Contribution from the Department of Chemistry, Gorlaeus Laboratories, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands

Reaction Products of [Pt(ethylenediamine)(dimethyl sulfoxide)Cl]Cl and [Pt(ethylenediamine)Cl_2] with d(GpG) and 5'GMP. Unambiguous Evidence for Stable 1:1 Intermediate N7 Adducts with Coordinated Dimethyl Sulfoxide

Edwin L. M. Lempers, Marieke J. Bloemink, and Jan Reedijk*

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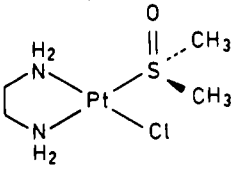
The reactions of [Pt(en)(Me_2SO)Cl]Cl, [Pt(en)(Me_2SO)(D_2O)](NO_3)$_2$, [Pt(en)Cl_2], and [Pt(en)(D_2O)$_2$](NO_3)$_2$ with d(GpG) and with 5'GMP have been investigated by ^{1}H magnetic resonance spectroscopy (en = ethylenediamine; Me_2SO = dimethyl sulfoxide). [Pt(en)(Me_2SO)X] (X = D_2O, Cl^-) and 5'GMP form an intermediate product [Pt(en)(Me_2SO)(5'GMP-*N7*)] (**1**), which consists of two rotamers **1a** and **1b**, the interconversion of which is slow on the NMR time scale at 294 K. The ratio **1a**:**1b** shifts from 2.0 at pH 5 to 1.2 at pH 11, as a result of the dehydronation at the guanine N1 atom. **1** may react further with a second equivalent of 5'GMP, forming [Pt(en)(5'GMP-*N7*)$_2$] (**2**) and free Me_2SO. When reacted with d(GpG), [Pt(en)(Me_2SO)X] (X = D_2O, Cl^-) forms two intermediate products [Pt(en)(Me_2SO){d(GpG)-*N7(1)*}] (**5**) and [Pt(en)(Me_2SO){d(GpG)-*N7(2)*}] (**6**) with a ratio of 70:30. Both **5** and **6** react further, each forming the chelate [Pt(en){d(GpG)-*N7(1),N7(2)*}] (**7**) and free Me_2SO. Both **5** and **6** consist of two rotamers (**5a,b**; **6a,b**), the interconversion of which occurs at an intermediate rate on the NMR time scale at 294 K. Also, [Pt(en)X_2] (X = D_2O, Cl^-) reacts with 5'GMP and d(GpG), forming respectively **2** and **7**. For the corresponding 1:1 intermediates [Pt(en)(D_2O)(5'GMP-*N7*)] (**3**), [Pt(en)Cl(5'GMP-*N7*)] (**4**), [Pt(en)Cl{d(GpG)-*N7(1)*}] (**8**), and [Pt(en)Cl{d(GpG)-*N7(2)*}] (**9**), no rotamers were found at room temperature, which is rationalized by the smaller size of Cl^- and D_2O compared to Me_2SO. The overall reactions of [Pt(en)Cl_2] with the guanine fragments are about a factor of 4-5 faster, compared to those of [Pt(en)(Me_2SO)Cl]Cl. These results indicate that for [Pt(en)(Me_2SO)Cl]Cl similar DNA adducts are formed as compared to the case of the well-known antitumor-active agents, like [*cis*-Pt(NH_3)$_2Cl_2$], and therefore the mechanism of action of both types of compounds might well be related to each other.

Introduction

Most platinum antitumor complexes obey the general formula [*cis*-Pt(Am)$_2X_2$] (Am is an amine ligand with at least one NH group, and X is a moderately strongly bound anionic leaving group such as chloride).[1,2] The bifunctional nature is probably necessary to form an intrastrand cross-link between two adjacent guanine bases in the DNA.[3,4] However, recently two cationic classes of platinum complexes with antitumor properties were described, which are much more soluble in water than the neutral complexes; they have the general formulas [*cis*-Pt(NH_3)$_2$(N-het)Cl]Cl (N-het is a heterocyclic amine like pyridine) and [Pt(diam)(R'R''SO)Cl](NO_3) (diam is a bidentate amine and R'R''SO is a substituted sulfoxide).[5,6] On the other hand, related monofunctional cationic complexes like [Pt(dien)Cl]Cl and [Pt(NH_3)$_3$Cl]Cl are antitumor inactive.[7,8] Therefore, the mechanism of action of these new compounds is unlikely to be the same as that of [*cis*-Pt(Am)$_2X_2$].

In vivo activation of both compounds forming respectively [*cis*-Pt(NH_3)(N-donor)]$^{2+}$ and [Pt(diam)]$^{2+}$ could well explain the observed antitumor activity. However, a recent study[9] in which the interactions between [*cis*-Pt(NH_3)$_2$(4-methylpyridine)Cl]Cl and d(GpG) were investigated proved that such an activation, at least for this particular compound, is unlikely. A similar activation mechanism for [Pt(diam)(R'R''SO)Cl](NO_3), however, is more reasonable in view of the known relatively labile sulfoxide ligand.[10] Even then, there are a few possible reaction paths, as proposed by Farrell et al.,[6] i.e. (i) extracellular hydrolysis to yield [Pt(diam)Cl_2], which then enters the cell, like [*cis*-Pt(NH_3)$_2Cl_2$], (ii) intracellular hydrolysis to yield the reactive diaqua species [*cis*-Pt(diam)(H_2O)$_2$]$^{2+}$, and (iii) intracellular hydrolysis to form [Pt(diam)(R'R''SO)(H_2O)]$^{2+}$, which reacts with DNA to give a well-defined sulfoxide-Pt-DNA intermediate with subsequent activation and displacement of sulfoxide by, most likely, a neighboring guanine base. Displacement studies as carried out by Farrell et al.[6] have pointed out that mechanism iii is most likely. Also, early replacement studies of [Pt(en)(Me_2SO)Cl]Cl with other ligands already pointed to a higher reactivity for Cl^- compared to Me_2SO.[11]

In the present study mechanism iii has been investigated in detail by reacting the simplest derivative, i.e. [Pt(en)(Me_2SO)Cl]Cl, with d(GpG) and with 5'GMP and by comparing its reaction products with those obtained from the neutral [Pt(en)Cl_2]. By characterization of all intermediates and reaction products, we expect to obtain more insight into the mechanism of these new and intriguing antitumor-active compounds.



[Pt(en)(Me_2SO)Cl]$^+$

Experimental Section

Materials. d(GpG) was synthesized via an improved phosphotriester method and used as its sodium salt.[12] 5'-Guanosine monophosphate (5'GMP), guanosine (Guo), and ethylenediamine were obtained from Sigma Chemicals and used without further purification. [*cis*-Pt(Me_2SO)$_2Cl_2$], [Pt(en)Cl_2], and [Pt(en)(H_2O)$_2$](NO_3)$_2$ were prepared from K_2PtCl_4 according to literature procedures.[13-15] [Pt(en)(Me_2SO)Cl]Cl was prepared from [*cis*-Pt(Me_2SO)$_2Cl_2$] according to a procedure by Romeo et al.[16] Anal. Calcd for $PtC_4H_{14}N_2Cl_2OS$: C,

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11.88; H, 3.47; N, 6.93; Cl, 17.57. Found: C, 11.93; H, 3.37; N, 6.96; Cl, 17.65. ^{1}H NMR: 0.31 (s, 6 H), −0.34 ppm (s, 4 H). IR: ν(Pt–Cl) 345 cm^{-1}, ν(Pt–S) 433 cm^{-1}, ν(S–O) 1145 cm^{-1}.

Preparation of [Pt(en)(Me$_2$SO)(NO$_3$)](NO$_3$). [Pt(en)(Me$_2$SO)Cl]Cl (0.20 g, 0.5 mmol) and AgNO$_3$ (0.17 g, 1 mmol) were stirred in 20 mL of H$_2$O for 24 h at room temperature in the dark. The AgCl precipitate was removed by filtration, and the solvent was removed under reduced pressure. The resulting yellow product was washed with 5 mL of MeOH and ether (yield 0.21 g). Anal. Calcd for PtC$_4$H$_{14}$N$_4$O$_7$S: C, 10.50; H, 3.06; N, 12.25. Found: C, 10.23; H, 2.89; N, 11.85 (Cl, 0.64). ^{1}H NMR: 0.28 (s, 6 H), −0.33 ppm (m, 2 H), −0.43 ppm (m, 2 H).

Instrumentation. ^{1}H NMR spectra were obtained in D$_2$O on a Bruker WM 300 spectrometer, and positive chemical shifts are reported downfield from TMA (tetramethylammonium nitrate). The pH values, reported as pH*, are not corrected for deuterium isotope effects. IR spectra (KBr pellets) were obtained on a Perkin-Elmer 580 spectrometer. Elemental analyses were measured by Microanalytical Laboratory, University College, Dublin.

Reactions in the NMR Tube. All reactions in D$_2$O were carried out in the NMR tube at 310 and 328 K and were followed by ^{1}H NMR spectroscopy as a function of time. Both temperatures gave the same reaction products, in approximately the same ratio, although with different reaction rates. At 328 K the reactions were sufficiently fast to follow them easily with ^{1}H NMR spectroscopy over a period of 10 h.

The following reactions were carried out: [Pt(en)(Me$_2$SO)X][17] (X = D$_2$O, Cl$^-$) (5 mM) + d(GpG) (5 mM), 5′GMP (5 mM, 10 mM); [Pt(en)Cl$_2$] (5 mM) + d(GpG) (5 mM), 5′GMP (5 mM, 10 mM). Furthermore, the Me$_2$SO hydrolysis of [Pt(en)(Me$_2$SO)Cl]Cl (5 mM) and of [Pt(en)(Me$_2$SO)(D$_2$O)](NO$_3$)$_2$ (5 mM) were also followed as a function of time. For reference purposes [Pt(en)(Me$_2$SO)(Guo-*N7*)], [Pt(en)(D$_2$O)(5′GMP-*N7*)], and [Pt(en)Cl(5′GMP-*N7*)] were prepared in the NMR tube. The first two were synthesized by reacting [Pt(en)(Me$_2$SO)(D$_2$O)] and [Pt(en)(D$_2$O)$_2$], respectively, with one equivalent of Guo and 5′GMP. [Pt(en)Cl(5′GMP-*N7*)] was prepared by adding an excess of NaCl to [Pt(en)(D$_2$O)(5′GMP-*N7*)]. No attempts were made to purify the products by column chromatography, given the short half-lives of the various species.

For monitoring the pH-dependent chemical shift behavior (294 K) of the ^{1}H signals of the products, the pH was adjusted with 0.1 and 1 M solutions of NaOD and DCl. The reported amounts of products were measured by integration (concentrations of 5 mM were used; estimated error is 10–15%) of the H8 and H1′ proton signals of the guanosine residues of both reaction products and starting compounds and of the coordinated Me$_2$SO protons.

Results and Discussion

Starting Products. The ^{1}H NMR and IR results for [Pt(en)(Me$_2$SO)Cl]Cl are in agreement with those described previously.[16] The infrared absorption at 1145 cm^{-1} can be assigned to ν(S–O) of the coordinated Me$_2$SO and is consistent with binding through sulfur.[18] The chemical shift of the methyl protons of the coordinated Me$_2$SO is downfield by 0.77 ppm compared to that of free Me$_2$SO (−0.46 ppm), again indicating sulfur coordination. Oxygen-bound Me$_2$SO is known to yield a downfield shift of at most 0.5 ppm.[19] The signal shows a weak ^{195}Pt satellite doublet ($^3J(^{195}\text{Pt}-^1\text{H})$ = ca. 22 Hz). The methylene protons of en show only a single peak and a weak ^{195}Pt satellite doublet ($^3J(^{195}\text{Pt}-^1\text{H})$ = ca. 42 Hz), even though the protons have a slightly different chemical environment.

The elemental analyses of [Pt(en)(Me$_2$SO)(NO$_3$)](NO$_3$) show the presence of 0.64% Cl, which indicates that an impurity of at most 3–5% [Pt(en)(Me$_2$SO)Cl]Cl or [Pt(en)(Me$_2$SO)Cl](NO$_3$) may be present. This amount of impurity could also be deduced from the ^{1}H NMR spectrum of the compound. Upon dissolution of [Pt(en)(Me$_2$SO)(NO$_3$)](NO$_3$) in D$_2$O, [Pt(en)(Me$_2$SO)(D$_2$O)](NO$_3$)$_2$ is formed.[15] Two complex multiplets for the methylene protons are observed, likely due to the occurrence of two conformations of the chelate ring. The signal of the methyl protons shows a weak ^{195}Pt satellite doublet ($^3J(^{195}\text{Pt}-^1\text{H})$ = ca. 21 Hz). Additional evidence for the identity of [Pt(en)(Me$_2$SO)(D$_2$O)](NO$_3$)$_2$ is the rapid conversion to [Pt(en)(Me$_2$SO)Cl]Cl, upon addition of NaCl, as seen by ^{1}H NMR spectroscopy.

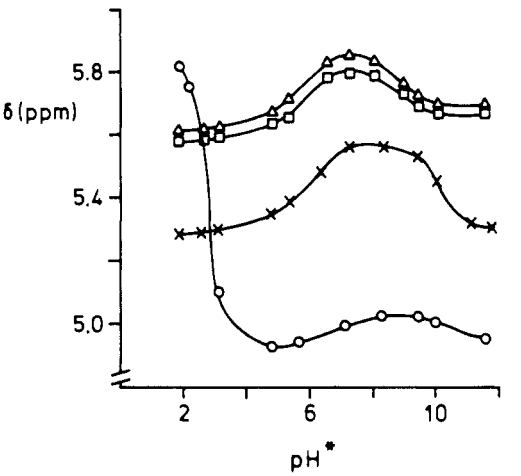

Figure 1. Plots showing the pH* dependence of the chemical shifts of the nonexchangeable base protons in free 5′GMP (○), [Pt(en)(Me$_2$SO)(5′GMP-*N7*)] (**1a**) (□), **1b** (△), and [Pt(en)(5′GMP-*N7*)$_2$] (**2**) (×) monitored at 294 K.

Reaction Conditions. Initially, we tried to carry out the reactions in phosphate buffer, pH 7 (100 mM). However, it appeared that [Pt(en)(Me$_2$SO)Cl]Cl, as well as [Pt(en)(Me$_2$SO)(D$_2$O)](NO$_3$)$_2$, reacts readily with the phosphate buffer, probably forming a phosphate-coordinated species[20] (^{1}H NMR: 0.26 (s, 6 H), −0.35 (m, 2 H), −0.42 ppm (m, 2 H)). Upon addition of an excess of NaCl, [Pt(en)(Me$_2$SO)Cl]Cl was generated. Because the formation of such phosphate-coordinated species could interfere with the studied reactions, it was decided to use no buffer at all. Therefore, the reaction pH could not be kept constant, but varied between 6 and 7.5 for the reactions of the chloro species, and was about 5 for the corresponding aqua species. Thus the reaction of the active species [Pt(en)(Me$_2$SO)Cl]Cl with the guanine fragments was performed near physiological pH values.

Complexes Formed with 5′GMP. The pH dependence of the chemical shift of the nonexchangeable base protons of 5′GMP and its platinum complexes **1a**, **1b**, and **2** is depicted in Figure 1. Compared to the case of 5′GMP, the following changes are apparent. The curves show no N7 (de)protonation effect at pH 2.5 anymore. In addition, the chemical shifts of these H8 protons are downfield by 0.5–0.8 ppm (neutral pH) compared to that of free 5′GMP. These observations prove that in **1a**, **1b**, and **2** the N7 atom of the guanine base is platinated.[21,22] Complex **2** was shown to be [Pt(en)(5′GMP-*N7*)$_2$] by comparison with the product obtained from a reaction, carried out separately, between [Pt(en)(D$_2$O)$_2$](NO$_3$)$_2$ and 2 equiv of 5′GMP. Upon reaction of [Pt(en)(Me$_2$SO)Cl]Cl with 1 equiv 5′GMP, besides the formation of **1a** and **1b**, small amounts of **2** and consequently also of free Me$_2$SO could be observed. This observation complicated the characterization of **1a** and **1b** slightly. Fortunately, the use of [Pt(en)(Me$_2$SO)(D$_2$O)](NO$_3$)$_2$ results in a faster platination step, resulting in the exclusive formation of **1a** and **1b**, while no free Me$_2$SO was formed. The observation that both [Pt(en)(Me$_2$SO)Cl]Cl and [Pt(en)(Me$_2$SO)(D$_2$O)](NO$_3$)$_2$ form **1a** and **1b** is direct evidence for substitution of Cl$^-$ and D$_2$O. Complexes **1a** and **1b** both react with a second equivalent 5′GMP, forming **2**, liberating Me$_2$SO only at that stage. These observations strongly suggest that both **1a** and **1b** have the formula [Pt(en)(Me$_2$SO)(5′GMP-*N7*)] and must be rotamers with slow rotation about the Pt–N7 bond on the NMR time scale at room temperature. The positions of the four Me$_2$SO signals (Table I)

(17) Charges of the coordination entity were omitted for clarity.
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Table I. Selected ^{1}H NMR Spectral Data at pH* 6.4 (294 K) for 5'GMP, d(GpG), and Guo and the Resulting Adducts with [Pt(en)XY] (X, Y = H_2O, Cl^-, Me_2SO) Together with Reference Compounds[a]

compd	δ(H8) (Gp–)	δ(H8) (–pG)	δ(H1)	$^3J_{1'2'}$	δ(SCH_3)
5'GMP		4.97	2.74	6.2	
[Pt(dien)(5'GMP-N7)][e]		5.66 (+0.69)	2.82	4.4	
[Pt(en)(Me_2SO)(5'GMP-*N7*)] (**1a**)		5.75 (+0.78)	2.82	3.6	0.10, 0.12[d]
[Pt(en)(Me_2SO)(5'GMP-*N7*)] (**1b**)		5.80 (+0.83)	2.87	5.4	0.14, 0.16[d]
[Pt(en)(5'GMP-*N7*)$_2$] (**2**)		5.48 (+0.51)	2.75	4.1	
[Pt(en)(D_2O)(5'GMP-*N7*)] (**3**)		5.72 (+0.75)	2.86	3.0	
[Pt(en)Cl(5'GMP-*N7*)] (**4**)		5.40 (+0.43)	2.81	4.8	
d(GpG)	4.57	4.82			
[Pt(en)(Me_2SO){d(GpG)-*N7(1)*}] (**5**)	5.43 (+0.86)	4.80 (–0.02)			0.16, 0.17[c]
[Pt(en)(Me_2SO){d(GpG)-*N7(2)*}] (**6**)	4.75 (+0.18)	5.50[c] (+0.68)			0.18, 0.19[c]
[Pt(en){d(GpG)-*N7(1),N7(2)*}] (**7**)	5.00 (+0.43)	5.30 (+0.48)			
[Pt(en)Cl{d(GpG)-*N7(1)*}] (**8**)	5.15 (+0.58)	4.80 (–0.02)			
[Pt(en)Cl{d(GpG)-*N7(2)*}] (**9**)	4.67 (+0.10)	5.20 (+0.38)	[b]		
[Pt(NH_3)$_3$(d(GpG)-*N7(1)*}][f]	5.27 (+0.70)	4.81 (–0.01)			
[Pt(NH_3)$_3$(d(GpG)-*N7(2)*}][f]	4.72 (+0.15)	5.33 (+0.51)			
[Pt(dien){d(GpG)-*N7(1)*}][f]	5.15 (+0.58)	4.80 (–0.02)			
[Pt(dien){d(GpG)-*N7(2)*}][f]	4.73 (+0.16)	5.19 (+0.37)			
Guo		4.81	2.73	5.8	
[Pt(en)(Me_2SO)(Guo-*N7*)] (**10**)		5.51 (+0.70)	2.79	4.8	0.17, 0.18

[a] Chemical shifts are in ppm relative to TMA; coupling constants (^3J(H1'–H2')) are in Hz; chemical shift differences upon platination are given in parentheses. [b] Not determined due to mixtures of compounds. [c] Measured at 328 K. At lower temperature, the signals broaden as a result of rotamer with intermediate rate of rotation on the NMR time scale (i.e. due to rotamers). [d] Measured at pH* 9.1 because separate signals could be observed at this pH. [e] Taken from ref 27. [f] Taken from ref 9.

for **1a** and **1b**, although upfield compared to those of [Pt(en)(Me_2SO)Cl]Cl, are indicative of coordination through the sulfur atoms.[19] Attempts to prepare [Pt(en)(Me_2SO)(5'GMP-*N7*)] by first reacting [Pt(en)(D_2O)$_2$](NO_3)$_2$ with 1 equiv of 5'GMP, forming [Pt(en)(D_2O)(5'GMP-*N7*)], and, subsequently, with a slight excess of Me_2SO failed. [Pt(en)(D_2O)(5'GMP-*N7*)] (**3**) was quickly formed, but upon subsequent reaction with an excess of Me_2SO several products, other than **1a** and **1b**, were found in small amounts (probably degradation products; they could not be characterized). It is interesting to note that use of Me_2SO as a solvent for [*cis*-Pt(NH_3)$_2$Cl$_2$] results also in a complex mixture of compounds.[23] None of the reported complexes in the present study, however, decomposed in the presence of the formed free Me_2SO. Probably this is the result of the low Me_2SO concentrations (<5 mM) in our case.

Upon reaction of [Pt(en)Cl$_2$] with 2 equiv of 5'GMP, again **2** was formed. One intermediate adduct could be detected and was assigned as [Pt(en)Cl(5'GMP-*N7*)] (**4**). This was confirmed by adding an excess of NaCl to **3**, forming **4**, as prepared separately. The chemical shift and coupling constant values for **2–4** (Table I) are in perfect agreement with those of similar complexes of [*cis*-Pt(NH_3)$_2$Cl$_2$].[24]

The most convincing evidence for the existence of the rotamer pair **1a** and **1b** is their coalescence, and sharpening of proton signals upon increasing the temperature, as is depicted in Figure 2; this process is reversible (energy of activation at coalescence was found to be 70.1 kJ/mol). Figure 2 presents only the H8 and the coordinated Me_2SO protons, but the same effect is observed on the H1' signals. This experiment has been performed at pH 9.1, because under these conditions the four methyl signals of the coordinated Me_2SO ligands are nonoverlapping (i.e., there is a slight pH dependence of these signals: <0.05 ppm). The relative intensities of the H8 signal decrease at higher temperatures, which can be explained by a slow proton H8 exchange with D_2O; this is known to occur especially for N7-platinated residues under these conditions.[25] Also at higher temperatures, there is some overall decomposition of the complexes, forming among other products free Me_2SO.

As is evident from Figure 3, the relative amounts of the two rotamers **1a**:**1b** are pH dependent, which is well correlated with

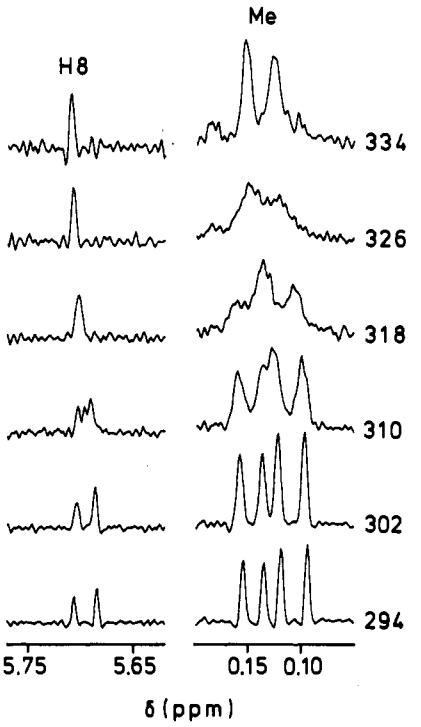

Figure 2. ^{1}H NMR spectra of the H8 and Me_2SO protons of the mixture of [Pt(en)(Me_2SO)(5'GMP-*N7*)] rotamers (**1a** and **1b**) as a function of temperature (pH* = 9.1), showing the appearance of diastereomers.

the pK_a of the 5'GMP N1 atom (see also Figure 1). After the last measurement at basic pH values, the sample was acidified and again measured; it gave the same result as earlier obtained at low pH. This proves that the observed effect is not the result of the selective exchange of the H8 and Me_2SO protons with D_2O of one of the two isomers.

The coupling constant ^3J(H1'–H2') of the two rotamers **1a** and **1b** are different (i.e., for the major rotamer **1a**, this value is 3.6 Hz, and for the minor rotamer **1b**, it is 5.4 Hz, compared to 6.2 Hz for free 5'GMP; see Table I). These values indicate that there is a difference in the conformation of the ribose ring of the two rotamers, resulting in an increase of the population of the N-conformer for **1a** compared to **1b**.[26]

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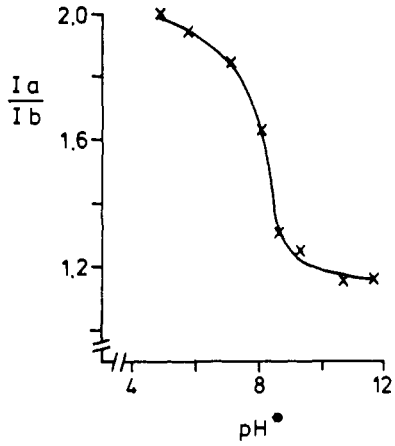

Figure 3. Ratio of the two rotamers **1a**:**1b** as a function of pH* at 294 K determined by relative integration of the H8, H1′, and Me_2SO protons. Both $[Pt(en)(Me_2SO)Cl]Cl$ and $[Pt(en)(Me_2SO)(D_2O)](NO_3)_2$ form **1a** and **1b** in the same ratio.

Rotamers of Pt complexes with 5′GMP have been observed previously.[27,28] However, in those studies amine groups were used with bulky substituents at nitrogen. For the complex $[Pt(en)(5'AMP\text{-}N7)_2]$, on the other hand, which can in a sense be compared to **2**, rotamers were observed.[29] The explanation for the difference between 5′AMP and 5′GMP is clearly the smaller size of the 6-oxo group in **2** compared to the 6-NH_2 group in $[Pt(en)(5'AMP\text{-}N7)_2]$.[29] To our knowledge compounds **1a** and **1b** are the first example of rotamers of Pt antitumor complexes with guanosine fragments, in this case as a result of the bulky leaving group Me_2SO. For related complexes like [*cis*-Pt(7-methylinosine)$(Me_2SO)Cl_2$] rotamers were also found.[30]

Complexes Formed with d(GpG). Three kinds of complexes, i.e. **5**–**7**, are formed between $[Pt(en)(Me_2SO)Cl]Cl$ and d(GpG). The pH dependence of the chemical shift of the nonexchangeable base protons of d(GpG) and its platinum complexes is depicted in Figure 4.[31] For **5** and **6** one of the curves and for **7** both curves of the H8 protons show an N1 protonation effect around pH 8.5 and no N7 protonation effect around pH 2.4. The chemical shifts of these H8 protons are downfield (neutral pH) compared to that of free d(GpG). All together, this indicates that the corresponding guanine bases are platinated at the N7 atoms.[21,22] Furthermore, in **7** one of the deoxyribose rings, probably of Gp–, adopts a single N conformation (i.e., the coupling pattern of the H1′ proton has changed to a doublet), which strongly points to chelate formation through both N7 atoms.[32] By a separate reaction between $Pt(en)Cl_2$ and d(GpG) **7** was again formed. Therefore, it is concluded that **7** is [Pt(en){d(GpG)-*N7(1),N7(2)*}]. The curvatures of the two remaining H8 signals in **5** and **6** are essentially the same (can only be compared in the pH range 3–8.5[31]) as that of free d(GpG), proving that only one guanine is platinated in both complexes. In fact, for **5** the H8 signal of –pG is hardly affected

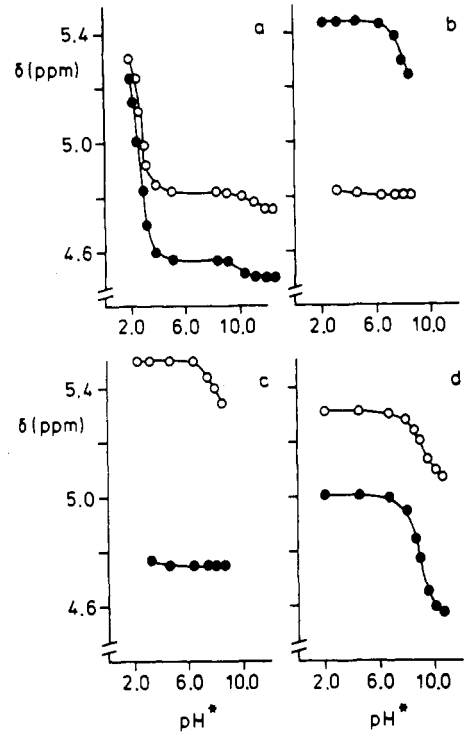

Figure 4. Plots showing the pH* dependence of the chemical shift of the nonexchangeable base protons in free d(GpG) (a), [Pt(en)(Me_2SO)[d(GpG)-*N7(1)*}] (**5**) (b), [Pt(en)(Me_2SO)[d(GpG)-*N7(2)*}] (**6**) (c), and [Pt(en){d(GpG)-*N7(1),N7(2)*}] (**7**) (d). Open symbols represent H8 of –pG; closed symbols represent H8 of Gp–. The results for parts b and c were monitored at 318 K, and the H8 signals could only be observed in the pH* range 3–8.5.[31]

upon platination, which suggests that the platinum is bound to Gp–, forming [Pt(en)(Me_2SO)[d(GpG)-*N7(1)*}]. Similar observations suggest that the platinum unit is bound to –pG in **6**, forming [Pt(en)(Me_2SO)[d(GpG)-*N7(2)*}].[33] In both **5** and **6**, Me_2SO remains coordinated, as concluded from the observation that initially there is no Me_2SO release during the reaction of $[Pt(en)(Me_2SO)(D_2O)](NO_3)_2$ with d(GpG) by which **5** and **6** are formed. The positions of the signals of the Me_2SO protons (Table I) in **5** and **6** are in agreement with sulfur coordination.[19] Both **5** and **6** react further, eventually forming **7** and free Me_2SO.

At 294 K the H8 signal of the platinated guanine bases in **5** and **6** are broadened. This might be the result of the occurrence of rotamers **5a**, **5b**, **6a**, and **6b**, just as seen for **1**, with intermediate rates of rotation about the Pt–N7 bond on the NMR time scale; at higher temperatures these signals sharpen. Attempts to retard the rotation sufficiently, by lowering the temperature to 274 K, to observe separate sets of signals for **5a**,**b** and for **6a**,**b** were not successful. The remaining H8 signals of the nonplatinated guanines of **5** and **6** were not broadened, indicating that only protons nearest the platinum coordination site are sensitive to the small differences between the pair of rotamers.

Upon reaction of $[Pt(en)Cl_2]$ with d(GpG), **7** is again formed. Two reactive intermediate adducts, i.e. **8** and **9**, could be detected which both react further, forming **7**. The intermediate adducts

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(30) Reilly, M. D.; Wilkowsky, K.; Shinozuka, K.; Marzilli, L. G. *Inorg. Chem.* **1985**, *24*, 37.
(31) The H8 signals of **5** and **6** could only be observed in the pH* range 3–8.5 due to a combination of factors: (a) The presence of a mixture of compounds (i.e. d(GpG), **5**, **6**, and **7**) resulted in overlap of several signals. (b) Only low concentrations could be obtained for **5** and **6** (i.e. 1.75 mM for **5** and 0.75 mM for **6**). (c) The high reactivity of **5** and **6** resulted in **7** and free Me_2SO. (d) A temperature of 318 K was required in order to sharpen the H8 signals of the platinated guanines of **5** and **6**. Although the H8 signals of the nonplatinated guanines in **5** and **6** could not be observed below pH* 3, it was clearly seen that they started to move downfield, which proves that there was no Pt coordination to N7.
(32) den Hartog, J. H. J.; Altona, C.; Chottard, J.-C.; Girault, J.-P.; Lallemand, J.-Y.; de Leeuw, F. A. A. M.; Marcelis, A. T. M.; Reedijk, J. *Nucl. Acids Res.* **1982**, *10*, 4715.
(33) In principle, a reversed assignment for **5**, **6**, and **8**, **9** cannot be completely ruled out (Table I); i.e., in that case isomer **5** would be [Pt(en)(Me_2SO)[d(GpG)-*N7(2)*}]. The present assignment is based on chemical shift similarities with related complexes[9] and therefore on a proposed assignment of the H8 signals in free d(GpG). The related complexes [*cis*-$Pt(NH_3)_2$(4-mepy)[d(GpG)-*N7(1)*}] (4-mepy = 4-methylpyridine), [*cis*-$Pt(NH_3)_2$(4-mepy)[d(GpG)-*N7(2)*}], [Pt(dien)[d(GpG)-*N7(1)*}] (dien = diethylenetriamine), [Pt(dien)[d(GpG)-*N7(2)*}], $[Pt(NH_3)_3$[d(GpG)-*N7(1)*}], and $[Pt(NH_3)_3$[d(GpG)-*N7(2)*}] could be unambiguously identified with enzymatic digestion techniques.[9,34] Similar experiments with **5**, **6**, **8**, and **9** were not performed, knowing the instability of these complexes forming **7** and free Me_2SO. For reference purposes the chemical shift values of the $[Pt(dien)]^{2+}$ and $[Pt(NH_3)_3]^{2+}$ complexes are indicated in Table I.
(34) Inagaki, K.; Kasuya, K.; Kidani, Y. *Chem. Lett.* **1983**, 1345.

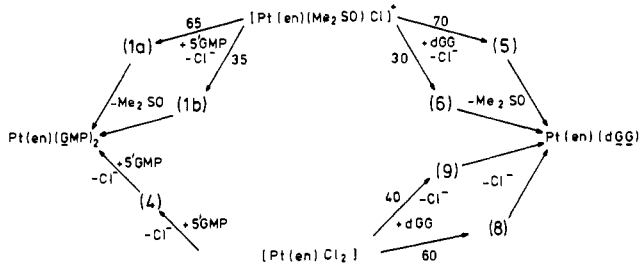
were identified as [Pt(en)Cl{d(GpG)-*N7(1)*}] (**8**) and [Pt(en)-Cl{d(GpG)-*N7(2)*}] (**9**). It is assumed that in **8** and **9** a chloride ion is still coordinated, instead of a D_2O ligand, because D_2O coordination would lead to a larger downfield shift of the H8 signals of the platinated guanines (compare complexes **3** and **4**; Table I).[24] The finding of a coordinated chloride in the intermediate species indicates that [Pt(en)Cl(H_2O)] is the predominant species which reacts with biomolecules, which is in agreement with recent results[35] on the interaction of [*cis*-$Pt(NH_3)_2Cl_2$] with DNA obtained by using ^{195}Pt NMR spectroscopy.

The ratio of product formation, which is approximately constant during reaction (for **5**:**6** this is 70:30 and for **8**:**9** it is 60:40), is comparable with the recently obtained results[9] for the $[Pt(dien)]^{2+}$, $[Pt(NH_3)_3]^{2+}$, and [*cis*-$Pt(NH_3)_2$(4-mepy)]$^{2+}$ complexes of d(GpG). The preference for initial platination at the 5'-guanine appears to differ from earlier studies,[25,27,34,36-41] in which a directing effect of a 5'-phosphate was found, enhancing the reactivity of the 3'-guanine. This discrepancy likely results from a number of factors; e.g. in previous studies a 5'-terminal phosphate was present[27,37-40] with far better directing properties; also, the use of more flexible ribodinucleotides,[25,34,41] allowing the phosphodiester group to direct the Pt unit more efficiently, may contribute to the observed difference in reactivity.

Structures of the Rotamer Pairs 1a,b, 5a,b, and 6a,b. It is assumed that in **1a** and **1b** the guanine bases are oriented in the anti position toward the sugar, as is the case for the related 1:1 complex [Pt(diethylenetriamine)(inosine-*N7*)].[42] Molecular-building studies have shown that restricted rotation about the Pt–N7 bond is likely, the restriction being due mainly to a steric hindrance between the relatively large Me_2SO ligand and O6 of the guanine ring. For the comparable compounds **3** and **4** in which the Me_2SO ligand is replaced respectively by the smaller H_2O and Cl^-, no indication at all is found for the presence of rotamers (i.e., only one sharp signal is observed; see Table I). Two possible orientations of the platinum unit are possible, one in which the ethylenediamine ligand is oriented at the same side of the plane of the guanine ring as the phosphate group and the oxygen in the ribose ring (i.e., **1a**) and one in which the ethylenediamine ring is oriented in the opposite direction (i.e., **1b**). In both diastereomers the two methyl groups of Me_2SO are "prochiral" and therefore are magnetically inequivalent, resulting in a total of four resonances. The proposed assignments for **1a** and **1b** are based on the following considerations: In **1a** a stabilizing hydrogen bond is possible between the phosphate oxygens and the NH_2 of ethylenediamine, as was observed earlier.[43] For this hydrogen bonding the phosphate must be located close to the ethylenediamine ring, and therefore an increase in the population of the N-conformer of the sugar ring is required. This is indeed observed (vide supra). Upon dehydronation of N_1 (pK_a = 8.5), the electron density at O6 increases, which will enhance its hydrogen bonding with the NH_2 of ethylenediamine. This will favor both the rotamers **1a** and **1b** equally. Therefore, a larger amount of rotamer **1b** would be expected. It remains to be investigated why the dehydronation of the phosphate group appears to have no effect on the ratio **1a**:**1b**, since such an effect was found for [Pt(en)-(5'AMP-*N7*)$_2$].[29]

For **5** and **6** the coalescence temperature appeared to be lower than it did for **1**. In **5** and **6** the phosphate group is likely to be less flexible, compared to that in **1**. Therefore, the rotamer pairs

Scheme I. Summary of the Reaction of [Pt(en)(Me_2SO)Cl]Cl and [$Pt(en)Cl_2$] with d(GpG) and 5'GMP (pH* 6–7.5)[a]



[a] The indicated values denote relative amounts (%) (estimated error is 10–15%) determined by integration of the H8 signals of the guanines. At both 310 and 328 K, the products are the same and are formed in similar ratios.

5a,b and **6a,b** cannot be stabilized that much. To test this hypothesis, it was decided to investigate [Pt(en)(Me_2SO)(Guo-*N7*)] (**10**), which lacks the phosphate group. The characterization was straightforward (see Table I). During cooling to 274 K, no sign of any splitting or broadening of signals was observed. This proves that the presence of the phosphate group decreases the rate of rotation about the Pt–N7 bond significantly. This observation is also in agreement with a study by Martin,[44] which indicates that phosphate–amine interactions in Pd complexes result in an increased stability of nucleotide complexes over analogues nucleoside complexes.

Mechanism of Antitumor Activity of [Pt(en)(Me_2SO)Cl](NO_3). The Me_2SO hydrolysis of [Pt(en)(Me_2SO)Cl]Cl and [Pt(en)-(Me_2SO)(D_2O)](NO_3)$_2$ proved to be slow at 328 K after 24 h, and small amounts of [$Pt(en)Cl_2$] (δ = –0.58 ppm) and [Pt-(en)(D_2O)$_2$](NO_3)$_2$ (δ = –0.66 ppm), respectively, were found to be formed. This slow hydrolysis is in agreement with the recent results obtained by Farrell.[6] The use of an amine forming a six-membered chelate ring (e.g., 1,1-bis(aminomethyl)cyclohexane) and sterically more demanding sulfoxides, like methyl phenyl (MePhSO), methyl benzyl (MeBzSO), and dibenzyl (Bz_2SO), increases the rate of hydrolysis[6] to 0.175 10^{-5} s^{-1}, but is still considerably slower than the Cl^- hydrolysis in [*cis*-$Pt(NH_3)_2Cl_2$] (k = 2.5 × 10^{-5} s^{-1})[45] (which proved to be the rate-determing step in its reaction with DNA[46]). Only the quite toxic diphenyl sulfoxide derivative has a rate of hydrolysis (k = 1.85 × 10^{-5} s^{-1})[6] comparable to that of [*cis*-$Pt(NH_3)_2Cl_2$]. On the basis of this slow hydrolysis of R'R''SO in relation to that of Cl^-, it was hypothesized[6] that, intracellularly, initially [Pt(diam)-(R'R''SO)(H_2O)]$^{2+}$ is formed, which reacts with DNA to give a sulfoxide–Pt–DNA intermediate. Subsequently, activation and displacement of sulfoxide most likely by a neighboring guanine base occur (mechanism iii; vide supra).

The resulting products (for an overview see Scheme I) of the reactions between [Pt(en)(Me_2SO)Cl]Cl and [$Pt(en)Cl_2$] with 5'GMP and d(GpG), for which it was proven unambiguously that the intermediate products still contain coordinated Me_2SO, are strongly supportive of this mechanism. During the reaction of [Pt(en)(Me_2SO)Cl]Cl with 5'GMP, initially **1a** and **1b** are formed, which react further to form **2** and free Me_2SO (overall $t_{1/2}$ value for the formation of **2** is ca. 9 h at 328 K). Although the present study does not deal with kinetics, the formation of **1a** and **1b** is clearly faster than the rate of hydrolysis of the Me_2SO ligand. Interestingly, the observation that the reaction of **1a** and **1b** toward **2** is significantly faster compared to the hydrolysis of the Me_2SO ligand in free [Pt(en)(Me_2SO)Cl]Cl is supportive for an increased rate of hydrolysis of the Me_2SO ligand in **1a** and **1b**. Indeed, when **1a** and **1b** are prepared in the absence of a second equivalent of 5'GMP, a hydrolysis reaction is observed, forming free Me_2SO

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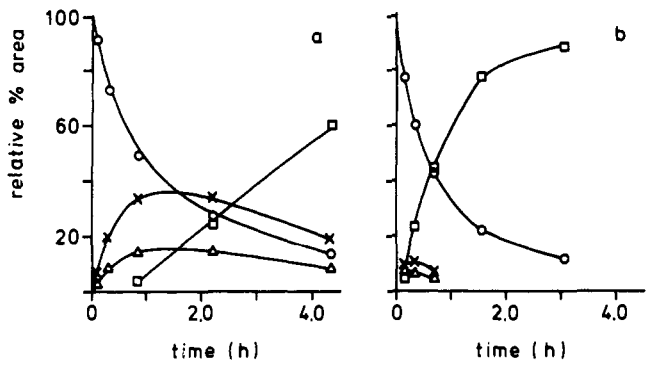

Figure 5. Formation of the products between d(GpG) (5 mM) and [Pt(en)(Me_2SO)Cl]Cl (5 mM) (a) and between d(GpG) (5 mM) and [Pt(en)Cl_2] (5 mM) (b), as a function of time (pH* 6–7.5). The indicated values denote relative amounts (%) at 328 K determined by integration of the H8 signals of the nonplatinated guanines: ○, d(GpG); ×, [Pt(en)(Me_2SO)]d(GpG)-*N7(1)*] (**5**) (a) and [Pt(en)Cl]d(GpG)-*N7(1)*] (**8**) (b); △, [Pt(en)(Me_2SO)]d(GpG)-*N7(2)*] (**6**) (a) and [Pt(en)Cl]d(GpG)-*N7(2)*] (**9**) (b); □, [Pt(en)]d(GpG)-*N7(1),N7(2)*] (**7**).

and decomposition products. Apparently, the steric interaction between the coordinated 5'GMP and Me_2SO, resulting in the appearance of rotamers, labilizes the Me_2SO ligand considerably. Evidence for the increased Pt–S bond length in **1**, but also in **5**, **6**, and **10**, compared to [Pt(en)(Me_2SO)Cl]Cl is the chemical shifts of the Me_2SO protons (ca. 0.2–0.1 ppm) upfield from that in [Pt(en)(Me_2SO)Cl]Cl (which is found at 0.31 ppm).

The reaction of [Pt(en)(Me_2SO)Cl]Cl with d(GpG) is faster (overall $t_{1/2}$ value for the formation of **7** is 3.75 h at 328 K) than its reaction with 5'GMP. This can be explained by assuming an increased reactivity of the intermediates **5** and **6** in relation to **1** due to the formation of **7** via an intramolecular reaction pathway.

The overall reaction rates[47] of [Pt(en)Cl_2] with 5'GMP and d(GpG), forming respectively **2** and **7**, are about a factor of 4–5 faster compared to those of its analogue [Pt(en)Me_2SO)Cl]Cl (e.g., see the reaction with d(GpG) as presented in Figure 5). Most likely, a combination of the following factors can explain this reduced reactivity for the Me_2SO complex:

(i) For the initial binding step [Pt(en)Cl_2] has two available coordination sites, whereas [Pt(en)(Me_2SO)Cl]Cl has only one (based on the assumption that the Me_2SO ligand is initially not reactive; vide supra).

(ii) For the initial approach of the nucleobase, [Pt(en)-(Me_2SO)Cl]Cl will be sterically hindered due to the relatively large Me_2SO ligand.

(iii) The Cl^- hydrolysis can be species dependent (i.e., the cis effect of a coordinated Me_2SO is a factor of 12.5 larger compared[48] to that of coordinated Cl^-).

(iv) Most importantly, the intermediate **1**, **5**, and **6** are much more stable compared to **4**, **8**, and **9**, which results in a retarded second platination step for [Pt(en)(Me_2SO)(G-*N7*)].

The first three points account for the difference in reactivity toward initial platination (approximately a factor of 1.5; see Figure 5).

Farrell et al.[6] have studied a number of complexes of platinum containing substituted sulfoxides [Pt(diam)(R'R''SO)Cl](NO_3). Of all these complexes, the Me_2SO derivatives proved to belong to the less active compounds. However, [Pt(en)(Me_2SO)Cl]Cl is very useful for studying reactions with nucleotides with ^{1}H NMR spectroscopy. The range of antitumor activities of the various compounds is probably not related to different overall mechanisms but has its origin in the reactivity of the compounds themselves both in reaction with DNA and in reaction with proteins. The rate of formation of intermediate species is likely to be dependent on the nature of R'R''SO. Steric effects and the rate of Cl^- hydrolysis will be species dependent. Further, chiral recognition can lead to different antitumor activities/reactivities.[6] In the chelate-forming step (i.e. the R'R''SO dissociation) the same considerations are of importance. As shown,[6] the rate of hydrolysis of R'R''SO in the free platinum complexes may be changed 50–80-fold by systematic substitution (in fact, Me_2SO forms the most stable compound[6]). A similar range of reactivities can occur in the intermediate species. As is shown for [Pt(en)(Me_2SO)Cl]Cl, relatively stable intermediate complexes **1**, **5**, and **6** are formed. However, for the sterically hindered sulfoxides, the reactivity of the intermediates can be higher (maybe again a factor of 50–80). The overall reactivity of [Pt(en)(Me_2SO)Cl]Cl compared to [Pt(en)Cl_2] is a factor of 4–5 smaller, which is mainly due to the formation of stable intermediates **1**, **5**, and **6**. Therefore, it is predicted that the difference in reactivity, for the comparable complexes with sterically hindered sulfoxides, leading to more reactive intermediates, will be smaller.

Concluding Remarks

The present study has led to the following conclusions: (1) Antitumor-active compounds [Pt(diam)(R'R''SO)Cl](NO_3), modeled by [Pt(en)(Me_2SO)Cl]Cl, form 1:1 complexes with 5'GMP and d(GpG) in which the Me_2SO ligand is still coordinated. (2) The intermediates are stable for a few hours at 328 K, whereas the corresponding intermediates formed with [Pt-(en)Cl_2] are barely detectable. (3) The rate of hydrolysis of Me_2SO is increased significantly when a guanine is coordinated at Pt. (4) Although the kinetics will be quite different, eventually compounds of formulas [Pt(diam)(R'R''SO)Cl](NO_3) and [Pt-(diam)Cl_2] will form the same products with 5'GMP and d(GpG). (5) In principle, also the same adducts with DNA can be expected and therefore the mechanisms of action of both types of compounds might well be related to each other. (6) Different ratios between the various DNA products remain possible. Future kinetic studies, also with GXG, AG, and GA fragments, are necessary to investigate this in detail.

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Registry No. **1**, 130669-53-3; **2**, 130669-54-4; **3**, 130669-55-5; **4**, 130669-56-6; **5**, 130698-35-0; **6**, 130698-36-1; **7**, 105810-26-2; **8**, 130698-37-2; **9**, 130698-38-3; **10**, 130669-57-7; d(GpG), 15180-30-0; 5'GMP, 85-32-5; [Pt(en)(Me_2SO)Cl]Cl, 62120-26-7; [Pt(en)-(Me_2SO)(NO_3)]NO_3, 130698-40-7; [Pt(en)(Me_2SO)(D_2O)](NO_3)$_2$, 130698-42-9; [Pt(en)Cl_2], 14096-51-6; [Pt(en)(D_2O)$_2$]$^{2+}$, 63609-29-0; [Pt(en)(Me_2SO)Cl]NO_3, 130669-58-8.

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