The $PtCl_4^{2-}$/Thiamin System. 2. Structure of *trans*-[Pt(dmso-*S*)(thiamin)Cl_2](Ph_4B) and Its Equilibria in dmso

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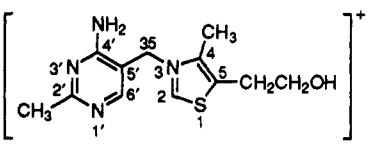
Reaction of thiamin nitrate with [Pt(dmso-*S*)Cl_3]$^-$ in aqueous solution leads to the formation of the cationic complex *trans*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$. Its tetraphenylborate salt was isolated, and its crystal structure is reported here: Space group $P2_12_12_1$, a=17.872(6) Å, b=18.822(5) Å, c=11.469(2) Å, V=3858(2) Å^3, Z=4, and final discrepancy factor R = 0.0363 for 2423 reflections with $F > 3\sigma(F)$. The reactions of this complex, Pt(thiamin)Cl_3, and a mixture of *cis*-Pt(dmso)$_2Cl_2$ and (thiamin)Cl were studied with high-field ^{1}H NMR spectroscopy and ^{195}Pt NMR spectroscopy in dmso. The reaction of Pt(thiamin)Cl_3 in dmso results in the formation of [Pt(dmso-*S*)Cl_3]$^-$ and *cis*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$, which subsequently partially isomerizes to *trans*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$. A 1:1 mixture of *cis*-Pt(dmso-*S*)$_2Cl_2$ and (thiamin)Cl yields *trans*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$ in the initial stage of the reaction, which then partly isomerizes to *cis*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$.

Introduction

The coordination chemistry of Vitamin B_1, also known as thiamin (structure I), is of interest since it is a cofactor for several



I

enzyme systems which also require a Mg^{2+} ion. In an earlier study of the complex Pt(thiamin)Cl_3 in dmso, we observed[1] dissociation of the complex to form free thiamin and [Pt(dmso-*S*)Cl_3]$^-$. However ^{1}H NMR of this solution suggested that free thiamin reacted with the [Pt(dmso-*S*)Cl_3]$^-$ anion to form a new thiamin complex of Pt(II). In this paper we report the isolation and structure of the product of this reaction, *trans*-[Pt(dmso-*S*)(thiamin)Cl_2](Ph_4B), **1**.

It is now widely accepted that the mechanisms of action of the antitumor drug *cis*-Pt$(NH_3)_2Cl_2$ involves attack on DNA. Thus, much has been devoted to studying the effects of Pt binding to nucleic acid constituents. While the binding of Pt to the endocyclic nitrogen of pyrimidine bases has been demonstrated in a number of cases,[2] secondary reactions at the Pt center have not been widely explored. Kong[3] and Marzilli[4] have investigated the chemistry of *cis*-Pt(dmso-*S*)$_2Cl_2$ with various nucleosides in dmso, and their findings suggest that several coordination equilibria at the Pt center are established in solution. The nature and relative proportions of the species involved in these equilibria reportedly varies with the nucleosides studied, and the factors determining this equilibrium distribution remain unclear.

In the second part of the study we report here, we show that the well-characterized complexes Pt(thiamin)Cl_3 and *trans*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$ are each part of an equilibrium established in dmso solution. The Pt coordination to the pyrimidine ring of thiamin provides a parallel to Pt–nucleoside chemistry, while the positive charge of the thiamin ligand, as opposed to the uncharged bases studied by others,[3,4] leads to some differences in the nature of the equilibria, the rate of its establishment, and the species present.

Experimental Section

Instrumentation and Methods. ^{1}H NMR spectra were obtained on a GE QE-300 NFT NMR spectrometer at 300 MHz. ^{195}Pt NMR spectra were obtained on a Nicolet NM-300 FT NMR spectrometer operating at 64.46 MHz using a pulse width of 15 μs and a relaxation delay of 0.5 s. In the ^{195}Pt NMR experiments a number of transients ranging from 800 to 14 000 were averaged and the resulting FID was multiplied by an exponential function (LB = 50 Hz) prior to Fourier transformation.

^{1}H NMR shifts were referenced internally using TMS, while ^{195}Pt NMR shifts were referenced externally using a 5% solution of H_2PtCl_6 in a 50/50 H_2O–D_2O mixture.

Synthesis of *trans*-[Pt(dmso-*S*)(thiamin)Cl_2](Ph_4B), 1. A 0.33-g amount (1 mmol) of thiamin nitrate was added to 50 mL of a solution 0.02 M in K[Pt(dmso)Cl_3].[5] Within minutes, the yellow color of the solution faded and subsequent addition of 0.38 g (1 mmol) of sodium tetraphenylborate dissolved in 200 mL of water resulted in the immediate formation of a heavy, off-white precipitate. After filtration, this precipitate was washed several times with water and dried under vacuo. Anal. Calcd for $C_{38}H_{43}N_4O_2S_2BPtCl_2$: C, 49.14; H, 4.67; N, 6.03; S, 6.90; B, 1.16; Pt, 21.00; Cl, 7.63. Found:[6] C, 49.49; H, 4.57; N, 5.86; S, 4.24; B, 1.52; Pt, 20.85; Cl, 7.47.

X-ray Crystallographic Studies. Diffraction-quality crystals were obtained by slow evaporation of a 0.25 M 50/50 acetone–water solution of **1** at room temperature. An off-white bladelike crystal with maximal dimensions 0.06 × 0.3 × 0.9 mm was glued with epoxy cement onto a glass fiber, with its longest edge parallel to the fiber. The cell parameters and their standard deviations were determined by a least-squares fit of the angular coordinates of 15 reflections with 2θ values from 28.7 to 38.0°. Partial rotation axial photographs and output from the Siemens $P\bar{1}$ diffractometer autoindexing routine showed the crystal system to be orthorhombic. Analysis of systematic absences ($h00$, $h = 2n + 1$; $0k0$, $k = 2n + 1$; $00l$, $l = 2n + 1$) suggested the space group $P2_12_12_1$, which was confirmed by satisfactory refinement of the structure to a low error index. Data collection and processing were carried out using standard procedures in our laboratory.[7] A summary of crystal and data collection parameters is given in Table IV. Data were corrected for a decay of about 10% on the basis of intensity of three check reflections measured every 100 reflections. Only data for which $I > 3\sigma(I)$ were used in the solution and refinement of the structure. Data were corrected for Lorentz and polarization effects, and an absorption correction was applied based

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Table I. ^{1}H NMR Spectra Data and Peak Assignments in dmf-d_7 (δ(TMS) = 0.0 ppm)

peak assgnt[a]	chem shift, ppm[b] (Hthiamin)-Cl_2	(thiamin)-NO_3	*trans*-[Pt(dmso-S)-(thiamin)Cl_2](Ph_4B)
H(2)	*c*	9.77, s, 1H	9.99, s, 1H
H(21′)	2.71, s, 3H	2.41, s, 3H	2.92, unresolved
H(35′)	5.89, s, 2H	5.63, s, 2H	5.71, s, 2H
H(41)	2.62, s, 3H	2.67, s, 3H	2.68, s, 3H
H(41′)	*c*	7.26, s, 2H	8.35, s, 2H
H(51)	3.20, t, 2H	3.20, t, 3H	3.21, t, 3H
H(52)	3.80, q, 2H	3.81, q, 2H	3.81, q, 2H
H(53)	*c*	5.41, t, 1H	5.41, s, 1H
H(6′)	8.49, s, 1H	8.23, s, 1H	8.47, s, 1H

[a] The protons are numbered according to the numbering scheme of the non-hydrogen atoms to which they are bound. [b] s = singlet, t = triplet, and q = quartet. [c] Deuterated by exchange with D_2O impurity in the solvent.

on six ψ scans[8] with 2θ values ranging from 9.34 to 42.32°. All calculations were carried out with the SHELXTL computer programs on a microvax computer.

Solution and Refinement of the Structure. The position of the Pt atom was deduced from a Patterson map, and subsequent difference Fourier maps revealed the position of all remaining non-hydrogen atoms. After the last cycle of least-squares refinement, which included anisotropic temperature factors for all atoms but which did not include hydrogen atoms, the largest parameter shift was less than 7% of its esd. The largest peak remaining in the final difference Fourier map was about 0.9 e/Å^3 and was located in the vicinity of the Pt atom. The structure was tested for absolute configuration by refining a model with inverted coordinates. The model with the lowest *R* value is the one reported here. The final positional parameters along with their standard deviations are listed in Table V for the platinum cation and Table 8 (supplementary material) for the tetraphenylborate anion. Figure 1 displays an XP drawing of **1** and its labeling scheme.

Results and Discussion

Description of the Structure. The content of one unit cell consists of four positively charged platinum complexes and four tetraphenylborate anions. The closest cation–anion contact is 3.34 Å between the hydroxyethyl O(53) position of a thiamin molecule and a carbon C(350) belonging to a phenyl ring of the anion.

The cation is composed of a central platinum(II) ion bound to two chloro ligands and to a dmso *trans* to a thiamin molecule. The platinum coordination sphere is square planar, as shown by a least-squares plane calculation (Table 9, supplementary material). The dmso moiety is bound to Pt through the sulfur, which is preferred over the oxygen as the coordination site for the heavier metals.[9] The Pt–S distance, 2.208(4) Å, is comparable to Pt–S distances in similar compounds.[10] The thiamin moiety is bound to Pt through N(1′) of the pyrimidine ring as consistently observed in structures of metal complexes of thiamin.[1] The Pt–N(1′) distance, 2.06(1) Å, is indistinguishable from the Pt–N distance in Pt(thiamin)Cl_3,[1] and the two Pt–Cl distances are also comparable to those found in Pt(thiamin)Cl_3.[1] The Pt–Cl(1) distance is about 0.02 Å longer than the Pt–Cl(2) bond, possibly due to a O(2)–Cl(1) electrostatic repulsion between the Cl(1) ligand and the S-bound dmso O(2) atom. Distances, Table VII, and angles, Table VI, within the thiamin ligand are generally consistent with complexed thiamin,[1,11–14] except for the C(2′)–N(1′)–C(6′) angle, which differs sharply from that observed in all other complexes. The value of 120(1)° in this structure is equivalent to the one in protonated thiamin, 121.0(8)°,[12] and is significantly larger than in all other thiamin complexes, which average 115°, a value also observed in the free base. This may be due to the coordination of an uncharged substituent –Pt(dmso-*S*)Cl_2, in this case, compared to negatively charged ones, such as $-Pt(Cl)_3^-$, in other cases.

Least-squares calculations indicate that both the thiazolium and pyrimidine rings are planar (Table 9, supplementary material). The dihedral angle between the coordination and the pyrimidine planes is 92°. As in the case of Pt(thiamin)Cl_3,[1] this conformation, which leaves the two planes nearly perpendicular, minimizes steric repulsions between the pyrimidine ring and the two chloro ligands. The torsion angles about the methylene bridge[15] $\phi_T = -4.1°$ and $\phi_P = 83.9°$ are similar to those obtained for Pt(thiamin)Cl_3 and correspond to the frequently observed F conformer[15] of thiamin.

The torsion angles which describe the conformation of the hydroxyethyl side chain[15] are $\phi_{51} = -89°$ and $\phi_{52} = -59°$. Unlike several similar structures there is no O(53)–S contact. The fact that the closest contact between the tetraphenylborate anion and [Pt(dmso-*S*)(thiamin)Cl_2]$^+$ is experienced by the latter through O(53) may prevent the hydroxyethyl chain from folding back over the thiazolium ring thus making an O(53)–S interaction impossible. O(53) and S are however simultaneously involved in two intermolecular interactions with the Cl(2) position of a neighboring molecule through a O(53)–Cl(2) hydrogen bond and a S–Cl(2) electrostatic contact (Table 10, supplementary material). There is also a hydrogen bond between the exocyclic N(41′) and the dmso O(2) position of a neighboring molecule (Table 9).

As in Pt(thiamin)Cl_3,[1] the limited accuracy of the C(4′)–N(41′) distance, 1.33(2) Å, excludes any comparison with the other complexes.

Discussion of the Structure. In comparison to all other thiamin containing structures, the structure of **1** displays the fewest intra- and intermolecular interactions. It is worth noting in particular that the thiazolium C(2)–H, whose acidic nature is repeatedly reflected by its hydrogen-bonding ability[1,13,14,16,17] and has been invoked in enzymatic mechanisms,[18] does not interact in this structure with any hydrogen-bond acceptor. While overlap of the pyrimidine rings was observed in all other monomeric complexes,[1,12,13] it is absent in this structure and so is any stacking interaction involving the anion phenyl rings. Finally, this is the first thiamin metal complex where the N(1′) substituent, –Pt(dmso-*S*)Cl_2 in this case, is not involved in bridging interactions between the pyrimidine and thiazolium rings despite the presence of its three hydrogen-bond acceptors (two chlorides and one oxygen).

Upon comparison of **1** and Pt(thiamin)Cl_3, one can suggest that the substitution of one chloro ligand by a dmso-*S* molecule, by making the N(1′) substituent neutral overall, has removed a major driving force for electrostatic contacts with the positively charged thiazolium. This results in the absence of a bridging interaction, as well as in the absence of hydrogen bond with H(2), and suggests that mild packing forces within the crystal are not significant in determining the conformation of thiamin. The observation that the F conformation is also favored by the isolated thiamin cation[1] points out an intrinsic stability of this conformation over the V or S conformations.

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Table II. ^1H NMR Spectral Data and Peak Assignments in dmso-d_6 (δ(TMS) = 0.0 ppm)

	chem shift, ppm[b]				
peak assgnt[a]	(thiamin)NO_3	*trans*-[Pt(dmso-S)-(thiamin)Cl_2](Ph$_4$B)	Pt(thiamin)Cl_3	(Hthiamin)Cl_2	(Hthiamin)($PtCl_4$)
H(21′), s, 3H	2.38	2.87	3.04	2.54	2.57
H(41′), s, 2H	7.15	8.00, s, 1H 8.35, s, 1H	7.80	9.23	8.94, s, 1H 9.20, s, 1H
H(6′), s, 1H	8.08	8.57	8.46	8.37	8.57

[a] The protons are numbered according to the numberng scheme of the non-hydrogen atoms to which they are bound. [b] s = singlet.

Table III. ^{195}Pt NMR Spectral Data ($\delta(PtCl_6^{2-})$ = 0.0 ppm)

compd	chem shift, ppm	compd	chem shift, ppm
Pt(thiamin)Cl_3[a]	−2915	Pt(dmso-S)(thiamin)Cl_2^+[b]	−3050
Pt(dmso-S)Cl_3^-[a]	−2965	Pt(dmso-S)$_2Cl_2$[a]	−3480

[a] In dmso-d_6. [b] In acetone-d_6.

Table IV. Summary of Crystal Parameters and Data Collection for *trans*-[Pt(dmso-S)(thiamin)Cl_2](Ph$_4$B)

compd	Pt(dmso-S)(thiamin)-Cl_2(Ph$_4$B)	radiation, Å	Mo Kα
formula	$C_{38}H_{43}N_4O_2S_2BPtCl_2$	μ, cm^{-1}	25.55
fw	928.72	abs coeffs	0.43–0.99
a, Å	17.872(6)	2θ limits, deg	3.0–45.0
b, Å	18.822(5)	tot. no. of observns	2840
c, Å	11.469(2)	unique data used ($I > 3\sigma(I)$)	2343
V, Å^3	3858(2)	final no. of variables	227
Z	4	*R*[a]	0.0363
density, g/cm	1.60 (calcd)	overdetermination ratio	10.3
space group	$P2_12_12_1$		

[a] $R = \sum(||F_o| - |F_d||)/\sum|F_o|$.

Table V. Positional Parameters for *trans*-[Pt(dmso-S)(thiamin)Cl_2]$^+$

atom	*x/a*	*y/b*	*z/c*
Pt	0.14030(3)	0.19180(3)	1.12198(5)
Cl(1)	0.2302(2)	0.1975(3)	0.9797(4)
Cl(2)	0.0511(2)	0.1955(3)	1.2627(3)
S(2)	0.2143(2)	0.1226(2)	1.2262(4)
N(1′)	0.0706(7)	0.2544(7)	1.022(1)
O(2)	0.2833(5)	0.1572(5)	1.2693(9)
C(12)	0.237(1)	0.0463(8)	1.142(2)
C(11)	0.171(1)	0.081(1)	1.349(2)
C(6′)	0.0187(8)	0.2210(8)	0.958(1)
C(2′)	0.0701(8)	0.3267(7)	1.030(1)
C(21′)	0.1235(8)	0.3607(8)	1.108(2)
N(3′)	0.0208(7)	0.3663(6)	0.971(1)
C(4′)	−0.0345(9)	0.3352(8)	0.907(1)
N(41′)	−0.0811(7)	0.3773(7)	0.848(1)
C(5′)	−0.0361(8)	0.2590(7)	0.898(1)
C(35′)	−0.1005(8)	0.2186(8)	0.845(1)
S	−0.0467(2)	0.2221(2)	0.5102(3)
N(3)	−0.0942(6)	0.2144(6)	0.7142(9)
C(4)	−0.1485(8)	0.1808(8)	0.647(1)
C(41)	−0.2171(9)	0.148(1)	0.710(2)
C(5)	−0.1299(8)	0.1775(7)	0.533(1)
C(51)	−0.1733(9)	0.1444(9)	0.432(1)
C(52)	−0.148(1)	0.070(1)	0.410(2)
O(53)	−0.071(1)	0.0683(8)	0.383(2)
C(2)	−0.0360(8)	0.2394(7)	0.653(1)

^1H NMR Characterization. **1** is soluble in several organic solvents. However, while it is stable in solvents like dmf or acetone, it reacts with dmso. The ^1H NMR chemical shifts of thiamin compounds vary significantly in different solvents (compare Tables I and II) so comparisons between compounds must be made in the same solvent. Accordingly, the spectra of thiamin hydrochloride, thiamin nitrate, and **1** were determined in dmf-d_7 (Table I).

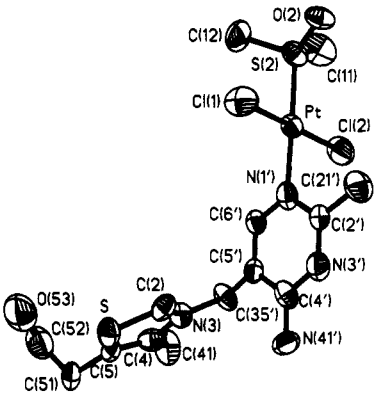


Figure 1. Perspective view of the *trans*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$ cation.

Table VI. Bond Angles (deg) in *trans*-[Pt(dmso-S)(thiamin)Cl_2]$^+$

Cl(2)–Pt–Cl(1)	175.6(1)	C(4′)–N(3′)–C(2′)	121(1)
S(2)–Pt–Cl(1)	89.6(1)	N(41′)–C(4′)–N(3′)	119(1)
S(2)–Pt–Cl(2)	93.1(1)	C(5′)–C(4′)–N(41′)	123(1)
N(1′)–Pt–Cl(1)	90.1(3)	C(4′)–C(5′)–C(6′)	118(1)
N(1′)–Pt–Cl(2)	87.3(3)	C(35′)–C(5′)–C(6′)	118(1)
N(1′)–Pt–S(2)	178.6(3)	C(35′)–C(5′)–C(4′)	123(1)
O(2)–S(2)–Pt	114.9(5)	C(2)–S–C(5)	92.6(6)
C(12)–S(2)–Pt	108.5(6)	C(4)–N(3)–C(35′)	121(1)
C(12)–S(2)–O(2)	110.4(8)	C(2)–N(3)–C(35′)	124(1)
C(11)–S(2)–Pt	115.4(6)	C(2)–N(3)–C(4)	114(1)
C(11)–S(2)–O(2)	106.8(8)	C(41)–C(4)–N(3)	118(1)
C(11)–S(2)–C(12)	99.8(8)	C(5)–C(4)–N(3)	112(1)
C(6′)–N(1′)–Pt	117(1)	C(5)–C(4)–C(41)	129(1)
C(2′)–N(1′)–Pt	122(1)	C(4)–C(5)–S	110(1)
C(2′)–N(1′)–C(6′)	120(1)	C(51)–C(5)–S	121(1)
C(5′)–C(6′)–N(1′)	121(1)	C(52)–C(51)–C(5)	111(1)
C(21′)–C(2′)–N(1′)	118(1)	O(53)–C(52)–C(51)	111(2)
N(3′)–C(2′)–N(1′)	122(1)	N(3)–C(2)–S	111(1)
N(3′)–C(2′)–C(21′)	120(1)		

Table VII. Bond Distances (Å) in *trans*-[Pt(dmso-S)(thiamin)Cl_2]$^+$

Pt–Cl(1)	2.293(4)	C(4′)–N(41′)	1.33(2)
Pt–Cl(2)	2.269(4)	C(4′)–C(5′)	1.44(2)
Pt–S(2)	2.208(4)	C(5′)–C(35′)	1.51(2)
Pt–N(1′)	2.06(1)	C(5)–S	1.73(1)
S(2)–O(2)	1.48(1)	C(2)–S	1.68(1)
S(2)–C(12)	1.78(2)	C(35′)–N(3)	1.50(2)
S(2)–C(11)	1.79(2)	C(2)–N(3)	1.34(2)
N(1′)–C(6′)	1.34(2)	N(3)–C(41)	1.55(2)
C(5′)–C(6′)	1.39(2)	C(4)–C(5)	1.36(2)
N(1′)–C(2′)	1.36(2)	C(5)–C(51)	1.53(2)
C(2′)–C(21′)	1.45(2)	C(51)–C(52)	1.50(3)
C(2′)–N(3′)	1.34(2)	C(52)–O(53)	1.41(3)
N(3′)–C(4′)	1.36(2)		

As for Pt(thiamin)Cl_3, most of the ^1H resonances of **1** occur somewhere between the corresponding resonances of protonated and unprotonated thiamin,[1] with H(2), H(6′), H(21′), and H(41′) experiencing the largest shift upon coordination, 0.2, 0.2, 0.5, and 1.1 ppm downfield, respectively, when compared with thiamin nitrate (Table I). However, comparison of the chemical shifts of **1** and Pt(thiamin)Cl_3 in dmso (Table II) shows noticeable differences occurring for H(21′), 0.17 ppm, H(6′), 0.11 ppm, and H(41′), 0.2 and 0.55 ppm. All other chemical shifts are within 0.05 ppm of each other and therefore can be considered equal if

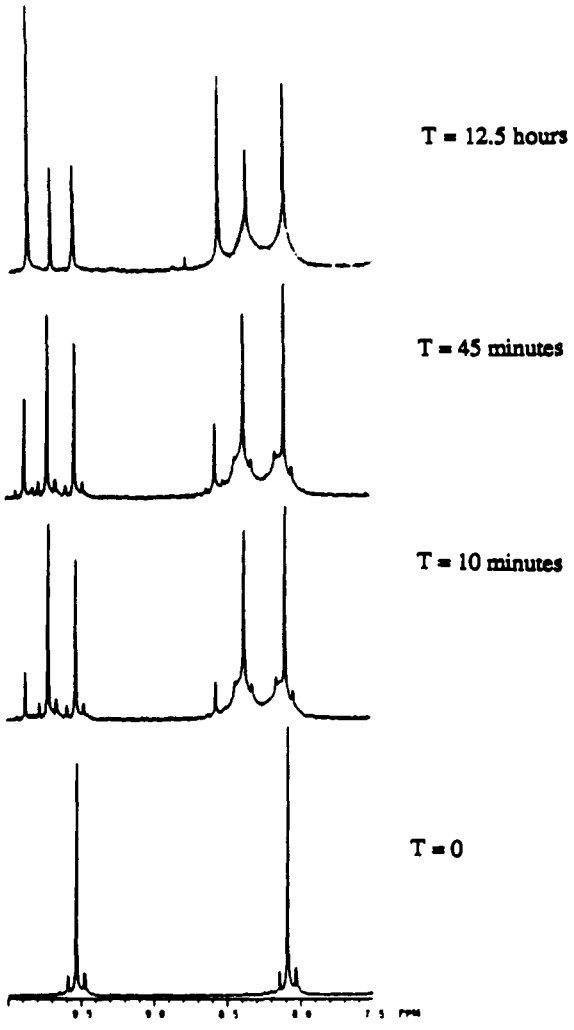


Figure 2. ^{1}H NMR spectra (7.5–10 ppm) of a mixture of Pt(dmso-*S*)$_2$Cl$_2$ and (thiamin)Cl in dmso-d_6 at various times after mixing. The spectrum at T = 0 contains only (thiamin)Cl.

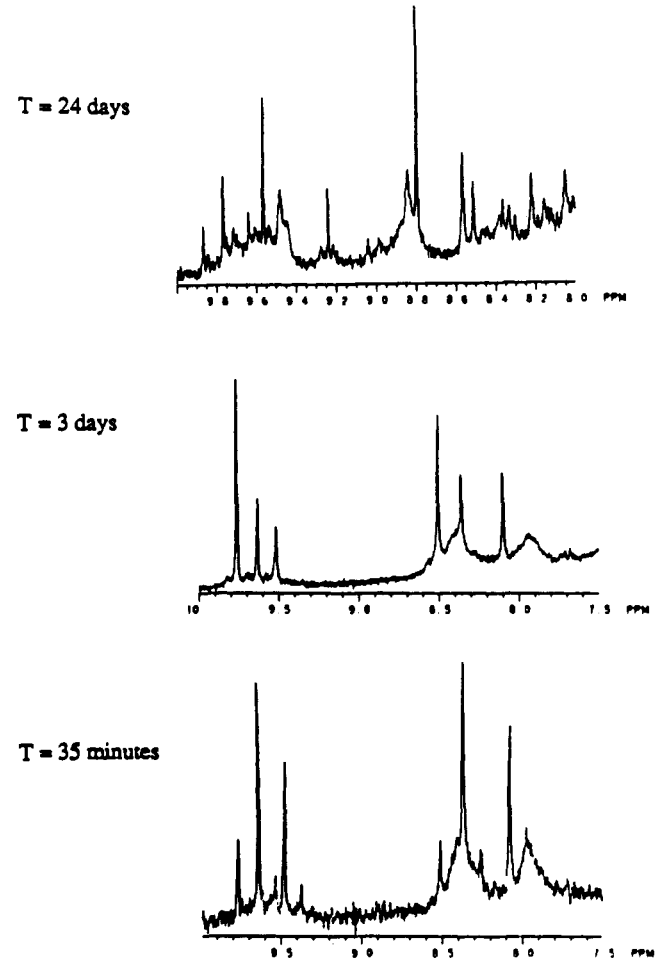


Figure 3. ^{1}H NMR spectra (7.5–10 ppm) of a solution of *trans*-[Pt(dmso-*S*)(thiamin)Cl$_2$]$^+$ in dmso-d_6 at various times.

one takes into account the dependence of these chemical shifts upon concentration, pH, and the presence of traces of water. The influence of substitution at N(1′) on the chemical shift of H(6′) is not clear since the values observed for the last two entries in Table II, both of which have a proton at N(1′), are both smaller and larger than those observed for the two compounds with Pt coordinated to N(1′). There is however a correlation between the relative values of H(21′) and H(41′) and the overall charge of the N(1′) substituent. In both H(thiamin)Cl$_2$ and H(thiamin)-PtCl$_4$, coordination of a proton at the N(1′) position shifts the H(21′) resonance to the upfield end of the range, while the H(41′) resonance is at the downfield end of the range.[1] On the other hand, in Pt(thiamin)Cl$_3$, the coordination of –PtCl$_3^-$, a negatively charged species, results in a strong downfield shift of the H(21′) resonance and simultaneously a strong upfield shift of H(41′) (Table II) (relative to protonated thiamin). In **1**, we have an intermediate situation where the coordination of a neutral species, –Pt(dmso-*S*)Cl$_2$, results in intermediate H(21′) and H(41′) chemical shifts.

The ^{1}H NMR spectral changes that occur upon aging of dmso solutions of Pt complexes of thiamin are best understood through a detailed description of the changes occurring in the downfield region of the spectrum where the H(2) and H(6′) resonances occur. The evolution of a D$_2$O solution of thiamin shows that the most downfield resonance slowly disappears due to deuterium exchange. This resonance is assigned to H(2).

Both H(2) and H(6′) chemical shifts are dependent on the chloride concentration in solution. An increasing chloride concentration possibly increases hydrogen bonding to the acidic H(2), resulting in a downfield shift of its resonance. This fact must be kept in mind for the interpretation of spectra when comparing the chemical shifts recorded in different experiments or at different times. Finally, the presence of broad H(41′) peaks in the H(6′) region contributes to the H(6′) peak height. Hence the height of the H(2) peak is used to approximate the relative proportions of the species present in solution.

Reaction of *cis*-Pt(dmso-*S*)$_2$Cl$_2$ with (thiamin)Cl in dmso. Upon addition of 1 equiv of *cis*-Pt(dmso)$_2$Cl$_2$ to a dmso solution of (thiamin)Cl, a second set of resonances (9.72, 8.37 ppm) appears, downfield from the corresponding free thiamin signals. The intensities of this second set suggest that a new species and thiamin are present in approximately equal amounts a few minutes after mixing. A third set of resonances even further downfield (9.82, 8.57 ppm), reveals the presence of a third, minor species (Figure 2). After 45 min, the free thiamin resonances have decreased in size, while the second set of peaks now represent the major product and the third species has also grown. With time this latter species becomes the major component. It has previously been established that, in aged solutions of thiamin, a cleavage reaction occurs to produce pyrimidinium polymers and free thiazole.[19] After 12.5 h, a new singlet appears at 8.8 ppm, which corresponds to the H(2) signal of this free thiazole, indicating that thiamin decomposition has begun.[19] Thus the reaction was not followed any longer.

The downfield set of peaks (9.72, 8.37 ppm) which appears in the initial stage of the reaction is assigned to *trans*-[Pt(dmso-*S*)(thiamin)Cl$_2$]$^+$ for the following reasons. First, the formation

(19) Zoltewicz, A.; Kauffman, G.; Uray, G. Thiamin: twenty years of progress. *Ann. N.Y. Acad. Sci.* **1981**, *378*, 7–13.

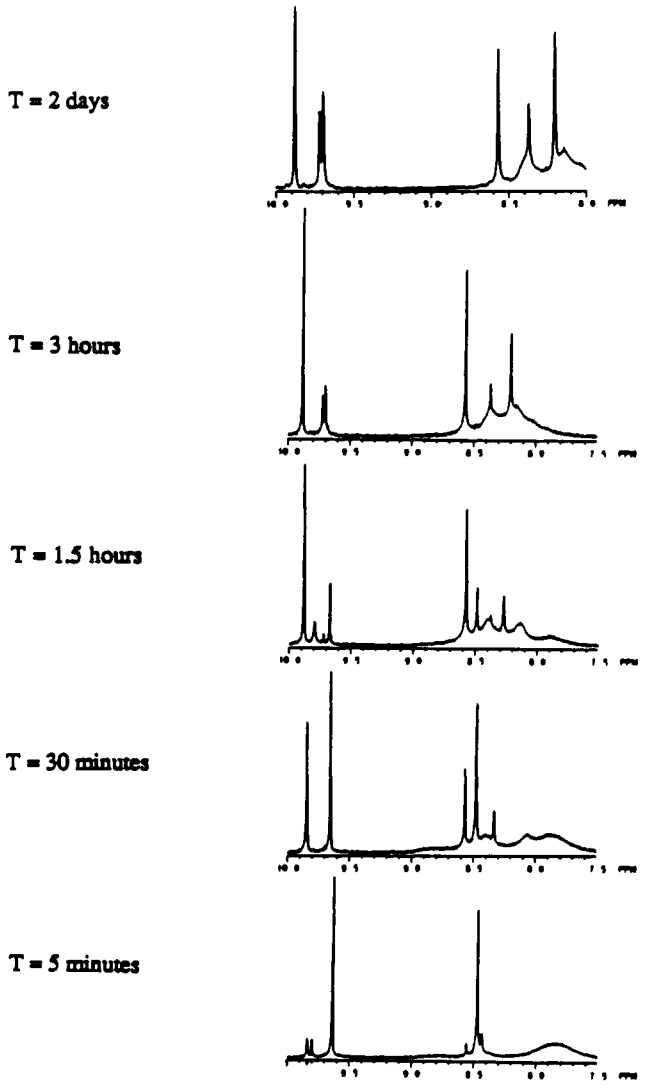


Figure 4. ^1H NMR spectra (7.5–10 ppm) of a solution of Pt(thiamin)Cl_3 in dmso-d_6 at various times.

of a *trans* complex was demonstrated to be the first step in the reaction of *cis*-Pt(dmso-*S*)$_2Cl_2$ with the nucleosides 7-MeIno and 7-Me-9-PrHX.[20] Second, the compound *trans*-[Pt(dmso-*S*)(thiamin)Cl_2](Ph_4B), whose *trans* conformation is unambiguously assigned by X-ray diffraction in this paper, produces a signal identical with that of the species in question, when freshly dissolved in dmso-d_6.

With time, the *trans* isomer is partially converted to the *cis* isomer, giving rise to the third set of peaks. This *trans–cis* isomerization has been observed in several cases for dmso solutions of Pt(dmso)(Nuc)Cl_2, where Nuc=guanosine, 4-picoline, and 2-picoline.[20] In each case the resonances of the *cis* isomer are downfield from the *trans* isomer and the *cis* complex becomes the dominant species in solution after several hours. In this case, however, significant amounts of the *trans* complex remain in solution until thiamin decomposition starts. Furthermore, the presence of free thiamin in solution indicates that it is a much weaker nucleophile than guanosine and/or picoline, since in these compounds no free base is observed. The positive charge carried by the thiazole moiety certainly decreases the ability of the thiamin molecule to act as a ligand.

Reaction of *trans*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$ in dmso. A fresh dmso solution of *trans*-[Pt(dmso-*S*)(thiamin)(Cl_2)](Ph_4B) shows two major sets of resonances at 9.72, 8.36 ppm and 9.53, 8.09 ppm, respectively, and a small, third set at 9.88 and 8.56 ppm (Figure 3). With time, the third set grows, which is accompanied by a sharp decrease in the size of the first set. After several days, a singlet appears at 8.8 ppm, indicating that thiamin decomposition has begun (Figure 3).

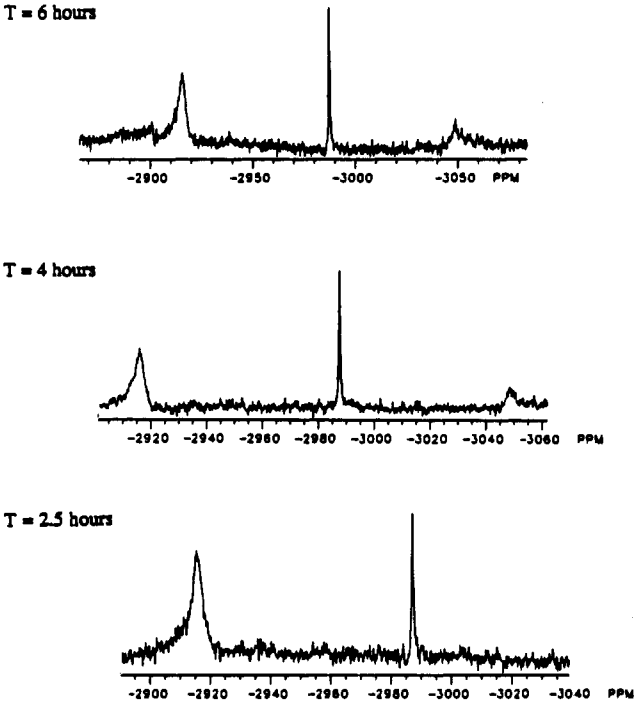


Figure 5. ^{195}Pt NMR spectra of a solution of Pt(thiamin)Cl_3 in dmso-d_6 at various times.

The situation here is similar to the one described in the previous section; *trans*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$ partly dissociates upon dissolution in dmso, and before a spectrum can be recorded, a ≈50/50 mixture of the original complex (9.72, 8.36 ppm) and free thiamin (9.53, 8.09 ppm) is present in solution. This points out not only the well-known strong *trans* labilizing effect of dmso but also the weakness of the Pt–N bond to thiamin. The *trans* complex then partly isomerizes to the *cis* isomer (9.88, 8.56 ppm) as described in the previous section. An equilibrium is reached after several hours where both isomers and free thiamin are present in an approximate 2:1:1 ratio (based on the H(2) resonance). This equilibrium remains stable for several days until free thiamin starts to decompose into its two components, giving rise to the characteristic thiazole H(2) signal at 8.8 ppm.[19]

Reaction of Pt(thiamin)Cl_3 in dmso. The spectrum of a freshly prepared dmso solution of Pt(thiamin)Cl_3 shows one major set of peaks (9.63, 8.47 ppm) and traces of two other components (9.82, 8.56 ppm) and 8.39 ppm (Figure 4). [Note: In Figure 4, the peak at 9.80 ppm is assigned to an impurity. The size of this signal did not vary with time and was not present in other samples of the same compound.] With time, the major set decreases in size while the set of downfield peaks (9.82, 8.56 ppm) increases. After 1.5 h this set has become dominant and a fourth set of peaks has appeared upfield (9.72, 8.39 ppm). After 3 h the original signals (9.63, 8.47 ppm) have completely disappeared and the two most downfield sets of peaks (9.72, 8.39 ppm and 9.82, 8.56 ppm) have grown. After several days, an equilibrium between these two complexes and free thiamin is reached which remains until the free thiazole singlet appears, some 17 days later, indicating thiamin decomposition.

The initial set of peaks (9.63, 8.47 ppm) is attributed to nondissociated, intact, Pt(thiamin)Cl_3. This complex was characterized by X-ray diffraction in our laboratory,[1] and conductance measurements in dmso show that a fresh solution yields a nearly zero value consistent with the presence of the nondissociated

(20) Reily, M. D.; Wilkowski, K.; Shinozuka, K.; Marzilli, L. *Inorg. Chem.* **1985**, *24*, 37–43.

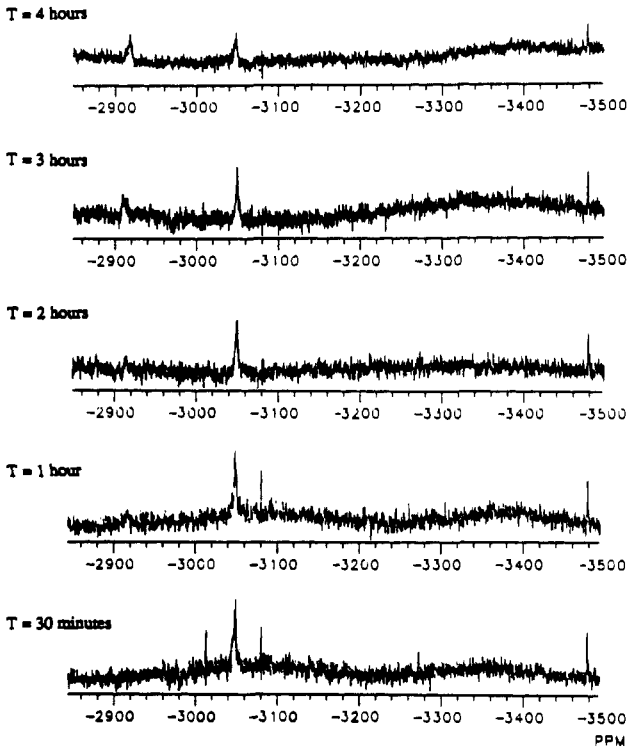


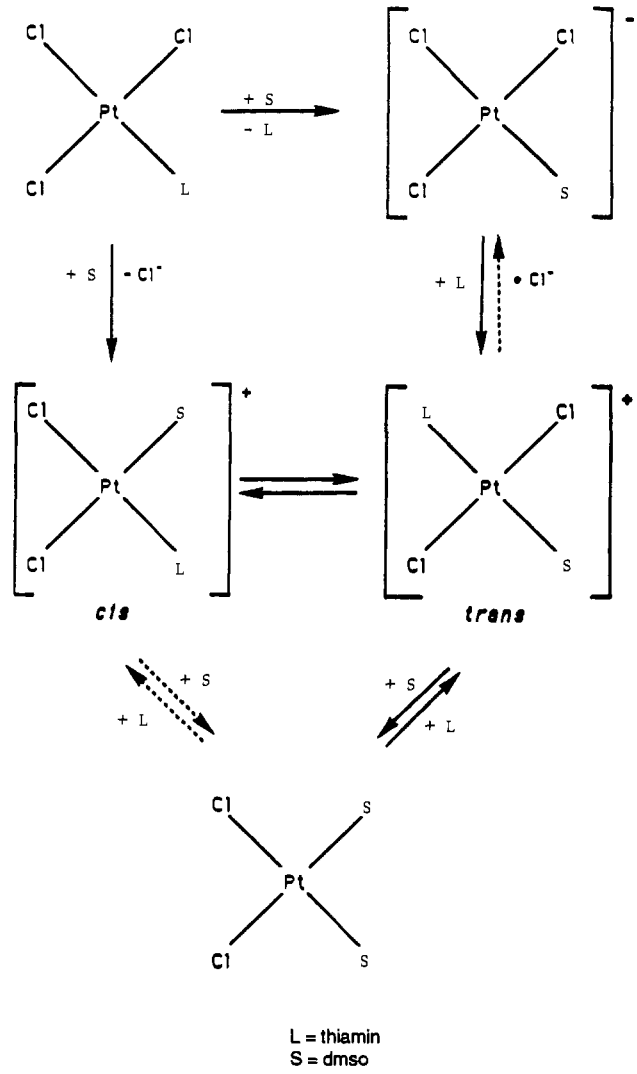
Figure 6. ^{195}Pt NMR spectra of a solution of *trans*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$ in dmso-d_6 at various times.

complex. The set at (9.82, 8.56 ppm) is attributed to *cis*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$, the isomerization product of the *trans* complex described in the previous section. This indicates an initial displacement of a *cis* Cl^- by a dmso molecule. The peak at 8.39 ppm is attributed to the presence of a small amount of free thiamin in solution (the origin of this species was elucidated by ^{195}Pt studies (vide supra), which show that a second pathway in the decomposition of Pt(thiamin)Cl_3 involves the displacement of thiamin with the subsequent formation of the [Pt(dmso-*S*)Cl_3]$^-$ anion). With time the *cis* complex (9.82, 8.56 ppm) isomerizes partially to the *trans* complex (9.72, 8.37 ppm) (Figure 4). The signals originating from both isomers grow at the expense of the original compound, and after several days, an equilibrium is reached involving the *cis* and *trans* complexes and free thiamin, consistent with the observations made in the two previous sections.

While studying the reaction of *cis*-Pt(dmso-*S*)$_2Cl_2$ with cytidine (cyd) in dmso, Marzilli reported[20] the species [*cis*-Pt(cyd)(dmso-*S*)$_2$Cl]$^+$ as an intermediate in the formation of *trans*-Pt(cyd)(dmso-*S*)Cl_2. In order to test for this possibility in our system, we added 1 equiv of $AgNO_3$ to an aged solution of *cis*-Pt(dmso-*S*)$_2Cl_2$ and (thiamin)Cl in dmso to generate *in situ cis* and *trans*-[Pt(dmso-*S*)$_2$(thiamin)Cl]$^{2+}$. A ^{1}H NMR spectrum recorded immediately after precipitation of AgCl shows two new resonances at 8.43 and 8.66 ppm, which we assign to the thiamin H(6′) resonance in these two complexes. These resonances were not detected at any point in the studies of *cis*-Pt(dmso-*S*)$_2Cl_2$ with (thiamin)Cl, *trans*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$, or Pt(thiamin)Cl_3 in dmso. Thus we conclude that the lifetime of [*cis*-Pt(dmso-*S*)$_2$(thiamin)Cl]$^{2+}$ is very short in the presence of Cl^- ions in solution. This is consistent with the high positive charge on this species.

^{195}Pt NMR Characterization. The ^{195}Pt NMR spectrum of **1** in dmso-d_6 shows the presence of one peak at −3050 ppm. Qualitatively, the relative values of the chemical shifts obtained in the $[PtCl_4]^{2-}$ series upon substitution of one or more chlorides can be rationalized in terms of the nature and numbers of the substituents. From Table III, we can infer that substitution of a chloride by either a dmso or a thiamin molecule will result in an upfield shift of the ^{195}Pt resonance, while substitution of a

Scheme I



dmso by a thiamin will result in a downfield shift. In this perspective the resonance of **1** is, as expected, located between those of Pt(thiamin)Cl_3 and Pt(dmso-*S*)$_2Cl_2$.

Within 30 min, the ^{195}Pt NMR spectrum of a freshly prepared solution of Pt(thiamin)Cl_3 shows two resonances at −2915 and −2985 ppm. The broad resonance at −2915 ppm is attributed to the undissociated Pt(thiamin)Cl_3, and the sharp resonance at −2985 ppm is attributed to Pt(dmso-*S*)Cl_3^- as previously reported.[1] These two signals remain for several hours after the solution is prepared (Figure 5). Since the ^{1}H NMR spectrum of a 3-h-old dmso solution of Pt(thiamin)Cl_3 (Figure 4) shows no trace of the original compound (9.63, 8.47 ppm), while a broad peak persists in the ^{195}Pt NMR spectrum (−2915 ppm), this ^{195}Pt signal must be due to two different complexes. From the ^{1}H NMR results, we assign the second compound to *cis*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$. Two observations support this hypothesis. First, ^{195}Pt NMR data on similar systems involving Pt(Xpy)(dmso-*S*)Cl_2, Xpy being various substituted pyridines,[4] show the *cis* compound to give rise to a signal at around −2900 ppm, while the resonance due to the *trans* complex is some 100–150 ppm upfield. Thus, the signal due to *trans*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$ being at −3050 ppm (Figure 6), the signal we assign to the *cis* isomer is 135 ppm downfield from it. Second, the ^{195}Pt NMR spectrum of a solution of *trans*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$ (−3050 ppm) (Figure 6) shows over a period of a few hours a second signal growing at −2915 ppm, corresponding to the *cis* isomer observed in the ^{1}H NMR study (Figure 3). Starting from *trans*-[Pt(dmso-*S*)(thiamin)Cl_2]$^+$, we are confident that the signal observed at −2915

ppm is not due to the presence of $Pt(thiamin)Cl_3$, for this would involve a very unlikely disproportionationlike process in which a chloride ion migrates from one molecule to another, displacing a dmso molecule. The second product of such a reaction would be $[Pt(dmso\text{-}S)_2(thiamin)Cl]^{2+}$. This species, which can be generated in situ by the addition of 1 equiv of $AgNO_3$ to a solution of the *trans* isomer (vide infra) gives rise to resonances not observed in the ^1H NMR study of *cis*-$[Pt(dmso\text{-}S)(thiamin)Cl_2]^+$ (Figure 3). Finally, the ^{195}Pt NMR spectrum of the *trans* isomer also shows the presence of $Pt(dmso\text{-}S)_2Cl_2$ as a third component (−3480 ppm)[21] (Figure 6), which correlates with the presence of free thiamin observed in the ^1H NMR study.

Discussion

The species observed in the reaction of $Pt(thiamin)Cl_3$, *trans*-$[Pt(dmso\text{-}S)(thiamin)Cl_2]^+$, or a mixture of $Pt(dmso\text{-}S)_2Cl_2$ and (thiamin)Cl in dmso are shown on Scheme I. Marzilli reported[20] that in the reaction of several nucleosides with *cis*-$Pt(dmso\text{-}S)_2Cl_2$ in dmso, the initial step was the displacement of Cl^-, in contradiction with Kong's results on similar systems, who advocates an initial displacement of dmso.[3] Although our results did not show the presence of the intermediate reported by Marzilli, we were able to generate such a species upon addition of $AgNO_3$. The fact that we do not observe this species, $[Pt(dmso\text{-}S)_2(thiamin)Cl]^{2+}$, in the presence of chloride could be due to its high reactivity toward Cl^- to rapidly yield **1**, thus preventing any significant amount of $[Pt(dmso\text{-}S)_2(thiamin)Cl]^{2+}$ from existing in solution.

We do not observe the presence of a complex with two thiamin ligands. However, Marzilli reported that *cis*-$[Pt(7\text{-}MeIno)_2(dmso\text{-}S)Cl]^+$ is present in the 1:1 reaction of *cis*-$Pt(dmso\text{-}S)_2Cl_2$ and 7-MeIno.[20] The pK_a of 7-MeIno is slightly greater than 6,[20] while the pK_a of the N(1′) of thiamin is around 5; therefore, the basicity of thiamin should not be responsible for the absence of a bis(thiamin) species. Rather, we anticipate that an unfavorable electrostatic interaction between $[Pt(dmso\text{-}S)(thiamin)Cl_2]^+$ and thiamin, which is positively charged, accounts for this difference in reactivity. This electrostatic argument may also be responsible for the partial dissociation occurring on dissolving $Pt(thiamin)Cl_3$ or *trans*-$[Pt(dmso\text{-}S)(thiamin)Cl_2]^+$. As a consequence of this dissociation, we detect by ^{195}Pt NMR the presence of significant amounts of $[Pt(dmso\text{-}S)Cl_3]^-$ (−2985 ppm) and $Pt(dmso\text{-}S)_2Cl_2$ (−3480 ppm).

Finally, contrary to the reaction of *cis*-$Pt(dmso\text{-}S)_2Cl_2$ with various nucleophiles (Nuc),[3,20] where *trans*-Pt(Nuc)(dmso-S)Cl_2 is the first observed product, the reaction of $Pt(thiamin)Cl_3$ in dmso yields first *cis*-$[Pt(dmso\text{-}S)(thiamin)Cl_2]^+$, indicating that Cl^- is a better *trans* director than thiamin. However, the fact that both $[Pt(dmso\text{-}S)Cl_3]^+$ and *cis*-$[Pt(dmso\text{-}S)(thiamin)Cl_2]^+$ are simultaneously generated in solution suggests that Cl^- and thiamin are ligands of similar strengths toward the Pt center.

Supplementary Material Available: Positional parameters for $[Ph_4B]^-$ (Table 8), best weighted least-squares planes for *trans*-$[Pt(dmso\text{-}S)(thiamin)Cl_2]^+$ (Table 9), hydrogen bonds (Table 10), bond distances (Table 11) and bond angles (Table 12) in $[Ph_4B]^-$, and anisotropic thermal parameters for *trans*-$[Pt(dmso\text{-}S)(thiamin)Cl_2]^+$ (Table 13) and $[Ph_4B]^-$ (Table 14) (7 pages). Ordering information is given on any current masthead page.

(21) Goggin, P. L.; Goodfellow, R. J.; Haddock, S. R.; Taylor, B. F.; Marshall, I. R. S. *J. Chem. Soc., Dalton Trans.* **1976**, 459–76.