5 : 1) in the original mixture, without identifying it (structures I and II).

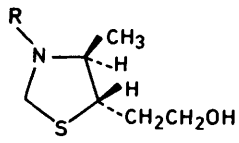
In the present work we also used only one of the two isomers, isolated with many recrystallizations. Our isomer shows $\delta(CH_3)$ at 1.1 p.p.m. in $CDCl_3$ and at 0.96 p.p.m. in $[^2H_6]$dmso (dmso = dimethyl sulphoxide), with $J = 6.4$ Hz (see Table 3 for the chemical shifts in other solvents).

This isomer was not identified again here, since the



I

syn



II

anti

chemical shifts of the C^5–H, C^4–H, $-CH_2-$ (of the bridge), and $-CH_2-O-$ groups coincide in one strong peak, with a maximum at 3.53 p.p.m. in $[^2H_6]$dmso (see Figure 2). The assignment of the other peaks is made as follows. The $C^{6'}$–H group appears at 7.78 p.p.m. as a singlet, while the amino-group is at 6.60 p.p.m. but disappears upon addition of a few drops of D_2O in the $[^2H_6]$dmso solutions. The hydroxyl group can also be assigned to the broad peak at 4.60 p.p.m. for similar reasons. The $C^{2'}$–CH_3 group of the pyrimidine ring appears as a singlet at 2.33 p.p.m., as in thiamine chloride hydrochloride.[29–31] The multiplet peak at 1.73 p.p.m. can be assigned to C^5–CH_2, since the triplet, expected for this group in thiamine chloride hydrochloride and L^2, is split in L^1 by the presence of C^5–H. Finally, the ill resolved quartet, centred at 4.03 p.p.m., is assigned to the $-CH_2-S-$ group. This methylenic group can roughly be considered as an A_2X

TABLE 3

Hydrogen-1 n.m.r. chemical shifts (δ/p.p.m.) of the compounds *

Compound	Solvent	$C^{6'}$–H	$C^{2'}$–CH_3	$-CH_2-S-$	C^4–CH_2-	C^5–H	$-CH_2-O-$	C^4–CH_3	C^4–H	$-CH_2-$ bridge	$-NH_2$	OH
L^1	$CDCl_3$	8.13 (s)	2.36 (s)	4.03 (q) $J = -5$ Hz	3.80 (m)		4.00 (m)	1.65 (s)		3.93 (s)	6.13 (br)	~4.00 (s)
L^1	0.1 mol dm^{-3} DCl	8.00 (s)	2.40 (s)	4.03 (q)	3.60 (m)		3.90 (m)	1.40 (d) $J = 2$ Hz		3.66 (s)		
L^1	D_2O	8.10 (s)	2.50 (s)	4.03 (q)	3.80 (m)		3.80 (m)	1.53 (d)		3.80 (m)		
L^1·HCl	$[^2H_6]$dmso	8.22 (s)	2.60 (s)	4.15 (q)	3.50 (m)		3.62 (m)	1.46 (s)		3.96 (s)	8.20 (s)	5.30 (br)
L^1·HCl	$[^2H_6]$dmso + 2 drops CF_3COOH	8.56 (s)										
L^1	0.1 mol dm^{-3} DCl	8.03 (s)	2.57 (s)	4.23 (q)	1.93 (m)	3.76 (m)	3.76 (m)	1.10 (d)	3.76 (m)	3.76 (m)		
L^1	$[^2H_6]$dmso	7.78 (s)	2.33 (s)	4.03 (q) $J = -9$ Hz	1.73 (m)	3.53 (m)	3.53 (m)	0.96 (d) $J = 6.4$ Hz	3.53 (m)	3.53 (m)	6.60 (s)	4.60 (br)
L^1	$[^2H_6]$dmso + 2 drops CF_3COOH	8.25 (s)										
L^{1D}	0.1 mol dm^{-3} DCl	8.10 (s)	2.46 (s)		1.90 (t)		3.63 (m)	0.96 (s)		3.63 (m)		
L^1·HCl	$[^2H_6]$dmso	8.40 (s)	2.56 (s)	4.23 (q)	1.83 (m)	3.85 (m)	3.85 (m)	1.05 (d)	3.85 (m)	3.85 (s)	7.56 (br)	4.53 (s)
L^1·HCl	$[^2H_6]$dmso + 2 drops CF_3COOH	8.55 (s)	2.56 (s)	4.40 (q)	1.93 (m)	4.06 (m)	4.06 (m)	1.31 (d)	4.06 (m)			
L^3	D_2O	8.10 (s)	2.50 (s)	4.10 (q)	2.16 (m)	3.63 (q)	3.96 (m)	1.06 (d)	3.63 (m)	3.63 (m)		
L^4	D_2O	8.13 (s)	2.50 (s)	4.06 (q)	2.10 (m)	3.70 (m)	3.85 (q)	1.03 (d)	3.70 (m)	3.70 (m)		
$[PtL^3{}_2Cl_2]\cdot 2HCl$	0.1 mol dm^{-3} DCl	8.27 (s)	2.50 (s)	4.50 (m)	4.50 (m)		3.75 (m)	1.62 (s)		4.16 (m)		
$[PtL^1{}_2Cl_2]\cdot 2HCl$	0.1 mol dm^{-3} DCl	8.41 (s)	2.63 (s)	4.56 (q) $J = -5$ Hz	2.06 (m)	3.80 (q)	3.80 (t)	1.50 (d)	3.80 (m)	3.80 (m)		
$[PtL^1{}_2Cl_2]\cdot 2HCl$	$[^2H_6]$dmso	8.50 (s)	2.56 (s)	4.36 (q)	2.06 (m)	4.00 (q)	3.43 (m)	1.06 (d)	4.00 (m)	4.00 (m)	9.20 (br)	4.36 (br)
$[PtL^1{}_2Cl_2]\cdot 2HCl$	$[^2H_6]$dmso + 2 drops CF_3COOH	8.53 (s)										
$[PtL^{1D}{}_2Cl_2]$	0.1 mol dm^{-3} DCl	8.50 (s)	2.63 (s)		2.03 (t)		3.73 (m)	1.20 (s)		3.73 (m)		
$[PdL^1{}_2Cl_2]\cdot 2HCl$	0.1 mol dm^{-3} DCl	8.36 (s)	2.60 (s)	4.56 (q)	2.03 (m)	4.13 (m)	3.66 (t)	1.46 (d)	4.13 (m)	4.13 (m)		
$[PtL^4{}_2Cl_2]\cdot 2HCl$	D_2O	8.13 (s)	2.60 (s)	4.50 (q)	2.33 (m)	4.30 (m)	4.30 (m)	1.50 (d)	4.30 (m)	4.30 (m)		
$[PdL^4{}_2Cl_2]\cdot 2HCl$	D_2O	8.13 (s)	2.64 (s)	4.53 (q)	2.26 (m)	4.35 (m)	4.35 (m)	1.50 (d)	4.35 (m)	4.35 (m)		
$[PtL^4{}_2Cl_2]\cdot 2HCl$	D_2O	8.13 (s)	2.70 (s)	4.50 (q)	2.30 (m)	4.25 (m)	4.25 (m)	1.56 (d)	4.25 (m)	4.25 (m)		

* s = Singlet, d = doublet, t = triplet, m = multiplet, q = quartet, br = broad.

system, isolated from the rest of the molecule. The non-equivalence of these protons can be explained if we assume that the sulphur and nitrogen atoms of thiazolidine are not in the same plane.[32] A greater downfield shift is expected for a methylenic group adjacent to two heteroatoms, especially to the more electronegative (than

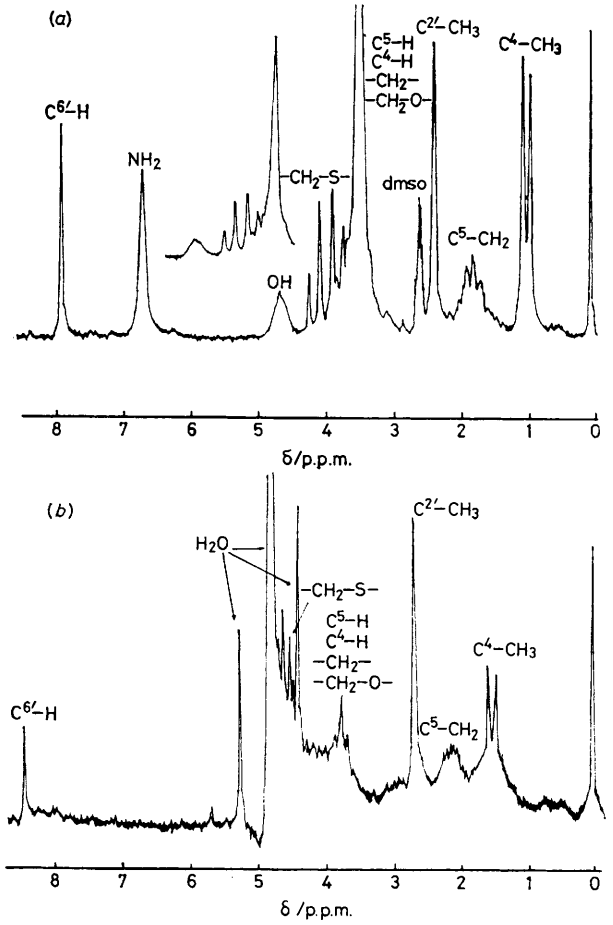
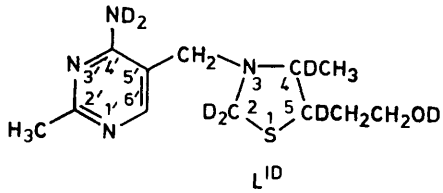


FIGURE 2 ^{1}H n.m.r. spectra of (*a*) L^1 in [$^2H_6$]dmso and (*b*) $[PtL^1_2Cl_2]\cdot 2HCl$ in 0.1 mol dm^{-3} DCl

C or S) nitrogen atom.[32,33] The coupling constant is $J_{gem.} = -9$ Hz (the minus sign is given to geminal protons).[34] The $J_{gem.}$ ($-CH_2-N-$) in thiazolidine has a value of -7.2 Hz.[32]

The above assignments are also supported by an examination of the ^{1}H n.m.r. spectrum of L^{1D} and L^2. Here again the peak at 8.10 p.p.m. is due to C$^{6'}$–H in 0.1 mol dm^{-3} DCl solutions. The C^4–CH_3 group appears at 0.96 p.p.m. as a singlet, not split by the adjacent C^4–D. The C$^{2'}$–CH_3 group again appears as a singlet at 2.46 p.p.m., while the C^5–CH_2 is a triplet at 1.90 p.p.m., split by the adjacent $-CH_2-O-$ group and not a multiplet, due to C^5–D. Finally, the $-CH_2-$ bridge and $-CH_2-O-$ groups coincide again at 3.63 p.p.m. The methylenic $-CD_2-S-$ group, shown in L^1 as a quartet, does not appear here. Similarly the OD and ND_2 groups are not observed.

In L^2 the assignments in $CDCl_3$ are: C$^{6'}$–H at 8.13 p.p.m., the amino-group at 6.13 p.p.m., and the two methyl groups C^4–CH_3 and C$^{2'}$–CH_3 as singlets at 1.65 and 2.36 p.p.m. respectively. The $-CH_2-S-$ group is again a quartet with $J = -5$ Hz at 4.03 p.p.m., while the C^5–CH_2 appears as a multiplet at 3.80 p.p.m. Finally, the $-CH_2-O-$ and –OH groups are at *ca.* 4.00 p.p.m. and the $-CH_2-$ bridge at 3.93 p.p.m. In D_2O or 0.1 mol dm^{-3}



DCl solutions, the split of the C^4–CH_3 group into a doublet with $J = 2$ Hz is possibly due to long range coupling with the $-CH_2-S-$ protons, through five σ bonds.[34,35]

Examination of the C$^{6'}$–H resonance chemical shift in the ^{1}H n.m.r. spectra of the ligands and the complexes with Pt^{II} and Pd^{II} again gives indications of the protonation and metallation sites. The 7.78 p.p.m. resonance of C$^{6'}$–H of the ligand L^1 in [$^2H_6$]dmso is shifted to 8.25 p.p.m. upon addition of two drops of CF_3COOH. In the protonated ligand $L^1\cdot HCl$, this peak is shown at 8.40 p.p.m. in both 0.1 mol dm^{-3} DCl and [$^2H_6$]dmso solutions. Upon addition of CF_3COOH a further shift to 8.55 p.p.m. is observed. The ligand L^2 shows the C$^{6'}$–H resonance at 7.95 p.p.m. in [$^2H_6$]dmso and at 8.00 p.p.m. in 0.1 mol dm^{-3} DCl. In $L^2\cdot HCl$ this resonance is shifted to 8.22 p.p.m. in [$^2H_6$]dmso. The complexes $[PtL^1_2Cl_2]\cdot 2HCl$ and $[PdL^1_2Cl_2]\cdot 2HCl$ show this resonance at 8.41 and 8.36 p.p.m. respectively in 0.1 mol dm^{-3} DCl. In [$^2H_6$]dmso solutions the first complex shows this resonance at 8.50 p.p.m. and it is further shifted to 8.53 p.p.m. upon addition of a few drops of CF_3COOH. The complex $[PtL^1_2Cl_2]$ decomposes in [$^2H_6$]dmso, but it shows a C$^{6'}$–H band at 8.20 p.p.m. in 0.1 mol dm^{-3} DCl. In the analogous complexes $[PtL^2_2Cl_2]\cdot 2HCl$ and $[PtL^2_2Cl_2]$ it is shown at 8.27 and 8.20 p.p.m. respectively in 0.1 mol dm^{-3} DCl.

In conclusion, protonation affects primarily the C$^{6'}$–H group of the ligands and the complexes. The protonation site is therefore the N$^{1'}$ atom of pyrimidine and the metallation site, possibly another heteroatom of the thiazolidine or thiazoline rings.[10]

Further evidence, for the metallation sites, is obtained from the ^{1}H n.m.r. spectra of the complexes. The complex $[PtL^1_2Cl_2]\cdot 2HCl$, in 0.1 mol dm^{-3} DCl, shows the $-CH_2-S-$ resonance at 4.56 p.p.m. as a quartet, with $J = -5$ Hz, shifted downfield by 0.53 p.p.m. as compared to the free ligand (Figure 2). The C^4–CH_3 is shown at 1.50 p.p.m., also shifted, by 0.40 p.p.m. (see Table 3). The maximum of the multiplet absorption due to the $-CH_2-$ bridge, $-CH_2-O-$, C^5–H, and C^4–H, is shown at 3.80 p.p.m., practically not shifted. The other resonances

are also practically not shifted in the complex $[PtL^1{}_2Cl_2]\cdot 2HCl$ and are seen at 2.63 p.p.m. for $C^{2'}$–CH_3, and at 2.06 p.p.m. for C^5–CH_2.

The $-CH_2-S-$ group shown at 4.03 p.p.m. in the ligand L^2 in D_2O shifts again at 4.50 p.p.m. in the complex $[PtL^2{}_2Cl_2]$ in 0.1 mol dm^{-3} DCl.

Finally, the complexes $[PtL^3{}_2Cl_2]\cdot 2HCl$ and $[PtL^4{}_2Cl_2]\cdot 2HCl$ in D_2O show the following resonances: $C^{6'}$–H at 8.13, $C^{2'}$–CH_3 at 2.60 and 2.70, $-CH_2-S-$ at 4.50, C^5–CH_2 at 2.33 and 2.30, $-CH_2-O$, C^5–H, C^4–H, and $-CH_2-$ bridge at 4.30 p.p.m. and 4.25 p.p.m., and for the C^4–CH_3 at 1.50 and 1.56 p.p.m., respectively. The most shifted group is again $-CH_2-S$ (*ca.* 0.44 p.p.m.). The $-CH_2-O$ group is shown at 3.85 p.p.m. in L^4 and is separated from the C^5–H, C^4–H, and $-CH_2-$ bridging groups at 3.70 p.p.m., obviously due to the presence of the phosphate. In the $[PtL^4{}_2Cl_2]\cdot 2HCl$ complex they all coincide again at 4.25 p.p.m. The details of the chemical shifts of the ligands and the complexes in different solvents are included in Table 3.

TABLE 4

Carbon-13 n.m.r. chemical shifts (δ/p.p.m.) of the compounds

Compound	4-CH_3	2′-CH_3	5-CH_2	C^5	C^2	5′-CH_2	OCH_2	C^4	$C^{5'}$	$C^{6'}$	$C^{4'}$	$C^{2'}$
L^1	14.1	25.1	34.6	46.4	51.9	55.5	61.5	64.0	110.3	154.3	162.4	165.8
$L^1\cdot HCl$	15.0	22.6	35.5	47.6	52.0	56.6	62.4	65.3	113.1	114.3	162.3	164.5
$[PtL^1{}_2Cl_2]\cdot 2HCl$	12.0	22.0	32.6	46.8	49.6	53.8	60.7	69.0	105.5	147.9	164.1	164.7
L^2	23.2	26.0	35.7	105.4	47.4	55.0	68.8	55.0	111.1	156.7	164.1	167.6
$[PtL^2{}_2Cl_2]\cdot 2HCl$ in $[^2H_6]$dmso	12.4	22.0	36.0	107.5		54.5	69.2		109.3	145.4	161.9	164.1
$[PtL^2{}_2Cl_2]\cdot 2HCl$ in D_2O	14.8	23.6	37.2				69.8		107.6	142.4	158.3	160.4

Carbon-13 N.M.R. Spectra.—The ^{13}C n.m.r. assignments of the ligands L^1 and L^2 have been made for the first time, based on the known ^{13}C n.m.r. spectra of thiamine hydrochloride,[36,37] pyrimidine derivatives,[38-40] and thiazole, thiazoline, and thiazolidine derivatives,[41-44] as well as off-resonance spectra. The assignments of $L^1\cdot HCl$ together with the complex $[PtL^2{}_2Cl_2]\cdot 2HCl$ have also been made and help to characterize $[PtL^1{}_2Cl_2]\cdot 2HCl$. The chemical shifts are given in Table 4 and examples of the spectra in Figure 3.

The ligand L^2 has resonances at 167.6, 164.1, 156.7, and 111.1 p.p.m., which can be assigned to the four carbons of the pyrimidine ring $C^{2'}$, $C^{4'}$, $C^{6'}$, and $C^{5'}$ respectively. The first two appear as singlets in the off-resonance spectra, and their sequence is analogous to similar aminomethylpyrimidine derivatives.[38] In thiamine hydrochloride, they coincide at 169.5 p.p.m.[36,37] The assignment of the two latter resonances is straightforward, because they appear as a doublet and a singlet respectively in the off-resonance spectra.

The pyrimidine carbon resonances for the ligand L^1 are assigned analogously, as follows: at 165.8 for $C^{2'}$, 162.4 for $C^{4'}$, 154.3 for $C^{6'}$, and 110.3 p.p.m. for $C^{5'}$.

The thiazoline C^2, C^4, and C^5 resonances of the ligand L^2 are shown at 47.4, 55.0, and 105.4 p.p.m., while for the thiazolidine ring of the ligand L^1 they appear at 51.9, 64.0, and 46.4 p.p.m. respectively. The first two resonances are shown as triplets (CH_2 group) in both ligands, while the two others are singlets in L^2 and doublets in L^1 (C and CH groups) in the off-resonance spectra. This assignment for L^2 is in accord with that of thiazoline derivatives, where the carbon atom adjacent to sulphur experiences a greater downfield shift than the carbon adjacent to nitrogen.[43] There is a similar agreement between the assignments for thiazolidine derivatives and L^1, where the sequence is reversed.[44]

The other carbon resonances are as follows: 23.2 and 26.0 p.p.m. for the two carbons of the methyl groups

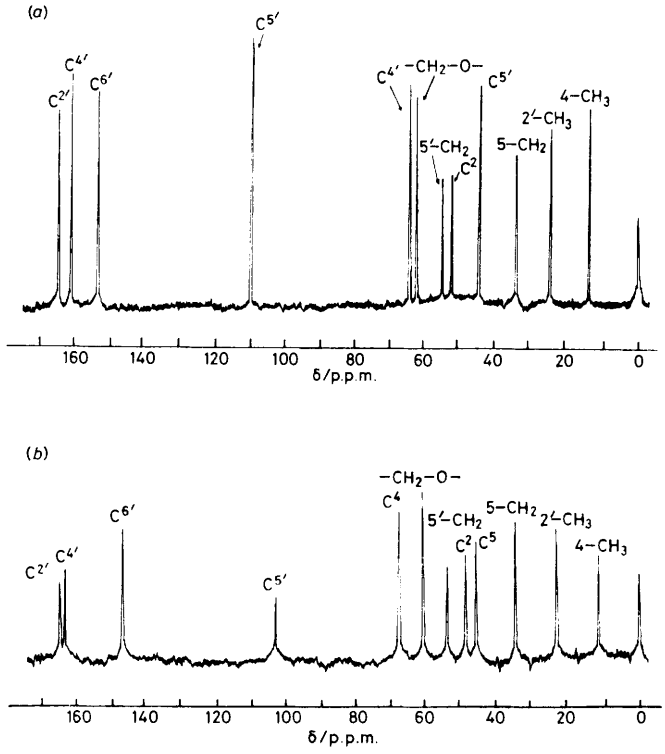


FIGURE 3 ^{13}C n.m.r. spectra of (*a*) L^1 and (*b*) $[PtL^1{}_2Cl_2]\cdot 2HCl$. Solvent $[^2H_6]$dmso in both cases

C^4–CH_3 and $C^{2'}$–CH_3 for L^2 and 14.1 and 25.1 p.p.m. for those of L^1. The C^5–CH_2 group appears at 35.7 and 34.6 p.p.m. for L^2 and L^1 respectively, while the OCH_2 group appears at 68.8 and 61.5 p.p.m. Finally, the

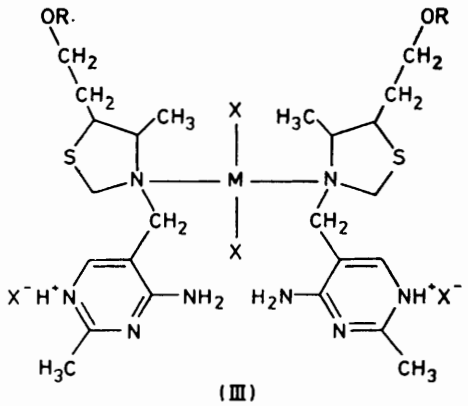
$-CH_2-$ bridge appears at 54.5 p.p.m. and 55.5 p.p.m. respectively.

Protonation of the ligand L^1 affects the pyrimidine resonances, while the thiazolidine carbon resonances remain practically unaffected (see Table 4). More specifically, in the ^{13}C n.m.r. spectrum of $L^1 \cdot HCl$, the $C^{2'}$ resonance is shown at 164.5 p.p.m., shifted upfield by 1.3 p.p.m., while the $C^{4'}$ at 162.3 p.p.m. is practically unshifted, relative to L^1. However, the carbon adjacent to $N^{1'}$ (considered as the protonation site) of the pyrimidine ring, $C^{6'}$, is shifted upfield by 10.0 p.p.m. and appears at 144.3 p.p.m. This value compares favourably with that of 149.4 p.p.m. for $C^{6'}$ in thiamine hydrochloride, where $N^{1'}$ is protonated.[36,37] Similar shifts are observed for $C^{6'}$ in all the pyrimidine derivatives, after protonation of the adjacent nitrogen.[38,40] A downfield shift is also observed for $C^{5'}$ (2.8 p.p.m.) and an upfield one for $C^{2'}-CH_3$ (2.5 p.p.m.). These results agree with an $N^{1'}$ protonation site for the ligands, as found with the other techniques.

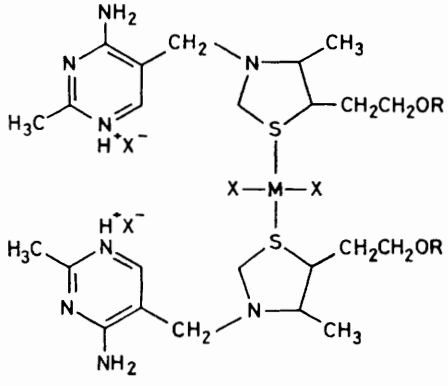
In the spectrum of the complex $[PtL^1_2Cl_2] \cdot 2HCl$, where both metallation of the thiazolidine ring and protonation of $N^{1'}$ are simultaneously expected, almost all the carbon resonances are shifted. Thus, the pyrimidine carbon resonances are shifted, as in the ligand $L^1 \cdot HCl$. In addition the C^4 resonance is shifted downfield by 5.0 p.p.m., while those of C^2 and C^4-CH_3 move upfield by 2.3 p.p.m. and 2.1 p.p.m. respectively. The C^5 resonance is practically unshifted.

In the complex $[PtL^2_2Cl_2] \cdot 2HCl$, the $C^{6'}$ and C^4-CH_3 resonances are both upfield shifted by 11.3 and 10.8 p.p.m. respectively, due to simultaneous protonation of $N^{1'}$ and metallation of the thiazoline ring. The $C^{2'}-CH_3$ resonance is also shifted upfield by 4.0 p.p.m., due to protonation of $N^{1'}$. In many cases, the carbon resonances of thiazoline are not seen at all for $[PtL^2_2Cl_2] \cdot 2HCl$; except for the pyrimidine skeletal carbon resonances, only the OCH_2, C^5-CH_2, $C^{2'}-CH_3$, and C^4-CH_3 carbons are seen.

Conclusions.—The results in the present study clearly show that the $N^{1'}$ atom is the protonation site, both in the free ligands and in the complexes. The metallation site however is not obvious, even though it clearly takes place through the thiazoline or thiazolidine rings. Direct evidence for the protonation and metallation sites is given by the ^1H and ^{13}C n.m.r. chemical shifts. Thus, while the protons or carbons adjacent to $N^{1'}$ of the pyrimidine ring are affected the most by protonation, the shifts of all the protons and carbons near to the possible coordination sites (N^3 and S) of thiazoline and thiazolidine rings are affected similarly by metallation. This is especially well illustrated by the ^{13}C n.m.r. spectrum of $[PtL^1_2Cl_2] \cdot 2HCl$ where, as well as the shifts of the pyrimidine carbons, the carbons C^4-CH_3, C^2, C^4, $C^{5'}-CH_2$ (bridge), and C^5-CH_2 are also considerably shifted, while the C^5 is practically unshifted. Finally, in $[PtL^2_2Cl_2] \cdot 2HCl$, the C^4-CH_3 carbon, together with the pyrimidine carbons, is shifted, while the others do not show up. Since the carbon atoms adjacent to N^3 of the thiazoline and thiazolidine rings are most shifted compared to C^5 which is not shifted, a $M-N^3$ bond seems more likely than an M–S bond. Although the latter cannot be unequivocally excluded with the present data alone, the former has also been found in complexes of metals with thiazole, thiazolidine, and their derivatives.[45-47] In conclusion, the two structures III and IV



(III)



(IV)

may be suggested for the isolated complexes (R = H, PO_3, or P_2O_7).

EXPERIMENTAL

Materials.—Potassium tetrachloroplatinate(II), potassium tetrachloropalladate(II), and palladium(II) chloride were from Johnson Matthey and Mallory Ltd.

The ligands L^1—L^4 were prepared according to literature methods.[4,28] The ligands L^1, L^3, and L^4 were mixtures of two diastereoisomers; subsequent recrystallizations resulted in the isolation of one isomer, as described.[28]

Methods.—The i.r. spectra were recorded on Beckman model 2050 or Perkin-Elmer 283 spectrophotometers as KBr pellets or Nujol mulls using NaCl or KBr windows. Hydrogen-1 n.m.r. spectra were recorded on a Varian model T60 or EM-360 spectrometer, using $SiMe_4$ or sodium 4,4-dimethyl-4-silapentanesulphonate as internal reference. Carbon-13 n.m.r. spectra were recorded with a Brucker WH-90 spectrometer, operating in the Fourier-transform mode and with proton noise decoupling at 22.62 Hz.

Chemical shifts were measured with internal [$^2H_6$]dmso and dioxane standards and converted to the $SiMe_4$ scale using δ([$^2H_6$]dmso) = 39.6 p.p.m. and δ(dioxane) = 67.4 p.p.m.

The conductivity measurements were performed on a Metrohm E-365 B conductoscope and the pH-metric titrations were carried out using a Metrohm model E-520 pH meter. The ligands and the complexes (10^{-3} mol dm^{-3}) were titrated with 10^{-3} mol dm^{-3} HCl or K[OH] solutions. Doubly distilled water was boiled before use, to remove any CO_2.

Melting points were determined in a W. Büchi melting-point apparatus and are uncorrected.

Elemental analyses were performed in the Laboratories of the National Hellenic Research Foundation, Athens.

Preparation of the Complexes.—[ML_2X_2]·2HX. The compound $K_2[MX_4]$ (M = Pd^{II} or Pt^{II}, X = Cl or Br) or $PdCl_2$ (0.6 mmol) was dissolved in water (30 cm^3) or 0.1 mol dm^{-3} HCl with heating and the pH adjusted to *ca.* 1. The corresponding ligand (1.2 mmol) was dissolved in H_2O (30 cm^3) or 0.1 mol dm^{-3} HCl and the pH adjusted to *ca.* 1. The two solutions were mixed, and stirred at room temperature for 24 h. The colour of the mixture became light yellow during this time. The mixture was then evaporated to dryness and treated with dmf (10 cm^3), the insoluble KCl was filtered off, and the resulting complex precipitated by an excess of acetone–diethyl ether (1 : 2). The precipitate was filtered off, washed with small amounts of acetone and diethyl ether, and dried, first at room temperature in the presence of $CaCl_2$ then by drying at 110 °C under vacuum in the presence of P_2O_5. The yields varied in the range 50—80%.

[ML_2X_2]. The compound $K_2[MCl_4]$ or $PdCl_2$ (0.5 mmol) was dissolved in H_2O (15 cm^3) or 0.1 mol dm^{-3} HCl with heating and the pH adjusted to *ca.* 5.5 using 0.1 mol dm^{-3} K[OH] solution. The corresponding ligand (1 mmol) was dissolved in 0.1 mol dm^{-3} HCl (15 cm^3) and the pH again adjusted to *ca.* 5.5. The two solutions were mixed at room temperature and stirred for 24 h. During this time, yellow crystals separated from the solution, which were filtered off and washed with small quantities of water, acetone, and diethyl ether. The precipitate was then dried first at room temperature in the presence of $CaCl_2$ and then at 110 °C under vacuum in the presence of P_2O_5. Yields 20—40%.

The complexes [ML_2X_2] can also be prepared from [ML_2X_2]·2HX, by dissolving the latter in D_2O and increasing the pH to *ca.* 5.5, with higher yields (*ca.* 40%).

Complexes [ML_2X_2]·2HX are also obtained from [ML_2X_2] by dissolving the latter in 0.1 mol dm^{-3} HX (10 cm^3) and causing precipitation with excess of acetone–diethyl ether (1 : 2) or by evaporating the solution to dryness.

The bromo-analogues of the above complexes were prepared either by using $K_2[MBr_4]$ as the starting material, or by dissolving the starting materials in 0.1 mol dm^{-3} HBr.

The Protonated Ligands L^2·HCl *and* L^1·HCl.—These were prepared by dissolving the appropriate ligands in 0.1 mol dm^{-3} HCl and allowing the solutions to evaporate slowly to dryness, at room temperature.

The Deuteriated Ligands and Complexes.—Deuteriation of the ligands or the complexes was in many cases achieved by treating them with D_2O, or preparing the complexes in D_2O or 0.1 mol dm^{-3} DCl solutions. The ligand L^{1D} was prepared by the same method as L^1,[28] but using $Na[BD_4]$ as reducing agent. The analogous complexes were synthesized using the deuteriated ligand L^{1D} in 0.1 mol dm^{-3} DCl or D_2O solutions.

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